Skin Cancer

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Abstract: Cancer is the cells that grow out of control. Cancer cells can also invade other tissues. Growing out of control and invading other tissues are what makes a cell a cancer cell. Involved in more than 100 diseases, the cancer can cause serious illness and death. Normally, the cells become cancer cells because of DNA damage. This material is a literature collection of the researches on the skin cancer.
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1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

Literatures

Abrahams, P. J., A. Houweling, et al. (1998). "Impaired DNA repair capacity in skin fibroblasts from various hereditary cancer-prone syndromes." Mutat Res **407**(2): 189-201.

Host-cell reactivation (HCR) of UV-C-irradiated herpes simplex virus type 1 (HSV-1) has been determined in skin fibroblasts from the following hereditary cancer-prone syndromes: aniridia (AN), dysplastic nevus syndrome (DNS), Von Hippel-Lindau syndrome (VHL), Li-Fraumeni syndrome (LFS) and a family with high incidence of breast and ovarian cancer. Cells from AN, DNS or VHL patients were found to exhibit heterogeneity in HCR. Cells from individuals belonging to an LFS family show reduced HCR in all cases where the cells were derived from persons carrying one mutated p53 allele, whereas cells derived from members with two wild-type alleles show normal HCR. LFS cells with reduced HCR also reveal reduced genome overall repair, and a slower gene-specific repair of the active adenosine deaminase (ADA) gene, but little if any repair of the inactive 754 gene. In the breast/ovarian cancer family, reduced HCR is observed in skin fibroblasts derived from both afflicted and unaffected individuals. In addition, these cells display lower survival after exposure to UV-C and exhibit higher levels of SCEs than those in normal cells. These observations indicate that various hereditary cancer-prone syndromes, carrying mutations in different tumor-suppressor genes, exhibit an unexplained impairment of the capacity to repair UV-damaged DNA.

Abrahams, P. J., A. Houweling, et al. (1992). "High levels of enhanced reactivation of herpes simplex virus in skin fibroblasts from various hereditary cancer-prone syndromes." Cancer Res **52**(1): 53-7.

The dose response of the enhanced reactivation (ER) of herpes simplex virus type 1 has been studied in UV-irradiated normal human skin fibroblasts and fibroblasts from the following hereditary cancer-prone syndromes: retinoblastoma, aniridia, polyposis coli, neurofibromatosis type 1 and 2, dysplastic nevus syndrome, Von Hippel-Lindau syndrome, multiple endocrine neoplasia type 2, and Bloom's syndrome. Surprisingly, much higher levels of ER were observed in all these genetically heterogeneous hereditary disorders than in normal human skin fibroblasts. These results suggest that loss of one allele of putative tumor suppressor genes may activate cellular processes that result in the induction of the ER response, and they support our previous observation suggesting that ER may somehow be related to the process of carcinogenesis (P. J. Abrahams et al., Cancer Res., 48: 6054-6057, 1988).

Ahsan, H., M. H. Aziz, et al. (2005). "Ultraviolet B exposure activates Stat3 signaling via phosphorylation at tyrosine705 in skin of SKH1 hairless mouse: a target for the management of skin cancer?" Biochem Biophys Res Commun **333**(1): 241-6.

Understanding the molecular determinants of ultraviolet (UV) response may lead to the development of novel targets; and therefore, better approaches for the management of cancers, which mainly arise due to the exposure of skin to UV (particularly its UVB spectrum). Signal transducer and activator of transcription (Stat) proteins have been

shown to activate multiple signaling pathways to contribute to oncogenesis. Here, we studied the regulation of Stat3 during UVB exposure-mediated responses in the skin of SKH-1 hairless mouse, a model regarded to possess relevance to human situations. Our data demonstrated that a single UVB (180 mJ/cm(2)) exposure to the skin of SKH-1 hairless mice resulted in significant upregulation in (i) protein levels of Stat3 and (ii) phosphorylation of Stat3 at tyrosine(705). Further, the activation of Stat3 was found to be associated with a decrease in apoptotic response of UVB and a gradual time-dependent increase in leukocyte infiltration and hyperplasia. In conclusion, we have demonstrated, for the first time, that UVB exposure to skin resulted in an activation of pro-survival protein Stat3. Based on our observation, we suggest that Stat3 could serve as a target for the management of UVB exposure-mediated damages including skin cancer.

Al-Khodairy, F. M., M. Kunhi, et al. (2004). "Defective repair of UV-induced DNA damage in cultured primary skin fibroblasts from Saudi thyroid cancer patients." Asian Pac J Cancer Prev **5**(2): 139-43.

This study was conducted to examine the sensitivity of primary skin fibroblasts from Saudi thyroid cancer (TC) patients to ultraviolet (UV) irradiation. Cell survival was studied by a colony forming assay and DNA repair defects with a host cell reactivation (HCR) assay using UV-irradiated Herpes Simplex Virus (HSV). In addition, p53 gene expression was examined in the same TC cells exhibiting enhanced radiosensitivity. Skin fibroblasts from TC patients (n=4) showed significantly enhanced sensitivity to UV radiation. The average UV dose to reduce survival to 37% of the initial survival (D(37)) value (in Jm(-2)) for fibroblasts from TC patients was 4.6 (3.7-5.6) compared to 7.3 (6.3-8.3) for healthy individuals (n=3). UV-sensitive xeroderma pigmentosum (XP) cells, which were used as positive control, were found to be extremely sensitive with a D(37) value of 0.6 Jm(-2). In a host cell reactivation assay, UV-irradiated HSV was tested for its plaque-forming ability (PFA), by plating infected fibroblasts from TC patients (used as host cells) on African Green Monkey (Vero) kidney cells to form plaques. A significant reduction in the PFA of the UV-irradiated virus (about three fold) on TC cells compared to fibroblasts from the healthy subjects was seen, suggesting a DNA-repair deficiency in the primary fibroblasts of the TC patients. Furthermore, no significant accumulation in radiation-induced p53 expression was observed in cells from the TC patients. Our results, based on a relatively small group of subjects, indicate that Saudi TC patients primary fibroblasts (non-cancerous in nature) may be carriers of cancer-susceptible gene(s) arising from defective DNA repair/processing. These results warrant a larger study to investigate the role of UV-induced bulky DNA damage in thyroid cancer susceptibility.

Ananthaswamy, H. N., S. M. Loughlin, et al. (1997). "Sunlight and skin cancer: inhibition of p53 mutations in UV-irradiated mouse skin by sunscreens." Nat Med **3**(5): 510-4.

UV-induced mutations in the p53 tumor suppressor gene play an essential role in skin cancer development. We report here that such mutations can be detected in UV-irradiated mouse skin months before the gross appearance of skin tumors. Application of SPF-15 sunscreens to mouse skin before each UV irradiation nearly abolished the frequency of p53 mutations. These results indicate that p53 mutation is an early event in UV skin carcinogenesis and that inhibition of this event may serve as an early end point for assessing protective measures against skin cancer development.

Ananthaswamy, H. N., S. M. Loughlin, et al. (1998). "Inhibition of UV-induced p53 mutations by sunscreens: implications for skin cancer prevention." J Investig Dermatol Symp Proc **3**(1): 52-6.

Ultraviolet (UV) radiation is a potent human carcinogen and it induces skin cancer in experimental animals. Recent studies have shown that unique mutations in the p53 tumor suppressor gene contribute to the development of human and mouse UV-induced skin cancers. Such mutations are also found in sun-damaged skin and actinic keratosis, suggesting that p53 mutations arise early during UV skin carcinogenesis. Our studies have shown that p53 mutations can be detected in UV-irradiated mouse skin months before the gross appearance of skin tumors, suggesting that p53 mutations can serve as a surrogate early biologic endpoint in skin cancer prevention studies. Indeed, application of sun protection factor 15 sunscreens to mouse skin before each UV irradiation resulted in an 88-92% reduction in the number of p53 mutations. Because p53 mutations represent an early essential step in photocarcinogenesis, these results imply that inhibition of this event may protect against skin cancer development.

Ananthaswamy, H. N., S. E. Ullrich, et al. (2002). "Inhibition of UV-induced p53 mutations and skin cancers by sunscreens: implication for skin cancer prevention." Exp Dermatol **11 Suppl 1**: 40-3.

The relationship between exposure to UVB radiation and development of skin cancer has been well established. Several studies have shown that

UVB induces unique mutations (C to T and CC to TT transitions) in the p53 tumor suppressor gene that are not commonly induced by other carcinogens. Our studies have demonstrated that UV-induced mouse skin cancers contain p53 mutations at a high frequency and that these mutations can be detected in UV-irradiated mouse skin well before the appearance of skin tumors. This observation suggested that it might be possible to use p53 mutations as a biological endpoint for testing the efficacy of sunscreens in photoprotection studies. Indeed, application of SPF 15 sunscreens to mouse skin before each UVB irradiation resulted in 88-92% reduction in the number of p53 mutations. Because p53 mutations represent an early essential step in photocarcinogenesis, these results imply that inhibition of this event may protect against skin cancer development. This hypothesis is confirmed by our finding that sunscreens used in p53 mutation inhibition experiments also protected mice against UVB-induced skin cancer.

Applebaum, K. M., M. R. Karagas, et al. (2007). "Polymorphisms in nucleotide excision repair genes, arsenic exposure, and non-melanoma skin cancer in New Hampshire." Environ Health Perspect **115**(8): 1231-6.

BACKGROUND: Arsenic exposure may alter the efficiency of DNA repair. UV damage is specifically repaired by nucleotide excision repair (NER), and common genetic variants in NER may increase risk for non-melanoma skin cancer (NMSC). OBJECTIVE: We tested whether polymorphisms in the NER genes XPA (A23G) and XPD (Asp312Asn and Lys751Gln) modify the association between arsenic and NMSC. METHODS: Incident cases of basal and squamous cell carcinoma (BCC and SCC, respectively) were identified through a network of dermatologists and pathology laboratories across New Hampshire. Population-based controls were frequency matched to cases on age and sex. Arsenic exposure was assessed in toenail clippings. The analysis included 880 cases of BCC, 666 cases of SCC, and 780 controls. RESULTS: There was an increased BCC risk associated with high arsenic exposure among those homozygous variant for XPA [odds ratio (OR) = 1.8; 95% confidence interval (CI), 0.9-3.7]. For XPD, having variation at both loci (312Asn and 751Gln) occurred less frequently among BCC and SCC cases compared with controls (OR = 0.8; 95% CI, 0.6-1.0) for both case groups. In the stratum of subjects who have variant for both XPD polymorphisms, there was a 2-fold increased risk of SCC associated with elevated arsenic (OR = 2.2; 95% CI, 1.0-5.0). The test for interaction between XPD and arsenic in SCC was of borderline significance ($p < 0.07$, 3 degrees of freedom). CONCLUSIONS: Our findings indicate a reduced NMSC risk in relation to XPD Asp312Asn and Lys751Gln variants. Further, these data support the hypothesis that NER polymorphisms may modify the association between NMSC and arsenic.

Armstrong, B. K., A. Kricker, et al. (1997). "Sun exposure and skin cancer." Australas J Dermatol **38 Suppl 1**: S1-6.

By 1927 for basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), and by 1955 for melanoma, the broad grounds for relating sun exposure to skin cancer had been established: that these are more frequent in residents of areas of high ambient solar irradiance, are more frequent in sun-sensitive people, occur mainly on sun-exposed body sites, are more frequent in people with high sun exposure, and are more frequent in people with benign sun-related skin conditions. The past 40 years have added both quantity and quality to the epidemiological evidence and, most recently, provided direct evidence that sun exposure is the cause of mutations in critical tumour suppressor genes in BCC, SCC and melanoma. Complete or more convincing answers are still needed to many questions of detail. They include whether the pattern of sun exposure is really important in, and acts independently of amount of sun exposure in, affecting the risk of melanoma and BCC; what the shape of the relationship between the amount of sun exposure and risk of BCC and melanoma is when the pattern of exposure is held constant; whether there really is a plateau in risk of BCC and melanoma beyond some level of the amount of exposure; whether this exposure-response relationship depends on cutaneous sensitivity to the sun and in what way; whether sunburn makes a specific contribution to the risk of skin cancer independent of the amount of sun exposure; whether sun exposure close to the time of diagnosis of skin cancer contributes anything to the development of the cancer; what the solar radiation action spectrum is for each kind of skin cancer; and whether sunscreens are effective in protecting against skin cancer.

Ashton, K. J., M. A. Carless, et al. (2005). "Cytogenetic alterations in nonmelanoma skin cancer: a review." Genes Chromosomes Cancer **43**(3): 239-48.

Since the advent of cytogenetic analysis, knowledge about fundamental aspects of cancer biology has increased, allowing the processes of cancer development and progression to be more fully understood and appreciated. Classical cytogenetic analysis of solid tumors had been considered difficult, but new advances in culturing techniques and the addition of new cytogenetic technologies have

enabled a more comprehensive analysis of chromosomal aberrations associated with solid tumors. Our purpose in this review is to discuss the cytogenetic findings on a number of nonmelanoma skin cancers, including squamous- and basal cell carcinomas, keratoacanthoma, squamous cell carcinoma in situ (Bowen's disease), and solar keratosis. Through classical cytogenetic techniques, as well as fluorescence-based techniques such as fluorescence in situ hybridization and comparative genomic hybridization, numerous chromosomal alterations have been identified. These aberrations may aid in further defining the stages and classifications of nonmelanoma skin cancer and also may implicate chromosomal regions involved in progression and metastatic potential. This information, along with the development of newer technologies (including laser capture microdissection and comparative genomic hybridization arrays) that allow for more refined analysis, will continue to increase our knowledge about the role of chromosomal events at all stages of cancer development and progression and, more specifically, about how they are associated with nonmelanoma skin cancer.

Asplund, A., A. C. Gustafsson, et al. (2005). "PTCH codon 1315 polymorphism and risk for nonmelanoma skin cancer." Br J Dermatol **152**(5): 868-73.

BACKGROUND: The PTCH tumour suppressor gene is involved in the development of nearly all basal cell carcinomas (BCCs) of the skin and a fraction of squamous cell carcinomas (SCCs). A nonconservative Pro/Leu nucleotide polymorphism within PTCH exon 23 at codon 1315 was recently reported to be potentially important for the development of breast epithelial cell cancers. Objectives Accordingly, the status of PTCH codon 1315 was analysed for a possible association with the development of nonmelanoma skin cancers (NMSCs) in a pilot study. Because skin cancer risk is affected by specific population-dependent phenotypes such as skin and hair colour, codon 1315 was also analysed for normal allele frequency variation in human populations having differing extents of eumelanin vs. phaeomelanin. METHODS: The single nucleotide polymorphism in codon 1315 of the human PTCH gene was analysed in genomic DNA from six different populations comprising 472 blood samples and from 170 patients in four different categories with NMSC. Polymerase chain reaction and pyrosequencing were used to determine the allele frequencies. Allelic loss was furthermore determined in tumours following microdissection. RESULTS: The Pro/Pro genotype frequency ranged from 30% to 65% between populations, with a significant trend for a reduced frequency of the Pro/Pro genotype in populations having lighter pigmentation (P = 0.020). Pro/Pro frequency showed an increasing trend with increasing tumour case severity (P = 0.027). In 260 samples from 180 Swedish patients with NMSC and a control group of 96 healthy ethnically matched volunteers, no statistically significant pairwise differences between groups were detected in the PTCH codon 1315 allelic distribution, neither was a difference seen for multiple or early onset cases of BCC in the Swedish population. In Swedish patients with single tumours, allelic loss (loss of heterozygosity) was observed in 20 of 30 (67%) patients with BCC and four of 22 (18%) patients with SCC, with no preference in the allele lost. In contrast, the Pro/Pro genotype was frequent in seven U.S. patients having multiple independent BCCs. One of these patients was heterozygous, enabling allelic loss studies. Of 20 independent tumours, 11 had lost an allele; 10 of the 11 had lost Leu, suggesting nonrandom loss that favoured retention of Pro (P = 0.0059). CONCLUSIONS: Our results indicate an association between the eumelanin-to-phaeomelanin shift and a shift from the Pro/Pro genotype to Leu-containing genotypes. Failure to lose Pro during the shift to phaeomelanin may be associated with an increased population risk for BCC and increased individual risk for multiple BCC. During development of a tumour, the effect of Pro may be magnified by loss of the Leu allele.

Athar, M., X. Tang, et al. (2006). "Hedgehog signalling in skin development and cancer." Exp Dermatol **15**(9): 667-77.

Basal cell carcinoma (BCC) is the most common human malignancy, affecting 750,000 Americans each year. The understanding of mutations that are known to activate hedgehog (Hh) signalling pathway genes, including PATCHED (PTCH), sonic hedgehog (Shh) and smoothened (Smo), has substantially expanded our current understanding of the genetic basis of BCC development. The Hh signalling pathway is one of the most fundamental signal transduction pathways in embryonic development. In skin, the Shh pathway is crucial for maintaining stem cell population, and for regulating hair follicle and sebaceous gland development. This pathway plays a minimal role in adult tissues, but is known to be activated in many neoplasms, including those arising in the skin. In this review, we attempt to summarize the results of published studies on some important aspects of the Shh pathway and its involvement in skin development and carcinogenesis. We also provide a description of various animal models that have been developed, based on our knowledge of the Shh pathway in human skin cancers. Additionally, we include a brief description of studies

conducted in our laboratory and by others on the chemoprevention of BCCs. This review therefore provides a current understanding of the role of the Shh pathway in skin development and neoplasia. It also provides a basis for the molecular target-based chemoprevention and therapeutic management of skin cancer.

Bastiaens, M. T., J. A. ter Huurne, et al. (2001). "Melanocortin-1 receptor gene variants determine the risk of nonmelanoma skin cancer independently of fair skin and red hair." Am J Hum Genet **68**(4): 884-94.

Melanocortin-1 receptor (MC1R) gene variants are associated with fair skin and red hair and, independently of these, with cutaneous malignant melanoma. The association of MC1R gene variants with nonmelanoma skin cancer is largely unknown. A total of 838 subjects were included in the present study: 453 patients with nonmelanoma skin cancer and 385 subjects with no skin cancer. The coding sequence of the human MC1R gene was tested using single-stranded conformation polymorphism analysis followed by sequencing of unknown variants. Risk of skin cancer dependent on the various MC1R gene variants was estimated using the exposure odds ratio. We investigated whether subjects with MC1R variant alleles were at increased risk of developing nonmelanoma skin cancer and, if so, whether this increased risk was mediated by fair skin and red hair. A total of 27 MC1R gene variants were found. The number of carriers of one, two, or three MC1R gene variants was 379 (45.2%), 208 (24.8%), and 7 (0.9%), respectively. A strong association between MC1R gene variants and fair skin and red hair was established, especially the variants Arg151Cys and Arg160Trp ($P < .0001$). Carriers of two variant alleles were at increased risk for developing cutaneous squamous cell carcinoma (odds ratio 3.77; 95% confidence interval [CI] 2.11-6.78), nodular basal cell carcinoma (odds ratio 2.26; 95% CI 1.45-3.52), and superficial multifocal basal cell carcinoma (odds ratio 3.43; 95% CI 1.92-6.15), compared with carriers of two wild-type alleles. Carriers of one variant allele had half the risk. The highest relative risks of nonmelanoma skin cancer were found in carriers of the Asp84Glu, His260Pro, and Asp294His variant alleles, and the risk was only slightly lower for carriers of the Val60Leu, Val92Met, Arg142His, Arg151Cys, and Arg160Trp variant alleles. When subjects were stratified by skin type and hair color, analysis showed that these factors did not materially change the relative risks. These findings indicate that MC1R gene variants are important independent risk factors for nonmelanoma skin cancer.

Batinac, T., G. Zamolo, et al. (2007). "Apoptosis in skin cancer development and regression." Coll Antropol **31 Suppl 1**: 23-8.

Non-melanoma skin cancers (NMSC) are the most common malignant tumors in white population and their incidence has been increasing worldwide. Molecular events regulating cell survival, apoptosis, growth arrest as well as cell differentiation, are important contributors to the overall kinetics of benign and malignant cell growth and play a role in their development, progression and regression. Failure of these pathways can result in the loss of control over proliferation and lead to tumor development through the inactivation of tumor suppressor genes or the activation of oncogenes. Also, immunological mechanisms have been implicated in a phenomenon of tumor progression as well as spontaneous tumor regression. We have tried to summarize the main events in etiopatogenesis, development, progression and in some cases skin cancer regression. Further studies are needed to elucidate completely the details of apoptotic control in normal skin and determine factors resulting in apoptotic disbalance and disease.

Bavinck, J. N., L. Gissmann, et al. (1993). "Relation between skin cancer, humoral responses to human papillomaviruses, and HLA class II molecules in renal transplant recipients." J Immunol **151**(3): 1579-86.

Human papillomaviruses (HPV), especially the epidermodysplasia verruciformis (EV)-associated HPV 5, 8, 14, 17, 20, and 47, are thought to play a role in the pathogenesis of some skin cancers in recipients of renal allografts. MHC class I and class II genes are involved in the cellular immune response to viral and tumor Ag. Little is known about humoral responses to HPV in recipients with and without skin cancer. We investigated the prevalence of antibodies to the early (E) protein E7 and the major capsid late (L) protein L1 of HPV 8. In addition, we studied the association of HLA class II molecules with these antibody responses. The E7 and L1 open reading frames of HPV 8 were bacterially expressed as beta-galactosidase fusion proteins, which were purified by preparative gel electrophoresis. Serum samples from 36 renal transplant recipients with and 91 recipients without skin cancer were screened for the presence of IgG and IgM antibodies to HPV 8 E7 and L1, by Western blot analysis. The detection of anti-HPV 8 L1 antibodies represents the immune response to HPV 8 and possibly other EV-associated HPV, because cross-reactivity between the representatives of this HPV subgenus can occur. The antibody responses to HLA Ag were used as controls. Recipients who had IgM antibodies but no IgG antibodies to L1 of HPV 8 (patients with no apparent class switch from IgM to IgG) had skin cancer in 50% of cases, whereas

recipients who produced IgG antibodies (patients with an apparently good humoral response to L1 of HPV 8) had skin cancer in only 18% of cases. The estimated relative risk of skin cancer in recipients with no class switch, compared with the risk in those with a good humoral response, was 4.5 (95% confidence interval, 1.1 to 18.1). We found no association between the antibody response to HLA Ag and the occurrence of skin cancer. A strong linkage between the absent class switch of antibody production in response to L1 of HPV 8 and HLA-DR7 was observed (relative risk, 26.2). Renal transplant recipients who have no apparent class switch from IgM to IgG production in response to Ag encoded by L1 of HPV 8 or possibly other EV-associated HPV are at an increased risk of skin cancer. The association with HLA-DR7 indicates a genetic control of skin cancer development or regression, involving genes in the class II region of the MHC.

Beaumont, K. A., Y. Y. Liu, et al. (2009). "The melanocortin-1 receptor gene polymorphism and association with human skin cancer." Prog Mol Biol Transl Sci **88**: 85-153.

The melanocortin-1 receptor (MC1R) is a key gene involved in the regulation of melanin synthesis and encodes a G-protein coupled receptor expressed on the surface of the melanocyte in the skin and hair follicles. MC1R activation after ultraviolet radiation exposure results in the production of the dark eumelanin pigment and the tanning process in humans, providing physical protection against DNA damage. The MC1R gene is highly polymorphic in Caucasian populations with a number of MC1R variant alleles associated with red hair, fair skin, freckling, poor tanning, and increased risk of melanoma and nonmelanoma skin cancer. Variant receptors have shown alterations in biochemical function, largely due to intracellular retention or impaired G-protein coupling, but retain some signaling ability. The association of MC1R variant alleles with skin cancer risk remains after correction for pigmentation phenotype, indicating regulation of nonpigmentary pathways. Notably, MC1R activation has been linked to DNA repair and may also contribute to the regulation of immune responses.

Beaumont, K. A., R. A. Newton, et al. (2005). "Altered cell surface expression of human MC1R variant receptor alleles associated with red hair and skin cancer risk." Hum Mol Genet **14**(15): 2145-54.

The human melanocortin-1 receptor gene (MC1R) encodes a G-protein coupled receptor that is primarily expressed on melanocytes, where it plays a key role in pigmentation regulation. Variant alleles are associated with red hair colour and fair skin, known as the RHC phenotype, as well as skin cancer risk. The R151C, R160W and D294H alleles, designated 'R', are strongly associated with the RHC phenotype and have been proposed to result in loss of function receptors due to impaired G-protein coupling. We recently provided evidence that the R151C and R160W variants can efficiently couple to G-proteins in response to alpha-melanocyte stimulating hormone. The possibility that altered cellular localization of the R151C and R160W variant receptors could underlie their association with RHC was therefore considered. Using immunofluorescence and ligand binding studies, we found that melanocytic cells exogenously or endogenously expressing MC1R show strong surface localization of the wild-type and D294H alleles but markedly reduced cell surface expression of the R151C and R160W receptors. In additional exogenous expression studies, the R variant D84E and the rare I155T variant, also demonstrated a significant reduction in plasma membrane receptor numbers. The V60L, V92M and R163Q weakly associated RHC alleles, designated 'r', were expressed with normal or intermediate cell surface receptor levels. These results indicate that reduced receptor coupling activity may not be the only contributing factor to the genetic association between the MC1R variants and the RHC phenotype, with MC1R polymorphisms now linked to a change in receptor localization.

Bendesky, A., A. Rosales, et al. (2007). "p53 codon 72 polymorphism, DNA damage and repair, and risk of non-melanoma skin cancer." Mutat Res **619**(1-2): 38-44.

A very common polymorphism of p53, that of codon 72, codes either for a proline (P72) or an arginine (R72). The two alleles differ in their biological properties: P72 is a stronger inducer of p21, while R72 induces 5-10 times more apoptosis. It is not known, however, whether this polymorphism influences genome stability. The influence of p53 codon 72 polymorphism on cancer risk has been studied for different types of cancer with mixed and inconsistent results. With respect to sporadic non-melanoma skin cancer (NMSC), there are few studies, with small sample sizes, and none in a Latinoamerican population. These studies have found no association between p53 genotype at codon 72 and NMSC. We analyzed whether p53 codon 72 genotype influences genomic stability and the sensitivity of cells to UVB. We also carried out a case-control study of NMSC in a Mexican population which included 204 BCC cases, 42 SCC cases, and 238 controls. There was no association between p53 genotype and basal levels of DNA damage, oxidative DNA damage sensitivity, or DNA repair capacity. R72 dominantly increased the in vitro sensitivity of cells to UVB-induced apoptosis.

There was no significant association either between p53 genotype and basal cell carcinoma (BCC), squamous cell carcinoma (SCC) or both combined.

Benjamin, C. L. and H. N. Ananthaswamy (2007). "p53 and the pathogenesis of skin cancer." Toxicol Appl Pharmacol **224**(3): 241-8.

The p53 tumor suppressor gene and gene product are among the most diverse and complex molecules involved in cellular functions. Genetic alterations within the p53 gene have been shown to have a direct correlation with cancer development and have been shown to occur in nearly 50% of all cancers. p53 mutations are particularly common in skin cancers and UV irradiation has been shown to be a primary cause of specific 'signature' mutations that can result in oncogenic transformation. There are certain 'hot-spots' in the p53 gene where mutations are commonly found that result in a mutated dipyrimidine site. This review discusses the role of p53 from normal function and its dysfunction in pre-cancerous lesions and non-melanoma skin cancers. Additionally, special situations are explored, such as Li-Fraumeni syndrome in which there is an inherited p53 mutation, and the consequences of immune suppression on p53 mutations and the resulting increase in non-melanoma skin cancer in these patients.

Benjamin, C. L., V. O. Melnikova, et al. (2008). "P53 protein and pathogenesis of melanoma and nonmelanoma skin cancer." Adv Exp Med Biol **624**: 265-82.

The p53 tumor suppressor gene and gene product are among the most diverse and complex been shown to have a direct correlation with cancer development and have been shown to occur in nearly 50% of all cancers. p53 mutations are particularly common in skin cancers and UV irradiation has been shown to be a primary cause of specific 'signature' mutations that can result in oncogenic transformation. There are certain 'hot-spots' in the p53 gene where mutations are commonly found that result in a mutated dipyrimidine site. This review discusses the role of p53 from normal function and its dysfunction in precancerous lesions, nonmelanoma and melanoma skin cancers. Additionally, molecules that associate with p53 and alter its function to produce neoplastic conditions are also explored in this chapter.

Benjamin, C. L., S. E. Ullrich, et al. (2008). "p53 tumor suppressor gene: a critical molecular target for UV induction and prevention of skin cancer." Photochem Photobiol **84**(1): 55-62.

The relationship between exposure to UV radiation and development of skin cancer has been well established. Several studies have shown that UVB induces unique mutations (C-->T and CC-->TT transitions) in the p53 tumor suppressor gene that are not commonly induced by other carcinogens. Our studies have demonstrated that UV-induced mouse skin cancers contain p53 mutations at a high frequency and that these mutations can be detected in UV-irradiated mouse skin well before the appearance of skin tumors. This observation suggested that it might be possible to use p53 mutations as a biologic endpoint for testing the efficacy of sunscreens in photoprotection studies. Indeed, application of SPF 15 sunscreens to mouse skin before each UVB irradiation resulted in reduction in the number of p53 mutations. Because p53 mutations represent an early essential step in photocarcinogenesis, these results imply that inhibition of this event may protect against skin cancer development. This hypothesis was confirmed by our finding that sunscreens used in p53 mutation inhibition experiments also protected mice against UVB-induced skin cancer.

Berg, R. J., A. de Vries, et al. (1997). "Relative susceptibilities of XPA knockout mice and their heterozygous and wild-type littermates to UVB-induced skin cancer." Cancer Res **57**(4): 581-4.

Although xeroderma pigmentosum (XP) patients are rare, carriers of XP genes (heterozygotes) are much more common. Whether such carriers have an increased skin cancer risk is unknown. Recently developed mouse models for XP have opened up the possibility of determining the skin cancer risk of heterozygotes relative to wild types. Therefore, the XPA knockout trait has been crossed into hairless mice, and squamous cell carcinomas of the skin have been induced by low daily UVB exposures for 500 days in all three genotypes (-/-, +/-, and +/+). The carcinogenic response of the heterozygotes did not significantly differ from that of their wild-type littermates. Tumors in the XPA -/- animals appeared with a latency time that was decreased by a factor of 4.2. From this, we estimate that a functional XPA gene provides a "protection factor" of 60 (95% confidence interval, 15-250) against UV carcinogenesis, which is greater protection than that against acute UV effects, such as erythema and edema (protection factor between 7 and 16). Deficient nucleotide excision repair appears to have a more dramatic impact on skin cancer susceptibility than on sensitivity to acute UV effects.

Berg, R. J., H. J. Ruven, et al. (1998). "Defective global genome repair in XPC mice is associated with skin cancer susceptibility but not with sensitivity to UVB induced erythema and edema." J Invest Dermatol **110**(4): 405-9.

It is generally presumed that xeroderma pigmentosum (XP) patients are extremely sensitive to developing UV erythema, and that they have a more than 1000-fold increased skin cancer risk. Recently established mouse models for XP can be employed to investigate the mechanism of these increased susceptibilities. In line with human data, both XPA and XPC knockout mice have been shown to have an increased susceptibility to UVB induced squamous cell carcinomas. In XPA knockouts, nucleotide excision repair of UV induced DNA photolesions is completely defective (i.e., both global genome repair and transcription coupled repair are defective). We determined the strand specific removal of cyclobutane pyrimidine dimers and pyrimidine [6-4] pyrimidone photoproducts from the p53 gene in cells from XPC knockout mice and wild-type littermates. Analogous to human XPC cells, embryonic fibroblasts from XPC knockout mice are only capable of performing transcription coupled repair of DNA photolesions. We show that these XPC knockout mice, in striking contrast to XPA knockout mice, do not have a lower minimal erythema/edema dose than their wild-type littermates. Hence, defective global genome repair appears to lead to skin cancer susceptibility, but does not influence the sensitivity to acute effects of UVB radiation, such as erythema and edema. The latter phenomena thus relate to the capacity to perform transcription coupled repair, which suggests that blockage of RNA synthesis is a key event in the development of UV erythema and edema.

Berman, B., O. A. Perez, et al. (2006). "Immunological strategies to fight skin cancer." Skin Therapy Lett **11**(5): 1-7.

Skin cancer is the most common human cancer, and is currently considered a global epidemic. Recently, there has been a growing interest in immunomodulators, or up-regulators of the immune response, for the treatment and cure of various forms of skin cancer, including melanoma and nonmelanoma skin cancers, cutaneous T-cell lymphoma, Kaposi's sarcoma, cutaneous extramammary Paget's disease, and vulvar intraepithelial carcinoma neoplasia. Strategies to augment the host's immune response against cancer cells and/or cancer cell antigenicity have been investigated, including recombinant cytokines, immunomodulators, dendritic cell immunization, tumor antigen vaccination, T-cell-based immunotherapy, and gene therapy. Although the current standard of care for most of these cancers includes Mohs micrographic surgery, curettage, and cryo-, laser-, or radiotherapy, immunomodulators are becoming essential in the treatment of patients who are poor surgical candidates and/or require noninvasive therapy.

Bhattacharyya, S. S., S. Paul, et al. (2009). "A synthetic coumarin (4-methyl-7 hydroxy coumarin) has anti-cancer potentials against DMBA-induced skin cancer in mice." Eur J Pharmacol **614**(1-3): 128-36.

Scopoletin, an alkaloid separated from ethanolic extract of the medicinal plant, Gelsemium sempervirens (Fam: Loganiaceae) has been reported to have anti-cancer potentials. The synthetic coumarin (4-Methyl-7 hydroxy coumarin) derived from resorcinol and ethyl aceto-acetate in presence of concentrated sulphuric acid is structurally close to scopoletin, being a coumarin derivative. Whether this synthetic compound also has anti-cancer potentials has been evaluated in vivo on DMBA (7,12-Dimethylbenz[a]anthracene) induced skin cancer in mice by analyzing results of several cytogenetic endpoints, Comet assay, and fluorescence activated cell sorting (FACS). Further, expressions of signal proteins like Aryl hydrocarbon receptor , p53, PCNA, Akt, Bcl-2, Bcl-xL, Bad, Bax, NF-kappaB Apaf, IL-6, Cytochrome-c, Caspase-3 and Caspase-9 were studied by immunoblot analysis along with histology of skin and immuno-histochemical localization of Aryl hydrocarbon receptor and PCNA in DMBA treated mice vis-a-vis carcinogen treated synthetic coumarin fed mice. Feeding of this synthetic coumarin induced positive modulations in expression of all biomarkers in DMBA administered mice, giving clues on its possible signaling pathway(s) - primarily through down-regulation of Aryl hydrocarbon receptor and PCNA and up-regulation of apoptotic proteins like Bax, Bad, Cytochrome c, Apaf, Caspase-3 and Caspase-9, resulting in an appreciable reduction in growth of papilloma in mice. Therefore, this synthetic coumarin shows promise for use in cancer therapy, particularly in skin cancer.

Bickers, D. R. and M. Athar (2000). "Novel approaches to chemoprevention of skin cancer." J Dermatol **27**(11): 691-5.

Protection against sun-induced damage leading to photocarcinogenesis in skin is a highly desirable goal. Among various strategies, chemopreventive approaches utilizing non-toxic agents to prevent the occurrence of precancerous lesions or their surrogate markers are potentially attractive. Epidemiological and experimental studies provide evidence that some naturally occurring chemical agents in the human diet can diminish cancer risk. Aside from water, tea is the most common beverage consumed worldwide. Black tea accounts for nearly 80% of total tea production. Black tea and

green tea are derived from the same plant, Camelia sinensis. Green tea contains monomeric polyphenols known as flavanols and black tea contains dimeric flavanols and polymeric polyphenols known as theaflavins (TFs) and thearubigins (TRs). Over the past fifteen years our laboratory has been exploring the feasibility of using tea and its constitutents as an approach to skin cancer prevention. We demonstrated that green tea, black tea and constituent polyphenols protect against chemical- and ultraviolet B (UVB)-induced carcinogenesis and reduce the growth of established tumors in skin. We have also shown the efficacy of green and black tea extracts against UVB and psoralen + ultraviolet A (PUVA)-induced early damage in skin. Although PUVA is highly effective in treating certain skin diseases, careful follow-up studies of cohorts of patients have shown that similar to UVB, PUVA treatment increases the risk for cutaneous squamous cell carcinoma and melanoma. We have found that oral administration of a standardized green tea extract (SGTE) prior to and during treatment of SKH-1 mice diminished PUVA-induced skin hyperplasia and hyperkeratosis. SGTE-treatment also inhibited PUVA-induced accumulation of c-fos and p53 proteins and epithelial hyperproliferation. Both topical application and oral administration of SGTE after PUVA-treatment reduced skin inflammation and cell hyperproliferation. Topical application of SGTE to human skin prior to PUVA-treatment inhibited the delayed skin inflammatory response. Similarly, oral and topical administration of standardized black tea extract (SBTE) and its two major polyphenolic sub-fractions protect against UVB-induced erythema in SKH-1 mice. Furthermore, topical application of tea extracts to human volunteers protects against UVB-induced erythema. In summary, these studies indicate that tea extracts are effective in reducing UVB- and PUVA-mediated DNA damage, expression of early response genes and early inflammatory changes in skin. These studies verify a conceptual rationale for employing naturally occurring dietary constitutents as an approach to cancer chemoprevention.

Bikle, D. D. (2004). "Vitamin D and skin cancer." J Nutr **134**(12 Suppl): 3472S-3478S.

Skin cancer is the most common cancer afflicting humans. These cancers include melanomas and 2 types of malignant keratinocytes: basal-cell carcinomas (BCC) and squamous-cell carcinomas (SCC). UV light exposure is linked to the incidence of these cancers. On the other hand, the skin is the major source of vitamin D-3 (cholecalciferol) and UV light is critical for its formation. Keratinocytes can convert vitamin D-3 to its hormonal form, 1,25 dihydroxyvitamin D(3) [1,25(OH)(2)D(3)] (calcitriol). 1,25(OH)(2)D(3) in turn stimulates the differentiation of keratinocytes, raising the hope that 1,25(OH)(2)D(3) may prevent the development of malignancies in these cells. We identified a number of mechanisms by which 1,25(OH)(2)D(3) regulates the differentiation of keratinocytes and explored where this regulation breaks down in SCCs. 1,25(OH)(2)D(3) regulates gene expression by activating the vitamin D receptor (VDR). When activated, the VDR binds to one of two coactivator complexes: DRIP or p160/SRC. Binding to DRIP occurs in the undifferentiated keratinocyte, but, as the cell differentiates, DRIP(205) levels fall and p160/SRC binding takes over as SRC3 expression increases. SCCs fail to respond to the prodifferentiating actions of 1,25(OH)(2)D(3). These cells have normal levels of VDR and normal binding of VDR to vitamin D response elements. However, they overexpress DRIP(205) such that the p160/SRC complex is blocked from binding to VDR. We hypothesize that failure of 1,25(OH)(2)D(3) to induce differentiation in SCCs lies at least in part with its failure to induce the replacement of the DRIP complex with the SRC complex in the promoters of genes required for differentiation.

Bikle, D. D., Y. Oda, et al. (2005). "Vitamin D and skin cancer: a problem in gene regulation." J Steroid Biochem Mol Biol **97**(1-2): 83-91.

The skin is the major source of Vitamin D(3) (cholecalciferol), and ultraviolet light (UV) is critical for its formation. Keratinocytes, the major cell in the epidermis, can further convert Vitamin D(3) to its hormonal form, 1,25-dihydroxyvitamin D(3) [1,25(OH)(2)D(3)] (calcitriol). 1,25(OH)(2)D(3) in turn stimulates the differentiation of keratinocytes, raising the hope that 1,25(OH)(2)D(3) may prevent the development of malignancies in these cells. Skin cancers (squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and melanomas) are the most common cancers afflicting humans. UV exposure is linked to the incidence of these cancers-UV is thus good and bad for epidermal health. Our focus is on the mechanisms by which 1,25(OH)(2)D(3) regulates the differentiation of keratinocytes, and how this regulation breaks down in transformed cells. Skin cancers produce 1,25(OH)(2)D(3), contain ample amounts of the Vitamin D receptor (VDR), and respond to 1,25(OH)(2)D(3) with respect to induction of the 24-hydroxylase, but fail to differentiate in response to 1,25(OH)(2)D(3). Why not? The explanation may lie in the overexpression of the DRIP complex, which by interfering with the normal transition from DRIP to SRC as coactivators of the VDR during differentiation, block the induction of

genes required for 1,25(OH)(2)D(3)-induced differentiation.

Bode, A. M. and Z. Dong (2000). "Signal transduction pathways: targets for chemoprevention of skin cancer." Lancet Oncol **1**: 181-8.

Chemoprevention can be defined as the use of substances to interfere with the process of cancer development. Although substantial progress has been made in elucidating the basis of carcinogenesis, further advances are needed to identify molecular and cellular targets for effective use of chemopreventive agents. Hundreds of compounds have been identified as potential chemopreventive agents. However, the safety and efficacy of each substance must be thoroughly investigated. Carcinogenesis is a multistage process in which numerous genes are affected. Many of these genes regulate important cellular functions, so they are prime targets for chemopreventive agents. A major focus of our work has been the elucidation of mechanism(s) explaining the anticancer actions attributed to several chemopreventive compounds, especially 'natural compounds' that are considered safe because they are present in commonly consumed foods and beverages. Of particular interest are selected drugs (eg aspirin) and certain dietary factors (eg green and black tea, resveratrol) and their influence on cell-signalling events coinciding with skin cancer promotion. This overview describes recent work from our laboratory and others focusing on molecular mechanisms of selected chemopreventive compounds in growth-related signal transduction pathways and skin cancer.

Boldrini, L., B. Loggini, et al. (2003). "Mutations of Fas (APO-1/CD95) and p53 genes in nonmelanoma skin cancer." J Cutan Med Surg **7**(2): 112-8.

BACKGROUND: There is considerable evidence that apoptosis plays an important role in the pathogenesis of a wide variety of skin diseases. Apoptosis failure may ensure the survival of transformed cells prone to sustain further genetic damage and it plays an important part in the development of tumors. Genetic alterations of Fas and p53, with consequent inactivation of gene protein products, may be involved in transcriptional downregulation of Fas. OBJECTIVE: We investigated Fas and its ligand expression in 30 cases of nonmelanoma skin cancer, 19 basal cell and 11 squamous cell carcinomas, and we also analyzed Fas and p53 status, in an attempt to detect putative alterations. METHOD: Fas and its ligand expression were evaluated by RT-PCR; the promoter and the entire coding region of Fas, and the coding exons 4-9 of p53 were investigated by polymerase chain reaction, single strand conformation polymorphism, and DNA sequencing. RESULTS: Fas alterations were found in 3/19 (15.8%) basal cell and in 4/11 (36.4%) squamous cell carcinomas. Five out of 25 cases (3/19 basal cell and 2/11 squamous cell carcinomas) were p53-mutated, and in the majority of these cases there were concomitant mutations of the Fas gene (c2 test; p = 0.035). CONCLUSION: Taken together, our findings highlight an involvement of the Fas/Fas-ligand system in the development of skin cancer, suggesting that the loss of its apoptotic function, in some cases linked to p53 alterations, may contribute to the self-maintenance of cancer cells.

Boukamp, P. (2005). "Non-melanoma skin cancer: what drives tumor development and progression?" Carcinogenesis **26**(10): 1657-67.

Non-melanoma skin cancer, i.e. basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most frequent tumors and their number is still increasing worldwide. Furthermore, immunosuppression in organ transplant patients strongly contributes to the increase in skin cancer incidence--being 65-250 times more frequent than in the general population. Often these patients suffer from a second and third lesion and the severity of these tumors is linked to their number. SCCs in transplant recipients also appear to be more aggressive. They tend to grow rapidly, show a higher rate of local recurrences and metastasize in 5-8% of the patients (all reviewed in Ref. 2). This largely differs from BCCs which are more frequent in the general population--at a ratio of 4:1 as compared with SCCs--but the number is only increased by a factor of 10 in transplant recipients. This may suggest that 'dormant' SCC precursor cells/lesions are present at a high frequency in the population but they are well controlled by the immune system. BCC, on the other hand, may be less dependent on immune surveillance thereby underlining its different etiology. While for BCC development the genetic hallmark is abrogation of the ptch-sonic hedgehog pathway, little is known about the causal alterations of SCCs. However, the complexity of the genetic alterations (numerical and structural aberration profiles) in SCCs argues for several levels of genomic instability involved in the generation and progression of skin cancer.

Brash, D. E., A. Ziegler, et al. (1996). "Sunlight and sunburn in human skin cancer: p53, apoptosis, and tumor promotion." J Investig Dermatol Symp Proc **1**(2): 136-42.

Sunlight is a carcinogen to which everyone is exposed. Epidemiology indicates that most carcinogenic sunlight exposure takes place several decades before the tumor arises. Some of the early events have been identified by searching for genes

having ultraviolet (UV)-specific mutations. Over 90% of squamous cell carcinomas and more than 50% of basal cell carcinomas from New England patients contain UV-like mutations in the p53 tumor suppressor gene. From the mutation pattern, it can be concluded that the carcinogenic DNA lesions were pyrimidine-cytosine photoproducts caused by the UVB portion of sunlight. Particular codons of the p53 gene are most susceptible, apparently because of slower DNA repair at specific sites. Sunlight is sufficiently mutagenic often to mutate both p53 alleles. These mutations are also found in the precancer for squamous cell carcinoma, actinic keratosis, implying an early role. The function of p53 in normal skin is indicated by the observation that inactivating p53 in mouse skin reduces the appearance of sunburn cells, apoptotic keratinocytes generated by UV overexposure. Skin thus appears to possess a p53-dependent "cellular proofreading" response to DNA damage in which precancerous cells self-destruct. If this response is reduced in a single cell by a prior p53 mutation, sunburn can thereafter select for clonal expansion of the p53-mutated cell into an actinic keratosis. Sunlight appears to act twice: as tumor initiator and as tumor promoter.

Brewster, A. M., A. J. Alberg, et al. (2004). "XPD polymorphism and risk of subsequent cancer in individuals with nonmelanoma skin cancer." Cancer Epidemiol Biomarkers Prev **13**(8): 1271-5.

BACKGROUND: Individuals with nonmelanoma skin cancer (NMSC) are at increased risk of developing subsequent cancers. Genetic predisposition to reduced DNA repair capacity may be an underlying susceptibility factor explaining the excess risk of malignancies. To test this hypothesis, a cohort study was conducted to examine the association between XPD Lys751Gln polymorphism and risk of a second primary cancer in individuals with NMSC. METHODS: A subgroup of 481 individuals with a history of NMSC who participated in the CLUE II community-based cohort was followed for the development of a second primary cancer. Blood specimens donated in 1989 were genotyped for the XPD Lys751Gln polymorphism using the 5' nuclease assay. Cox proportional regression with delayed entry was used to calculate the incidence rate ratio (IRR) and 95% confidence interval (95% CI) for risk of developing a second primary cancer according to XPD genotype. All statistical tests were two sided. RESULTS: Eighty individuals developed a second primary cancer. The most frequent occurring cancers were of the prostate (18%), lung (15%), and breast (15%). Persons with at least one Gln allele had an increased risk of a second primary cancer compared with the reference Lys/Lys genotype (adjusted IRR 2.22, 95% CI 1.30-3.76). When the reference category was limited to never smokers with the Lys/Lys genotype, the risk of developing a second primary cancer associated with having at least one Gln allele was increased >3-fold in both never smokers (IRR 3.93, 95% CI 1.36-11.36) and ever smokers (IRR 6.14, 95% CI 2.17-17.37). CONCLUSION: These findings suggest that individuals with NMSC who have the variant XPD Gln allele are at increased risk of developing a second primary cancer.

Buckman, S. Y., A. Gresham, et al. (1998). "COX-2 expression is induced by UVB exposure in human skin: implications for the development of skin cancer." Carcinogenesis **19**(5): 723-9.

Extensive documentation has validated the role of UV irradiation as a tumor initiator and promoter, inducing both squamous and basal cell carcinomas. Human epidermis is a tissue which undergoes active metabolism of arachidonic acid to prostaglandins which is regulated by the action of prostaglandin H synthase (also known as cyclooxygenase). One mechanism for the promotional activity of UV light may involve its ability to induce prostaglandin formation. Work in our laboratory has demonstrated that acute exposure of human keratinocytes to UVB irradiation results in increased production of prostaglandin E2 (PGE2). When cultured human keratinocytes were examined after irradiation with 30 mJ/cm2 UVB in vitro, Western blot analysis showed a 6-fold increase in COX-2 protein which was evident at 6 h and peaked 24 h after irradiation. Furthermore, when human subjects were irradiated on sun-protected skin with up to four times their minimal erythema dosage (MED) and biopsied 24 h later, upregulation of COX-2 protein expression was observed via immunofluorescence microscopy. RNAase protection assays supported this observation, showing induction of COX-2 message which peaked at approximately 12 h following irradiation in vitro. Furthermore, human squamous cell carcinoma biopsies exhibited strongly enhanced staining for COX-2 protein via immunohistochemistry and Western analysis when compared to normal non-sun-exposed control skin. Together, these data demonstrate acute upregulation of COX-2 via UVB irradiation and suggest the need for further studies of COX-2 expression as a potential pharmacological target mediating human skin tumor development.

Burns, F. J., S. Chen, et al. (2002). "The action of a dietary retinoid on gene expression and cancer induction in electron-irradiated rat skin." J Radiat Res **43 Suppl**: S229-32.

Current models of radiation carcinogenesis generally assume that the DNA is damaged in a

variety of ways by the radiation and that subsequent cell divisions contribute to the conversion of the damage to heritable mutations. Cancer may seem complex and intractable, but its complexity provides multiple opportunities for preventive interventions. Mitotic inhibitors are among the strongest cancer preventive agents, not only slowing the growth rate of preneoplasias but also increasing the fidelity of DNA repair processes. Ionizing radiation, including electrons, is a strong inducer of cancer in rat skin, and dietary retinoids have shown potent cancer preventive activity in the same system. A non-toxic dietary dose of retinyl acetate altered gene expression levels 24 hours after electron irradiation of rat skin. Of the 8740 genes on an Affymetrix rat expression array, the radiation significantly (5 fold or higher) altered 188, while the retinoid altered 231, including 16 radiation-altered genes that were reversely altered. While radiation strongly affected the expression of stress response, immune/inflammation and nucleic acid metabolism genes, the retinoid most strongly affected proliferation-related genes, including some significant reversals, such as, keratin 14, retinol binding protein, and calcium binding proteins. These results point to reversal of proliferation-relevant genes as a likely basis for the anti-radiogenic effects of dietary retinyl acetate.

Burnworth, B., S. Popp, et al. (2006). "Gain of 11q/cyclin D1 overexpression is an essential early step in skin cancer development and causes abnormal tissue organization and differentiation." Oncogene **25**(32): 4399-412.

Non-melanoma skin cancers, in particular keratoacanthomas (KAs) and squamous cell carcinomas (SCCs), have become highly frequent tumor types especially in immune-suppressed transplant patients. Nevertheless, little is known about essential genetic changes. As a paradigm of 'early' changes, that is, changes still compatible with tumor regression, we studied KAs by comparative genomic hybridization and show that gain of chromosome 11q is not only one of the most frequent aberration (8/18), but in four tumors also the only aberration. Furthermore, 11q gain correlated with amplification of the cyclin D1 locus (10/14), as determined by fluorescence in situ hybridization, and overexpression of cyclin D1 protein (25/31), as detected by immunohistochemistry. For unraveling the functional consequence, we overexpressed cyclin D1 in HaCaT skin keratinocytes. These cells only gained little growth advantage in conventional and in organotypic co-cultures. However, although the control vector-transfected cells formed a well-stratified and orderly differentiated epidermis-like epithelium, they showed deregulation of tissue architecture with an altered localization of proliferation and impaired differentiation. The most severe phenotype was seen in a clone that additionally upregulated cdk4 and p21. These cells lacked terminal differentiation, exhibited a more autonomous growth in vitro and in vivo and even formed tumors in two injection sites with a growth pattern resembling that of human KAs. Thus, our results identify 11q13 gain/cyclin D1 overexpression as an important step in KA formation and point to a function that exceeds its known role in proliferation by disrupting tissue organization and thereby allowing abnormal growth.

Campbell, C., A. G. Quinn, et al. (1993). "The relation between p53 mutation and p53 immunostaining in non-melanoma skin cancer." Br J Dermatol **129**(3): 235-41.

Extensive study of the p53 gene has established its role as a tumour-suppressor gene, and the involvement of mutant p53 in a wide spectrum of human malignancy. Many mutations of p53 result in a protein product that is abnormally stable, so that it becomes readily detectable by immunocytochemistry. In contrast, under normal conditions, it has been considered that levels of wild-type p53 were too low to be detectable. Although positive immunocytochemistry has been used as a marker of mutation, recent evidence suggests that this assumption may not always be valid. We have carried out both PCR-sequencing of exons 5-8 of the p53 gene in 20 basal cell carcinomas (BCC), and immunocytochemistry of these tumours with the anti-p53 antibody DO7. Twenty cases of Bowen's disease, in which we had previously documented mutations, were also immunostained. We report a low rate of p53 mutation in the BCCs we examined (2/20), and a discrepancy between tumours with positive immunostaining and those with mutation in both Bowen's disease and BCC. Of eight tumours in which we detected mutation, only four were immunopositive: of 19 immunopositive samples, only four showed detectable mutation. We discuss the implications of our results for the use of positive immunostaining in clinical diagnosis, and the involvement of p53 in skin carcinogenesis.

Campbell, C., A. G. Quinn, et al. (1993). "Codon 12 Harvey-ras mutations are rare events in non-melanoma human skin cancer." Br J Dermatol **128**(2): 111-4.

ras mutations have been reported as an early event in some human malignancies and in the mouse skin model of multistep carcinogenesis; early studies in human non-melanoma skin cancers have reported variable rates of ras mutations. A recent study, however, has reported a high frequency of activating

mutations of the Harvey-ras proto-oncogene in non-melanoma skin cancers, and the site specificity of the mutation at the second position of codon 12 prompted us to re-examine the importance of Ha-ras codon 12 mutations as an early event in the development of these tumours, using a combination of PCR and restriction fragment polymorphism of codon 12 of the Ha-ras gene. Dilution experiments confirmed that the method was sensitive and capable of detecting mutations at this codon when only 4% of the total alleles are mutated. We were surprised to find no mutations in the 40 basal cell carcinomas, 12 squamous cell carcinomas and 12 cases of Bowen's disease studied. We conclude that Ha-ras codon 12 mutations are rare events in human non-melanoma skin cancer in the U.K. The marked differences in the frequency of codon 12 Ha-ras mutations in published studies may relate to either technical artefacts, or differences in the molecular epidemiology between areas of low and high sun exposure.

Canamasas, I., A. Debes, et al. (2003). "Understanding human cancer using Drosophila: Tid47, a cytosolic product of the DnaJ-like tumor suppressor gene l2Tid, is a novel molecular partner of patched related to skin cancer." J Biol Chem **278**(33): 30952-60.

Recessive mutations of the Drosophila gene lethal(2)-tumorous imaginal discs (l(2)tid) cause neoplastic growth of the anlagen of the adult organs, the imaginal discs. Here we report that the three proteins encoded by this evolutionarily conserved gene, Tid50, Tid47, and Tid40, identified as members of the DnaJ cochaperone family, are destined for different cellular compartments, build complexes with many proteins in a developmental stage-specific manner, and are likely to be involved in different cellular processes. We show that the cytosolic Tid47 molecule is a novel component of the Hedgehog (Hh)-Patched (Ptc) signaling regulating cell/tissue polarity and spatial patterning during development and is associated with human tumors such as basal cell carcinoma (BCC) and medulloblastoma. We provide functional evidence for its direct in vivo interaction with the Hh-bound Ptc receptor during signal transmission. Because loss of l(2)tid causes neoplastic transformation of Hh-responsive cells, we suggest that Tid47 may at least act as a guardian of the Hh signaling gradient by regulating Ptc homeostasis in the tissue. Finally, we show that the expression of htid-1, the human counterpart of l(2)tid, is altered in human BCCs. We demonstrate that in BCCs loss of htid expression correlates with loss of differentiation capacity of the neoplastic cells similar to that found in the Drosophila tumor model.

Capell, B. C., B. E. Tlougan, et al. (2009). "From the rarest to the most common: insights from progeroid syndromes into skin cancer and aging." J Invest Dermatol **129**(10): 2340-50.

Despite their rarity, diseases of premature aging, or "progeroid" syndromes, have provided important insights into basic mechanisms that may underlie cancer and normal aging. In this review, we highlight these recent developments in Hutchinson-Gilford progeria syndrome (HGPS), Werner syndrome, Bloom syndrome, Cockayne syndrome, trichothiodystrophy, ataxia-telangiectasia, Rothmund-Thomson syndrome, and xeroderma pigmentosum. Though they are caused by different mutations in various genes and often result in quite disparate phenotypes, deciphering the molecular bases of these conditions has served to highlight their underlying basic similarities. Studies of progeroid syndromes, particularly HGPS, the most dramatic form of premature aging, have contributed to our knowledge of fundamental processes of importance to skin biology, including DNA transcription, replication, and repair, genome instability, cellular senescence, and stem-cell differentiation.

Carless, M. A. and L. R. Griffiths (2008). "Cytogenetics of melanoma and nonmelanoma skin cancer." Adv Exp Med Biol **624**: 227-40.

Cytogenetic analysis of melanoma and nonmelanoma skin cancers has revealed recurrent aberrations, the frequency of which is reflective of malignant potential. Highly aberrant karyotypes are seen in melanoma, squamous cell carcinoma, solar keratosis and Merkel cell carcinoma with more stable karyotypes seen in basal cell carcinoma, keratoacanthoma, Bowen's disease, dermatofibrosarcoma protuberans and cutaneous lymphomas. Some aberrations were common amongst a number of skin cancer types including rearrangements and numerical abnormalities of chromosome 1, -3p, +3q, partial or entire trisomy 6, trisomy 7, +8q, -9p, +9q, partial or entire loss of chromosome 10, -17p, +17q and partial or entire gain of chromosome 20. Combination of cytogenetic analysis with other molecular genetic techniques has enabled the identification of not only aberrant chromosomal regions, but also the genes that contribute to a malignant phenotype. This review provides a comprehensive summary of the pertinent cytogenetic aberrations associated with a variety of melanoma and nonmelanoma skin cancers.

Caulin, C., T. Nguyen, et al. (2007). "An inducible mouse model for skin cancer reveals distinct roles for gain- and loss-of-function p53 mutations." J Clin Invest **117**(7): 1893-901.

Mutations in ras and p53 are the most prevalent mutations found in human nonmelanoma skin cancers. Although some p53 mutations cause a loss of function, most result in expression of altered forms of p53, which may exhibit gain-of-function properties. Therefore, understanding the consequences of acquiring p53 gain-of-function versus loss-of-function mutations is critical for the generation of effective therapies for tumors harboring p53 mutations. Here we describe an inducible mouse model in which skin tumor formation is initiated by activation of an endogenous K-ras(G12D) allele. Using this model we compared the consequences of activating the p53 gain-of-function mutation p53(R172H) and of deleting the p53 gene. Activation of the p53(R172H) allele resulted in increased skin tumor formation, accelerated tumor progression, and induction of metastasis compared with deletion of p53. Consistent with these observations, the p53(R172H) tumors exhibited aneuploidy associated with centrosome amplification, which may underlie the mechanism by which p53(R172H) exerts its oncogenic properties. These results clearly demonstrate that p53 gain-of-function mutations confer poorer prognosis than loss of p53 during skin carcinogenesis and have important implications for the future design of therapies for tumors that exhibit p53 gain-of-function mutations.

Cesinaro, A. M., A. Ubiali, et al. (2007). "Mismatch repair proteins expression and microsatellite instability in skin lesions with sebaceous differentiation: a study in different clinical subgroups with and without extracutaneous cancer." Am J Dermatopathol **29**(4): 351-8.

Muir-Torre syndrome (MTS) is defined as the association of a sebaceous tumor or keratoacanthoma and an extracutaneous neoplasm, mainly from the gastrointestinal or genitourinary tracts. MTS is related to hereditary non-polyposis colorectal cancer (HNPCC), a syndrome with germline mutations in the mismatch repair (MMR) gene(s), leading to microsatellite instability (MSI). In this study, using immunohistochemistry and a microsatellite instability assay, we analyzed the incidence of MMR gene abnormalities in 79 sebaceous lesions from 70 patients, 26 of whom also had an extracutaneous visceral neoplasm. We were unable to investigate the family histories of our patients regarding other tumors in order to assess which of our cases met the Amsterdam criteria. Defective MMR protein expression (MMR-) was found in 18/70 (25.7%) patients, with an identical distribution between those having an isolated skin tumor (11/44, 25.0%) and those with an extracutaneous cancer (7/26, 25.4%). In the sporadic group, MMR negative lesions were significantly more frequent in extrafacial areas (P = 0.03). High concordance was found between MMR expression in sebaceous lesions and the extracutaneous neoplasm in the same patient (20/23, 86.9%), as well as between MMR expression and microsatellite status (18/20, 90%). In conclusion, this study confirms the value of immunohistochemistry to identify MMR defective tumors. However, since only a minority of sebaceous neoplasms in patients who also have an extracutaneous cancer display MMR defects, these techniques are of limited value for the identification of "clinically defined" MTS.

Chandramouli, A., J. Shi, et al. (2007). "Haploinsufficiency of the cdc2l gene contributes to skin cancer development in mice." Carcinogenesis **28**(9): 2028-35.

The Cdc2L gene encodes for the cyclin-dependent kinase 11 (CDK11) protein. Loss of one allele of Cdc2L and reduced CDK11 expression has been observed in several cancers, implicating its association with carcinogenesis. To directly investigate the role of CDK11 in carcinogenesis, we first generated cdc2l haploinsufficient mice by gene trap technology and then studied the susceptibility of these gene-trapped (cdc2l(GT)) mice to chemical-mediated skin carcinogenesis in the 7,12-dimethylbenz[a]anthracene (DMBA)/12-O-tetradecanoylphorbol-13-acetate (TPA)-induced two-stage skin carcinogenesis model. Wild-type and cdc2l(GT) mice were subjected to a single topical application of initiation by DMBA and promotion twice a week for 19 weeks with TPA. At 19 weeks, 70% of the cdc2l(GT) mice and 60% of the cdc2l+/+ mice developed benign papillomas. However, there was an overall 3-fold increase in the average number of tumors per mouse observed in cdc2l(GT) mice as compared with cdc2l+/+ mice. There was also an increased frequency of larger papillomas in cdc2l(GT) mice. By using the polymerase chain reaction-restriction fragment length polymorphism assay, we found A to T transversion mutations at the 61st codon of H-ras gene in the papilloma tissue of both cdc2l(GT) mice and cdc2l+/+ mice. Ki-67 staining revealed increased proliferation in the papillomas of cdc2l(GT) (77.75%) as compared with cdc2l+/+ (30.84%) tumors. These studies are the first to show that loss of one allele of cdc2l gene, encoding CDK11, facilitates DMBA/TPA-induced skin carcinogenesis in vivo.

Cheepala, S. B., W. Yin, et al. (2009). "Identification of the B-Raf/Mek/Erk MAP kinase pathway as a target for all-trans retinoic acid during skin cancer promotion." Mol Cancer **8**: 27.

BACKGROUND: Retinoids have been studied extensively for their potential as therapeutic and chemopreventive agents for a variety of cancers, including nonmelanoma skin cancer (NMSC). Despite their use for many years, the mechanism of action of retinoids in the prevention of NMSC is still unclear. In this study we have attempted to understand the chemopreventive mechanism of all-trans retinoic acid (ATRA), a primary biologically active retinoid, in order to more efficiently utilize retinoids in the clinic. RESULTS: We have used the 2-stage dimethylbenzanthracene (DMBA)/12-O-tetradecanoylphorbol-13-acetate (TPA) mouse skin carcinogenesis model to investigate the chemopreventive effects of ATRA. We have compared the gene expression profiles of control skin to skin subjected to the 2-stage protocol, with or without ATRA, using Affymetrix 430 2.0 DNA microarrays. Approximately 49% of the genes showing altered expression with TPA treatment are conversely affected when ATRA is co-administered. The activity of these genes, which we refer to as 'counter-regulated', may contribute to chemoprevention by ATRA. The counter-regulated genes have been clustered into functional categories and bioinformatic analysis has identified the B-Raf/Mek/Erk branch of the MAP kinase pathway as one containing several genes whose upregulation by TPA is blocked by ATRA. We also show that ATRA blocks signaling through this pathway, as revealed by immunohistochemistry and Western blotting. Finally, we found that blocking the B-Raf/Mek/Erk pathway with a pharmacological inhibitor, Sorafenib (BAY43-9006), induces squamous differentiation of existing skin SCCs formed in the 2-stage model. CONCLUSION: These results indicate that ATRA targets the B-Raf/Mek/Erk signaling pathway in the 2-stage mouse skin carcinogenesis model and this activity coincides with its chemopreventive action. This demonstrates the potential for targeting the B-Raf/Mek/Erk pathway for chemoprevention and therapy of skin SCC in humans. In addition our DNA microarray results provide the first expression signature for the chemopreventive effect of ATRA in a mouse skin cancer model. This is a potential source for novel targets for ATRA and other chemopreventive and therapeutic agents that can eventually be tested in the clinic.

Chen, J., X. Cheng, et al. (2006). "An unexpected role for keratin 10 end domains in susceptibility to skin cancer." J Cell Sci **119**(Pt 24): 5067-76.

Keratin 10 (K10) is a type I keratin that is expressed in post-mitotic suprabasal keratinocytes of the skin. Based on cell culture experiments and transgenic mouse studies, it has been proposed that K10 suppresses cell proliferation and tumor formation in the skin. Furthermore, the ability of K10 to suppress cell proliferation was mapped to its unique N- and C-terminal protein domains. In the present study, we modified the endogenous keratin 14 (K14) gene of mice using a knock-in approach to encode a chimeric keratin that consists of the K14 rod domain fused to the K10 head and tail domains (K1014chim). This transgene was expressed in the basal layer of the epidermis and the outer root sheath of hair follicles. Unexpectedly, we found that the K10 end domains had no effect on basal keratinocyte proliferation in vivo. Moreover, when subjected to a chemical skin carcinogenesis protocol, papilloma formation in mutant mice was accelerated instead of being inhibited. Our data suggest that the increased tumor susceptibility of K1014chim mice is in part due to a suppression of apoptosis in mutant keratinocytes. Our results support the notion that intermediate filaments, in addition to their function as cytoskeletal components, affect tumor susceptibility of epithelial cells.

Chen, Y. C., L. Xu, et al. (2003). "Genetic polymorphism in p53 codon 72 and skin cancer in southwestern Taiwan." J Environ Sci Health A Tox Hazard Subst Environ Eng **38**(1): 201-11.

The Pro/Pro polymorphism of p53 codon 72 has been reported to be related to bladder and lung cancer, but its relationship with skin cancer is unclear. We assessed the hypothesis that there is a relationship between the p53 codon 72, Pro/Pro polymorphism, cumulative arsenic exposure, and the risk of skin cancer in a hospital-based case-control study in southwestern Taiwan. From 1996 to 1999, 93 newly-diagnosed skin cancer patients at the National Cheng-Kung University (NCKU) Hospital and 71 community controls matched on residence were recruited in southwestern Taiwan. The genotype of p53 codon 72 (Arg/Arg, Arg/Pro, or Pro/Pro) was determined for all subjects by polymerase chain reaction-restricted fragment length polymorphism (PCR-RFLP). A questionnaire was administered to each subject for collection of demographic information, personal habits, disease history, diet information, and other relevant questions. The Pro/Pro (homozygous) genotype was more frequent in skin cancer patients (cases, 20%; controls, 12%; P = 0.37). Subjects with the susceptible genotype Pro/Pro and heterozygous (intermediate) genotype Pro/Arg had 2.18 and 0.99 times risk of skin cancer than the wild type Arg/Arg (95% confidence interval, 0.74-4.38; 95% confidence interval, 0.44-2.21), respectively. Compared with subjects with 18.5 < BMI < 23, subjects with BMI > 18.5 had 5.78 times risk of skin cancer (95% confidence interval, 1.06 to 31.36) after adjusting for

other risk factors. There was no interaction between BMI and genotype, but the sample size was small. The risk of skin cancer did not significantly vary by tumor cell-type. The risk of skin cancer is increased in individuals with the Pro/Pro genotype. Larger, confirmatory studies are needed to clarify the role of constitutional polymorphisms in p53 and skin cancer risk.

Cheo, D. L., L. B. Meira, et al. (2000). "Ultraviolet B radiation-induced skin cancer in mice defective in the Xpc, Trp53, and Apex (HAP1) genes: genotype-specific effects on cancer predisposition and pathology of tumors." Cancer Res **60**(6): 1580-4.

Mutations in nucleotide excision repair (NER) genes in humans result in the UV-induced skin cancer-prone disease xeroderma pigmentosum (XP). Mouse models that mimic XP have provided an informative experimental system with which to study DNA repair, as well as the molecular pathology of UV radiation-induced skin cancer. We reported previously that mice defective in the Xpc gene (Xpc-/-) are highly predisposed to UVB radiation-induced skin cancer and that the appearance of skin cancer is more rapid in Xpc Trp53 double mutants. Extended studies now demonstrate an increased predisposition to UVB radiation-induced skin cancers in Xpc heterozygous mice compared with normal mice. We also show that Xpc Trp53 double heterozygous mutants are more predisposed to skin cancer than Trp53 single heterozygous mice. No mutations were detected in the cDNA of the remaining Xpc allele, suggesting that haploinsufficiency of the Xpc gene may be operating and is a risk factor for UVB radiation-induced skin cancer in mice. Skin tumors from Xpc-/- mice were exclusively well or moderately well-differentiated squamous cell carcinomas. In Xpc+/+ and Xpc+/- mice, many of the squamous cell carcinomas were less well differentiated. We also documented previously increased predisposition to UV radiation-induced skin cancers in Xpc-/- Apex+/- mice. Here we show the absence of mutations in the cDNA of the remaining Apex allele, a further suggestive indication of haploinsufficiency and its resulting predisposition to skin cancer. The Trp53 and Apex heterozygous conditions altered the skin tumor spectrum to more poorly differentiated forms in all Xpc genotypes.

Cheo, D. L., L. B. Meira, et al. (1996). "Synergistic interactions between XPC and p53 mutations in double-mutant mice: neural tube abnormalities and accelerated UV radiation-induced skin cancer." Curr Biol **6**(12): 1691-4.

The significance of DNA repair to human health has been well documented by studies on xeroderma pigmentosum (XP) patients, who suffer a dramatically increased risk of cancer in sun-exposed areas of their skin [1,2]. This autosomal recessive disorder has been directly associated with a defect in nucleotide excision-repair (NER) [1,2]. Like human XP individuals, mice carrying homozygous mutations in XP genes manifest a predisposition to skin carcinogenesis following exposure to ultraviolet (UV) radiation [3-5]. Recent studies have suggested that, in addition to roles in apoptosis [6] and cell-cycle checkpoint control [7] in response to DNA damage, p53 protein may modulate NER [8]. Mutations in the p53 gene have been observed in 50% of all human tumors [9] and have been implicated in both the early [10] and late [11] stages of skin cancer. To examine the consequences of a combined deficiency of the XPC and the p53 proteins in mice, we generated double-mutant animals. We document a spectrum of neural tube defects in XPC p53 mutant embryos. Additionally, we show that, following exposure to UV-B radiation, XPC p53 mutant mice have more severe solar keratosis and suffer accelerated skin cancer compared with XPC mutant mice that are wild-type with respect to p53.

Conti, C. J. (2002). "Vascular endothelial growth factor: regulation in the mouse skin carcinogenesis model and use in antiangiogenesis cancer therapy." Oncologist **7 Suppl 3**: 4-11.

Of the various mechanisms responsible for tumor neovascularization, the angiogenesis process, in particular vascular endothelial growth factor (VEGF), is described here as a target for cancer therapy. While hypoxia is a trigger of tumor angiogenesis, various alterations in oncogenes and tumor suppressor genes also have been reported to induce VEGF expression in tumors. The regulation of VEGF has been investigated in chemically induced mouse squamous cell carcinoma of the skin. In this cancer model, VEGF expression appears to be dependent on ras oncogene activation as well as the epidermal growth factor receptor. Thus, in addition to VEGF, oncogene signaling pathways may be relevant targets in antiangiogenesis cancer therapies. The central role of VEGF in angiogenesis has led to the development of several drugs targeting the pathway of this growth factor. The present paper provides an overview of these drugs and their stage of development. In the near future, clinical trials using anti-VEGF drugs and other antiangiogenic agents, such as endostatin and angiostatin, will yield valuable information about their potential for cancer therapy.

Danaee, H., H. H. Nelson, et al. (2002). "Microsatellite instability at tetranucleotide repeats in skin and bladder cancer." Oncogene **21**(32): 4894-9.

Recently, a novel form of MSI has been described that occurs only at tetranucleotide repeat markers. This has been termed elevated microsatellite instability at selected tetranucleotide repeats (EMAST). EMAST has been related to alterations of the p53 gene, and to the nature of the repeat sequence. We initially tested whether loss of heterozygosity (LOH) at the p53 and the patched (ptch) genes was related to EMAST in a series of 61 non-melanoma skin cancer (NMSC) tumors. We then analysed a series of 57 primary bladder cancers for the presence of EMAST, testing whether this was related to mutation or expression of the p53 gene. In both NMSC and bladder tumors we found a high prevalence of EMAST (75.4 and 43.9%). In NMSC the prevalence of EMAST was higher in tumors that had either p53 or ptch LOH, although the difference was not statistically significant. There was a significant association of extensive EMAST (three or more loci) with mutations in p53 among the bladder cancer tumors, but no indication of elevated EMAST in tumors with abnormal p53 staining without mutation. The association of EMAST with p53 mutation was confined to non-invasive disease. Hence, EMAST likely reflects a particular pattern of somatic events that are interactive with p53 mutation, particularly common in skin cancer and limited to non-invasive disease in bladder cancer.

Darwiche, N., A. Ryscavage, et al. (2007). "Expression profile of skin papillomas with high cancer risk displays a unique genetic signature that clusters with squamous cell carcinomas and predicts risk for malignant conversion." Oncogene **26**(48): 6885-95.

Chemical induction of squamous tumors in the mouse skin induces multiple benign papillomas: high-frequency terminally benign low-risk papillomas and low-frequency high-risk papillomas, the putative precursor lesions to squamous cell carcinoma (SCC). We have compared the gene expression profile of twenty different early low- and high-risk papillomas with normal skin and SCC. Unsupervised clustering of 514 differentially expressed genes ($P<0.001$) showed that 9/10 high-risk papillomas clustered with SCC, while 1/10 clustered with low-risk papillomas, and this correlated with keratin markers of tumor progression. Prediction analysis for microarrays (PAM) identified 87 genes that distinguished the two papilloma classes, and a majority of these had a similar expression pattern in both high-risk papillomas and SCC. Additional classifier algorithms generated a gene list that correctly classified unknown benign tumors as low- or high-risk concordant with promotion protocol and keratin profiling. Reduced expression of immune function genes characterized the high-risk papillomas and SCC. Immunohistochemistry confirmed reduced T-cell number in high-risk papillomas, suggesting that reduced adaptive immunity defines papillomas that progress to SCC. These results demonstrate that murine premalignant lesions can be segregated into subgroups by gene expression patterns that correlate with risk for malignant conversion, and suggest a paradigm for generating diagnostic biomarkers for human premalignant lesions with unknown individual risk for malignant conversion.

Daya-Grosjean, L. (2008). "Xeroderma pigmentosum and skin cancer." Adv Exp Med Biol **637**: 19-27.

The hypersensitivity of DNA repair deficient xeroderma pigmentosum (XP) patients to solar irradiation results in the development of high levels of squamous and basal cell carcinomas as well as malignant melanomas in early childhood. Indeed, XP presents a unique model for analysing the effects of unrepaired DNA lesions in skin carcinogenesis. The skin cancer predisposition, observed in XP patients, is due to the mutator gene activity of XP cells which lead to high levels of UV specific modifications of crucial regulatory genes in skin cells leading to Cancer. Thus, the high levels of UV specific mutations, seen in oncogenes and tumor suppressor genes, which have been characterized in XP tumors, clearly demonstrate the major role of the UV component of sunlight in skin cancer development. The UV specific C to T and the tandem CC to TT UV signature transition mutations found in XP tumors are located at bipyrimidine sequences, the preferred UV targets in DNA. The same UV specific alterations are seen in key regulatory genes in sporadic skin cancers but at lower frequencies than those found in XP tumors.

Dazard, J. E., H. Gal, et al. (2003). "Genome-wide comparison of human keratinocyte and squamous cell carcinoma responses to UVB irradiation: implications for skin and epithelial cancer." Oncogene **22**(19): 2993-3006.

To gain insight into the transformation of epidermal cells into squamous carcinoma cells (SCC), we compared the response to ultraviolet B radiation (UVB) of normal human epidermal keratinocytes (NHEK) versus their transformed counterpart, SCC, using biological and molecular profiling. DNA microarray analyses (Affymetrix), approximately 12000 genes) indicated that the major group of upregulated genes in keratinocytes fall into three categories: (i). antiapoptotic and cell survival factors, including chemokines of the CXC/CC subfamilies (e.g. IL-8, GRO-1, -2, -3, SCYA20), growth factors (e.g. HB-EGF, CTGF, INSL-4), and proinflammatory

mediators (e.g. COX-2, S100A9), (ii). DNA repair-related genes (e.g. GADD45, ERCC, BTG-1, Histones), and (iii). ECM proteases (MMP-1, -10). The major downregulated genes are DeltaNp63 and PUMILIO, two potential markers for the maintenance of keratinocyte stem cells. NHEK were found to be more resistant than SCC to UVB-induced apoptosis and this resistance was mainly because of the protection from cell death by secreted survival factors, since it can be transferred from NHEK to SCC cultures by the conditioned medium. Whereas the response of keratinocytes to UVB involved regulation of key checkpoint genes (p53, MDM2, p21(Cip1), DeltaNp63), as well as antiapoptotic and DNA repair-related genes - no or little regulation of these genes was observed in SCC. The effect of UVB on NHEK and SCC resulted in upregulation of 251 and 127 genes, respectively, and downregulation of 322 genes in NHEK and 117 genes in SCC. To further analyse these changes, we used a novel unsupervised coupled two-way clustering method that allowed the identification of groups of genes that clearly partitioned keratinocytes from SCC, including a group of genes whose constitutive expression levels were similar before UVB. This allowed the identification of discriminating genes not otherwise revealed by simple static comparison in the absence of UVB irradiation. The implication of the changes in gene profile in keratinocytes for epithelial cancer is discussed.

de Gruijl, F. R. (1999). "Skin cancer and solar UV radiation." Eur J Cancer **35**(14): 2003-9.

Ultraviolet (UV) radiation in sunlight is the most prominent and ubiquitous physical carcinogen in our natural environment. It is highly genotoxic but does not penetrate the body any deeper than the skin. Like all organisms regularly exposed to sunlight, the human skin is extremely well adapted to continuous UV stress. Well-pigmented skin is clearly better protected than white Caucasian skin. The sun-seeking habits of white Caucasians in developed countries are likely to have contributed strongly to the increase in skin cancer observed over the last century. Skin cancer is by far the most common type of cancer in the U.S.A. and Australia, which appears to be the result of an 'unnatural displacement' of people with sun-sensitive skin to sub-tropical regions. Although campaigns have been successful in informing people about the risks of sun exposure, general attitudes and behaviour do not yet appear to have changed to the extent that trends in skin cancer morbidity and the corresponding burden on public healthcare will be reversed. The relationship between skin cancer and regular sun exposure was suspected by physicians in the late 19th century, and subsequently substantiated in animal experiments in the early part of the 20th century. UV radiation was found to be highly genotoxic, and DNA repair proved to be crucial in fending off detrimental effects such as mutagenesis and cell death. In fact, around 1940 it was shown that the wavelength dependence of mutagenicity paralleled the UV absorption by DNA. In the 1970s research on UV carcinogenesis received a new impetus from the arising concern about a possible future depletion of the stratospheric ozone layer: the resulting increases in ambient UV loads were expected to raise skin cancer incidences. Epidemiological studies in the last decades of the 20th century have greatly refined our knowledge on the aetiology of skin cancers. Analyses of gene mutations in skin carcinomas have identified UV radiation as the cause. The relationship between the most fatal skin cancer, i.e. malignant melanoma and solar UV exposure is, however, still unclear and needs to be clarified to optimise preventive measures and minimise mortality from skin cancers.

de Gruijl, F. R. (2002). "p53 mutations as a marker of skin cancer risk: comparison of UVA and UVB effects." Exp Dermatol **11 Suppl 1**: 37-9.

The epidermis is excellently adapted to the sun's ultraviolet (UV) radiation. The p53 protein plays a crucial role in the orchestration of a cell's response to UV-induced damage, and more specifically to DNA damage. This response appears to differ between differentiated (suprabasal) and undifferentiated (basal) epidermal cells. The latter are the most likely targets in UV carcinogenesis. The UVB-related mutations in p53 genes of human carcinomas from sun-exposed skin indicate that rendering p53 dysfunctional is an important (early) step in the formation of these tumors. Experiments in hairless mice confirm this finding for UVB-driven carcinogenesis, but not for UVA1-(365-nm)-driven carcinogenesis. Microscopic clusters of preneoplastic cells overexpressing mutant p53 occur in chronically UVB-exposed murine skin long before the ultimate carcinomas. The number of these clusters at a certain time-point appears to be predictive of the tumor risk at latter time-points. These UVB-induced p53 clusters appear to be suitable surrogates of tumors in short-term experiments.

de Gruijl, F. R., H. J. van Kranen, et al. (2001). "UV-induced DNA damage, repair, mutations and oncogenic pathways in skin cancer." J Photochem Photobiol B **63**(1-3): 19-27.

Repair of UV induced DNA damage is of key importance to UV-induced skin carcinogenesis. Specific signal transduction pathways that regulate cell cycling, differentiation and apoptosis are found to be corrupted in skin cancers, e.g., the epidermal growth-stimulating Hedgehog pathway in basal cell carcinomas (BCCs). Mutations in genes coding for

proteins in these pathways lead to persistent disturbances that are passed along to daughter cells, e.g., mutations in the gene for the Patched (PTCH) protein in the Hedgehog pathway. Thus far only the point mutations in the P53 gene from squamous cell carcinomas and BCCs, and in PTCH gene from BCC of xeroderma pigmentosum (XP) patients appear to be unambiguously attributable to solar UV radiation. Solar UVB radiation is most effective in causing these point mutations. Other forms of UV-induced genetic changes (e.g., deletions) may, however, contribute to skin carcinogenesis with different wavelength dependencies.

de Oliveira, W. R., P. L. Rady, et al. (2004). "Association of p53 arginine polymorphism with skin cancer." Int J Dermatol **43**(7): 489-93.

BACKGROUND: The presence of arginine at codon 72 in p53 protein is proposed to be a genetic risk factor in human papillomavirus (HPV)-related carcinogenesis. OBJECTIVE: To study the prevalence of p53 polymorphism at codon 72 in skin biopsies of epidermodysplasia verruciformis (EV) patients compared to DNA samples from healthy individuals. PATIENTS AND METHODS: DNA samples extracted from normal skin and tumor biopsies of 22 Brazilian patients with EV and blood samples from 27 healthy Brazilian individuals were studied for p53 codon 72 polymorphisms using restriction fragment length polymorphism (RFLP) analysis. RESULTS: All EV patients with the malignant form of EV were homozygous for arginine (Arg/Arg) at codon 72 of the p53 gene, in contrast to none with the benign form ($P < 0.0001$). CONCLUSIONS: p53 arginine polymorphism is likely to be associated with the development of skin malignancies in EV patients from Brazil.

de Villiers, E. M., A. Ruhland, et al. (1999). "Human papillomaviruses in non-melanoma skin cancer." Semin Cancer Biol **9**(6): 413-22.

Recent data suggest that additional factors, other than UV radiation, are involved in the etiology of non-melanoma skin cancer. These include alterations in the tumor suppressor genes, p53, p16$L*I*U$LINK4a$L*I$L/CDKN2A, p21$L*I*U$LWAF1/CIP1$L*I$L and the PTCH gene, as well as cytokines. Papillomavirus infections have been implicated in the etiology of non-melanoma skin cancer. The interaction of tumor suppressor genes and cytokines with the oncoproteins of high-risk mucosal HPV types have been studied in detail, but very little is known about the cutaneous HPV types. We have studied the effect of UV radiation on the URRs of HPV 1, 2, 3, 5, 7, 20, 23, 27, 38, 41, and 77. Neither the CAT-expression and promoter activity of these HPV types, nor presence or absence of wild-type or mutated p53 in the cell lines used, could be related to the DNA sequence homology between the different HPV types or their biological behavior.

Delehedde, M., S. H. Cho, et al. (1999). "Altered expression of bcl-2 family member proteins in nonmelanoma skin cancer." Cancer **85**(7): 1514-22.

BACKGROUND: Differentiation, proliferation, and cell death are coordinated tightly within the epidermis. Alterations within keratinocytes that disrupt these processes are believed to contribute to the development of nonmelanoma skin cancers (NMSC). In the current study the authors examined the expression of selected members of the bcl-2 gene family in the skin and in case-matched samples of NMSC. METHODS: Immunohistochemistry was performed on tissue sections using antibodies against bcl-2, bcl-x, bax, and bak. Case-matched frozen nonneoplastic skin samples and tumor tissues were used for Western blot analysis. RESULTS: In normal epidermis, bcl-2 oncoprotein is expressed in keratinocytes of the basal layer but is down-regulated in suprabasal layers. The proapoptotic bax protein is expressed at low levels in basal keratinocytes and is up-regulated in suprabasal layers. The bcl-x and bak proteins both are expressed in the basal and spinous strata but are down-regulated in the granular cell layer. Both bcl-2 and bax were diffusely cytosolic whereas bcl-x and bak exhibited a distinct perinuclear distribution. Squamous cell carcinomas (SCC) were negative for bcl-2 whereas bcl-2 increased 5.5-fold in basal cell carcinomas (BCC). The distribution of bcl-x and bax proteins within BCC and SCC overlapped and were associated with squamous differentiation. Bax protein was increased twofold to threefold in NMSC. An increase in bak protein also was observed in SCC. However, bak was diffusely cytosolic within BCC in contrast to the perinuclear distribution in nonneoplastic keratinocytes. CONCLUSIONS: These findings suggest that altered expression of bcl-2 family members may play a role in the pathogenesis of NMSC.

D'Errico, M., A. Calcagnile, et al. (1996). "Genetic alterations in skin cancer." Ann Ist Super Sanita **32**(1): 53-63.

Cancer is a multi-stage process in which the accumulation of genetic changes allows clonal expansion of abnormal cells that will eventually form a tumor. Skin cancer is the most common malignancy affecting human beings. Mutations of the tumor suppressor gene p53 are often found in non-melanoma skin cancer and pre-invasive lesions, like actinic keratosis. The type of mutations detected in the p53 gene strongly indicate UV light as the initiating and

promoting agent in skin cancer development. Chromosome instability is also an early event in skin tumor formation. However, despite the huge amount of information available in the literature on molecular markers of skin cancers, much remains to be uncovered about the progression of genetic events that separate normal sun-exposed epidermis from skin cancer. In this paper the following issue will be addressed: how far are we from being able to define a human model for multistage skin carcinogenesis in humans?

D'Errico, M., A. Calcagnile, et al. (1999). "Factors that influence the DNA repair capacity of normal and skin cancer-affected individuals." Cancer Epidemiol Biomarkers Prev **8**(6): 553-9.

DNA repair capacity (DRC) was studied in 49 patients affected by basal cell carcinoma (BCC) and 68 cancer-free controls belonging to a larger case-control population enrolled for studying BCC risk factors. DRC was measured in the subjects' peripheral blood lymphocytes by using a host-cell reactivation assay that measures cellular activation of a reporter gene irradiated with UV light. A statistically significant age-related decline in DRC was observed in the controls from 20 to 70 years of age but not in the BCC cases. When the DRC values of the BCC patients and controls were compared by age, young BCC cases (age, < or =40 year) repaired less than the controls, although the difference was not statistically significant. Conversely, older BCC patients (age, >40 years) presented an enhanced repair capacity ($P < 0.001$) as compared with their controls. The search for possible factors associated with the high repair rate of elderly BCC cases revealed that both target cell physiology and life-style habits may affect host DNA repair. Smoking was the variable that explained most of the increase in DRC among older patients. The understanding of how these factors affect host DRC will be relevant for a correct use of this biomarker.

Descargues, P., A. K. Sil, et al. (2008). "IKKalpha, a critical regulator of epidermal differentiation and a suppressor of skin cancer." Embo J **27**(20): 2639-47.

IkappaB kinase alpha (IKKalpha), one of the two catalytic subunits of the IKK complex involved in nuclear factor kappaB (NF-kappaB) activation, also functions as a molecular switch that controls epidermal differentiation. This unexpected function requires IKKalpha nuclear translocation but does not depend on its kinase activity, and is independent of NF-kappaB signalling. Ikkalpha(-/-) mice present with a hyperproliferative and undifferentiated epidermis characterized by complete absence of a granular layer and stratum corneum. Ikkalpha-deficient keratinocytes do not express terminal differentiation markers and continue to proliferate even when subjected to differentiation-inducing stimuli. This antiproliferative function of IKKalpha is also important for the suppression of squamous cell carcinogenesis. The exact mechanisms by which nuclear IKKalpha controls keratinocyte proliferation and differentiation remained mysterious for some time. Recent studies, however, have revealed that IKKalpha is a major cofactor in a TGFbeta-Smad2/3 signalling pathway that is Smad4 independent. This pathway controls cell cycle withdrawal during keratinocyte terminal differentiation. Although these are not the only functions of nuclear IKKalpha, this multifunctional protein is a key regulator of keratinocyte and epidermal differentiation and a critical suppressor of skin cancer.

Diesel, B., M. Seifert, et al. (2004). "Towards a complete picture of splice variants of the gene for 25-hydroxyvitamin D31alpha-hydroxylase in brain and skin cancer." J Steroid Biochem Mol Biol **89-90**(1-5): 527-32.

Recently, we reported amplification of the gene encoding the P450 Cytochrome 25-hydroxyvitamin D(3)1alpha-hydroxylase (CYP27B1) in 25% of human malignant glioma. Additionally, we reported the first alternative splice variants of CYP27B1. Here, we developed and employed a highly specific approach that combined nested and touchdown PCR to clone full length CYP27B1. In addition, we identified several new splice variants in human melanoma, glioblastoma multiforme (GBM), cervix carcinoma and kidney cell lines. All of the examined cell lines showed a similar expression pattern of the CYP27B1 variants. The new splice variants that were termed Hyd-V5, -V6, -V7, and -V8 were cloned and sequenced. All but one of the new variants showed an insertion of intron 1 leading to a premature termination signal and to truncated proteins without ferredoxin and haem-binding site of the P450 protein. There was no influence of 1alpha,25(OH)(2)D(3) on the expression pattern of the splice variants in melanoma cell line SkMel28.

DiGiovanna, J. J. (2001). "Retinoid chemoprevention in patients at high risk for skin cancer." Med Pediatr Oncol **36**(5): 564-7.

Patients who develop large numbers of skin cancers suffer increased morbidity and mortality. A high skin cancer risk can result from inherited disorders such as xeroderma pigmentosum (abnormal repair of UV-induced DNA damage) or the nevoid basal cell carcinoma syndrome (tumor suppressor gene abnormality). The efficacy of systemic retinoid skin cancer chemoprevention was first demonstrated in these disorders. Since the mechanism of cancer

prevention was not thought to involve correction of the underlying defect causing the disorder, individuals at high risk for new skin cancers from other causes may also benefit from this approach. With the success of organ transplantation, there is a growing population of transplant recipients living long, active lives who also have sustained chronic UV damage. This population is at high risk for developing aggressive squamous cell carcinomas. In this population, extensive skin involvement with human papilloma virus induced warts and actinic keratoses results in difficulty with diagnosis and monitoring for these dangerous malignancies. Patients who have received treatment with agents that cause DNA damage, such as X-radiation, may also have a high skin cancer risk. Retinoid chemoprevention may also be of benefit in the management of selected patients with these iatrogenic conditions. This evolving therapeutic role has heightened the need for the development of new retinoids, with more efficacy and less toxicity, for cancer chemoprevention.

Djuzenova, C., B. Muhl, et al. (2004). "Normal expression of DNA repair proteins, hMre11, Rad50 and Rad51 but protracted formation of Rad50 containing foci in X-irradiated skin fibroblasts from radiosensitive cancer patients." Br J Cancer **90**(12): 2356-63.

About 5% of oncology patients treated by radiation therapy develop acute or late radiotoxic effects whose molecular mechanisms remain poorly understood. In this study, we evaluated the potential role of DNA repair proteins in the hypersensitivity of cancer patients to radiation therapy. The expression levels and focal nuclear distribution of DNA repair proteins, hMre11, Rad50 and Rad51 were investigated in skin fibroblasts strains derived from cancer patients with adverse early skin reaction to radiotherapy using Western blot and foci immunofluorescence techniques, respectively. Cells from cancer patients with normal reaction to radiotherapy as well as cells from apparently healthy subjects served as controls. Cellular radiosensitivity after in vitro irradiation was assessed by the clonogenic survival assay. The clonogenic survival assay and Western blot analysis of the DNA repair proteins did not reveal any abnormalities in cellular radiosensitivity in vitro and in protein expression levels or their migration patterns in the fibroblasts derived from cancer patients with hypersensitive reaction to radiotherapy. In contrast, in vitro irradiated cells from radiosensitive patients exhibited a significantly higher number of nuclei with focally concentrated Rad50 protein than in both control groups. The observed alteration of the distribution of radiation-induced Rad50 foci in cells derived from cancer patients with acute side reactions to radiotherapy might contribute to their radiation therapy outcome. These data suggest the usefulness of the Rad50 foci analysis for predicting clinical response of cancer patients to radiotherapy.

Doig, J., C. Anderson, et al. (2006). "Mice with skin-specific DNA repair gene (Ercc1) inactivation are hypersensitive to ultraviolet irradiation-induced skin cancer and show more rapid actinic progression." Oncogene **25**(47): 6229-38.

Ercc1 has an essential role in the nucleotide excision repair (NER) pathway that protects against ultraviolet (UV)-induced DNA damage and is also involved in additional repair pathways. The premature death of simple Ercc1 mouse knockouts meant that we were unable to study the role of Ercc1 in the skin. To do this, we have used the Cre-lox system to generate a skin-specific Ercc1 knockout. With a Cre transgene under control of the bovine keratin 5 promoter we achieved 100% recombination of the Ercc1 gene in the epidermis. Hairless mice with Ercc1-deficient skin were hypersensitive to the short-term effects of UV irradiation, showing a very low minimal erythemal dose and a dramatic hyperproliferative response. Ultraviolet-irradiated mice with Ercc1-deficient skin developed epidermal skin tumours much more rapidly than controls. These tumours appeared to arise earlier in actinic progression and grew more rapidly than tumours on control mice. These responses are more pronounced than have been reported for other NER-deficient mice, demonstrating that Ercc1 has a key role in protecting against UV-induced skin cancer.

Drouin, R. and J. P. Therrien (1997). "UVB-induced cyclobutane pyrimidine dimer frequency correlates with skin cancer mutational hotspots in p53." Photochem Photobiol **66**(5): 719-26.

Ultraviolet light has been identified as the major carcinogen in skin cancer and the p53 tumor suppressor gene is a major target for UV-induced mutations. The mutations are probably caused by unrepaired UV-induced cyclobutane pyrimidine dimers (CPD) and possibly by the less frequent pyrimidine (6-4) pyrimidone photoproducts. While hot spots for p53 mutations in human nonmelanoma skin tumors correspond quite well to slow spots for CPD repair in cultured cells irradiated with the model mutagen 254 nm UVC (which is not present in terrestrial sunlight), they do not all coincide with sequences that are initially frequently damaged by 254 nm UVC. Using LMPCR (ligation-mediated polymerase chain reaction), we show that environmentally relevant UVB light induces CPD at CC and Pyr(m)C positions much more frequently than does UVC light, and that all eight skin cancer hot spots in p53 are also hot spots for UVB-induced CPD.

Our results show that methylation of dipyrimidine sites (Pyr(m)CpG) is associated with an increase rate of CPD formation upon UVB irradiation. Consequently, DNA methylation may increase the mutagenic potential of UVB and explains that several p53 mutation hot spots are found at Pyr(m)CpG. The distribution patterns of CPD formation and the photofootprint patterns found along exons 5 and 6 of p53 gene are suggestive of DNA folding into nucleosomes.

Dunn, D. S., H. Inoko, et al. (2006). "The association between non-melanoma skin cancer and a young dimorphic Alu element within the major histocompatibility complex class I genomic region." Tissue Antigens **68**(2): 127-34.

A non-melanoma skin cancer (NMSC) susceptibility locus within the major histocompatibility complex (MHC) class I region was previously identified telomeric of the HLA-C gene using high-density microsatellite markers. Here, we have extended the previous microsatellite study by using the same DNA samples obtained from 154 NMSC patients and 213 normal controls from the town of Busselton in Western Australia and examined the relationship between five polymorphic Alu insertions (POALINs) within the MHC class I region and their association with NMSC. The genotype distribution of the AluyTF insertion that is located within the NMSC susceptibility region telomeric of the HLA-C gene was significantly increased according to the Fisher's exact test in the NMSC patients, and it was not in Hardy-Weinberg equilibrium in the control group. There was no difference between the cancer patients and controls for the genotypes of the AluyMICB locus within intron 1 of the MICB gene and the other three POALINs (AluyHJ, AluyHG and AluyHF) that are located within the genomic region of the HLA-A, -G and -F gene cluster. The test for significant linkage disequilibrium for 10 pairs of POALIN loci and estimations of two locus POALIN haplotype frequencies also revealed AluyTF differences between the cases and controls. In conclusion, the MHC class I POALIN, AluyTF, that is located within the NMSC susceptibility locus and near the HLA-C gene was strongly associated with NMSC. This finding, using five different polymorphic Alu insertion markers, supports the previous microsatellite association study that one or more genes located in close proximity to the AluyTF insertion has a potential role in NMSC.

Durham, S. E., K. J. Krishnan, et al. (2003). "Mitochondrial DNA damage in non-melanoma skin cancer." Br J Cancer **88**(1): 90-5.

Mitochondrial DNA (mtDNA) damage, predominantly encompassing point mutations, has been reported in a variety of cancers. Here we present in human skin, the first detailed study of the distribution of multiple forms of mtDNA damage in nonmelanoma skin cancer (NMSC) compared to histologically normal perilesional dermis and epidermis. We present the first entire spectrum of deletions found between different types of skin tumours and perilesional skin. In addition, we provide the first quantitative data for the incidence of the common deletion as well as the first report of specific tandem duplications in tumours from any tissue. Importantly, this work shows that there are clear differences in the distribution of deletions between the tumour and the histologically normal perilesional skin. Furthermore, DNA sequencing of four mutation 'hotspot' regions of the mitochondrial genome identified a previously unreported somatic heteroplasmic mutation in an SCC patient. In addition, 81 unreported and reported homoplasmic single base changes were identified in the other NMSC patients. Unlike the distribution of deletions and the heteroplasmic mutation, these homoplasmic mutations were present in both tumour and perilesional skin, which suggests that for some genetic studies the traditional use of histologically normal perilesional skin from NMSC patients may be limited. Currently, it is unclear whether mtDNA damage has a direct link to skin cancer or it may simply reflect an underlying nuclear DNA instability.

Duvic, M., B. Helekar, et al. (2000). "Expression of a retinoid-inducible tumor suppressor, Tazarotene-inducible gene-3, is decreased in psoriasis and skin cancer." Clin Cancer Res **6**(8): 3249-59.

Tazarotene-induced gene-3 (TIG-3), isolated from human keratinocytes treated with the retinoic acid receptor-selective retinoid Tazarotene, is homologous to H-rev, a class II tumor suppressor. TIG-3 gene localized to chromosome 11q23, a site of loss of heterozygosity in several malignancies. Retinoids influence epidermal differentiation and are used to treat and prevent skin cancer. Therefore, we studied TIG-3 mRNA expression in psoriasis and in basal and SCCs by in situ hybridization and a quantitative QT-RT-PCR assay. Psoriasis lesions had significantly lower staining (median, 3) than paired normal control skin (median, 4; $P = 0.012$). TIG-3 mRNA was significantly higher in normal control skin ($P = 0.001$), in paired adjacent skin (median, 3; $P = 0.007$), and in overlying epidermis (median, 3.0; $P = 0.0001$) than in 21 SCC specimens as a group (median, 1.5).

Dwyer, T., J. M. Stankovich, et al. (2004). "Does the addition of information on genotype improve prediction of the risk of melanoma and nonmelanoma skin cancer beyond that obtained from skin phenotype?" Am J Epidemiol **159**(9): 826-33.

The authors quantified improvement in predicting cutaneous malignant melanoma, basal cell carcinoma, and squamous cell carcinoma of the skin made possible by information on common variants of the melanocortin-1 receptor gene (MC1R) in a 1998-1999 population-based case-control study of subjects aged 20-59 years of northern European ancestry in Tasmania, Australia. Melanin density at the upper inner arm was estimated by spectrophotometry. DNA samples were genotyped for five MC1R variants: Val60Leu, Asp84Glu, Arg151Cys, Arg160Trp, and Asp294His. Among controls (n = 267), variant carriers, versus noncarriers, had lower ($p < 0.01$) mean melanin concentrations. Increased risk conferred by genotype was restricted mainly to those with the darkest skins: for subjects with at least 2% melanin, the odds of carrying each additional variant were higher for cutaneous malignant melanoma (n = 39; odds ratio = 1.45, 95% confidence interval: 0.87, 2.44), basal cell carcinoma (n = 35; odds ratio = 1.86, 95% confidence interval: 1.14, 3.02), and squamous cell carcinoma (n = 42; odds ratio = 2.67, 95% confidence interval: 1.50, 4.74) cases than for controls (n = 135). Adding MC1R information to prediction based on age, sex, and cutaneous melanin increased the area under the receiver operating characteristic curve by 1.4% (cutaneous malignant melanoma), 3.2% (basal cell carcinoma), or 2.0% (squamous cell carcinoma). The improvement in prediction was probably too small to be valuable in a clinical setting.

Edwards, M. J., R. C. Thomas, et al. (2003). "Retinoblastoma gene expression in human non-melanoma skin cancer." J Cutan Pathol **30**(8): 479-85.

BACKGROUND: The aberrant expression of both the retinoblastoma and p53 tumor suppressor genes has been associated with more aggressive tumors, metastasis and lower survival. METHODS: We have evaluated immunohistochemically the expression of pRB in a panel of non-melanoma skin cancers containing p53 somatic mutations. RESULTS: Nuclear anti-p53 staining was detected in 18 (72%) differentiated squamous cell carcinomas, six (100%) undifferentiated squamous cell carcinomas and seven (28%) basal cell carcinomas. A correlation was observed between p53 expression and the proliferative activity of differentiated squamous cell carcinomas ($P < 0.066$), undifferentiated squamous cell carcinomas ($P < 0.05$) and basal cell carcinomas ($P < 0.01$). Tumors were selected for mutant p53 expression by PCR-directed DNA sequencing and pRB expression measured immunohistochemically. Anti-pRB reactivity was detected in the nuclei of basal and suprabasal layer cells of normal epidermis, and in the proliferative compartment of all the differentiated squamous cell carcinomas, and basal cell carcinomas. A correlation was observed between pRB expression and the proliferative activity of the differentiated squamous cell carcinomas ($P < 0.01$) and basal cell carcinomas ($P < 0.025$). However, anti-pRB reactivity was not detected in the six anti-p53 reactive undifferentiated squamous cell carcinomas.

Erb, P., J. Ji, et al. (2008). "Apoptosis and pathogenesis of melanoma and nonmelanoma skin cancer." Adv Exp Med Biol **624**: 283-95.

Skin cancers, i.e., basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma, belong to the most frequent tumors. Their formation is based on constitutional and/or inherited factors usually combined with environmental factors, mainly UV-irradiation through long term sun exposure. UV-light can randomly induce DNA damage in keratinocytes, but it can also mutate genes essential for control and surveillance in the skin epidermis. Various repair and safety mechanisms exist to maintain the integrity of the skin epidermis. For example, UV-light damaged DNA is repaired and if this is not possible, the DNA damaged cells are eliminated by apoptosis (sunburn cells). This occurs under the control of the p53 suppressor gene. Fas-ligand (FasL), a member of the tumor necrosis superfamily, which is preferentially expressed in the basal layer of the skin epidermis, is a key surveillance molecule involved in the elimination of sunburn cells, but also in the prevention of cell transformation. However, UV light exposure downregulates FasL expression in keratinocytes and melanocytes leading to the loss of its sensor function. This increases the risk that transformed cells are not eliminated anymore. Moreover, important control and surveillance genes can also be directly affected by UV-light. Mutation in the p53 gene is the starting point for the formation of SCC and some forms of BCC. Other BCCs originate through UV light mediated mutations of genes of the hedgehog signaling pathway which are essential for the maintainance of cell growth and differentiation. The transcription factor Gli2 plays a key role within this pathway, indeed, Gli2 is responsible for the marked apoptosis resistance of the BCCs. The formation of malignant melanoma is very complex. Melanocytes form nevi and from the nevi melanoma can develop through mutations in various genes. Once the keratinocytes or melanocytes have been transformed they re-express FasL which may allow the expanding tumor to evade the attack of immune effector cells. FasL which is involved in immune

evasion or genes which govern the apoptosis resistance, e.g., Gli2 could therefore be prime targets to prevent tumor formation and growth. Attempts to silence these genes by RNA interference using gene specific short interfering RNAs (siRNAs) or short hairpin RNAs (shRNAs) have been functionally successful not only in tissue cultures and tumor tissues, but also in a mouse model. Thus, siRNAs and/or shRNAs may become a novel and promising approach to treat skin cancers at an early stage.

Evke, E., F. Z. Minbay, et al. (2009). "Immunohistochemical detection of p53 protein in basal cell skin cancer after microwave-assisted antigen retrieval." J Mol Histol **40**(1): 13-21.

p53 is the most frequently altered tumor-suppressor gene in skin cancer. In normal tissues the p53 protein (wild type) has a very short half-life and it is not detectable immunohistochemically. In contrast, the mutant p53 protein has an extended half-life in tumor cells and can be detected by immunohistochemical methods. p53 is widely used as an indicator of tumor aggression and progression. Fixation methods especially formaldehyde based fixation may mask the immunohistochemical detection of p53 protein but antigen retrieval methods enhance the inmmunohistochemical detection of p53 protein by remodification of protein structure. This study was designed to evaluate the efficacy of different fixatives, of microwaving and microwave pretreatment method to retrieve p53 immunoreactivity in paraffin-embedded non-lesioned (adjacent normal tissue) human skin samples or pathological human skin samples diagnosed as basal cell carcinoma. The samples were fixed at RT and/or in microwave oven either in neutral buffered formalin or alcohol for different time periods. For antigen retrieval, the sections were irradiated in a microwave oven for 5 cycles in 10 mM citrate buffer (pH 6.00). In this study the effects of six different fixation methods on the immunohistochemical staining have been investigated in basal cell tumor specimens. The application of antigen retrieval method was also examined and compared. Optimal results were obtained using samples fixed in alcohol either at room temperature (24 h) or in microwave oven.

Gailani, M. R. and A. E. Bale (1997). "Developmental genes and cancer: role of patched in basal cell carcinoma of the skin." J Natl Cancer Inst **89**(15): 1103-9.

Many genes originally identified because of their role in embryonic development are also important in postnatal control of cell growth and differentiation. Mutations in some of these genes have been shown to cause cancer. Basal cell carcinoma (BCC) of the skin is the most common cancer in humans. More than 750000 new cases are diagnosed annually, and the incidence is rising. BCCs are slow-growing, locally invasive tumors that rarely metastasize but can result in extensive morbidity through local recurrence and tissue destruction. Epidemiologic studies suggest that sunlight (particularly UVB radiation) is a strong risk factor for BCC formation, although other factors are also involved. The nevoid basal cell carcinoma syndrome (NBCCS), a rare genetic disorder, is characterized by predisposition to BCCs and other tumors as well as to a wide range of developmental defects. NBCCS maps to chromosome 9q22.3, and loss of heterozygosity at this site in both sporadic and hereditary BCCs suggests that it functions as a tumor suppressor. The gene for NBCCS was recently cloned and is the human homologue of the Drosophila gene "patched." Genetic studies in Drosophila show that patched is part of the hedgehog signaling pathway, which is important in determining embryonic patterning and cell fate in multiple structures of the developing embryo. Human patched is mutated in both hereditary and sporadic BCCs, and inactivation of this gene is probably a necessary, if not sufficient, step for BCC formation. Delineation of the biochemical pathway in which patched functions may lead to rational medical therapy for BCCs and possibly for other tumors associated with NBCCS.

Gasparro, F. P. (2000). "The role of PUVA in the treatment of psoriasis. Photobiology issues related to skin cancer incidence." Am J Clin Dermatol **1**(6): 337-48.

Photochemotherapy with methoxsalen (8-methoxypsoralen) and long wavelength ultraviolet (UV) radiation (referred to as 'PUVA' for psoralen plus UVA) is commonly used to treat psoriasis and vitiligo. These vastly different diseases respond to the therapy by different mechanisms even though the immediate effects of the therapy--the photomodification of cellular biomolecules--is the same for each. Because psoriasis is not cured by PUVA, patients receive many treatments over their lifetime and have a significantly increased risk for the development of skin cancers (primarily squamous cell carcinomas). In this article the basic aspects of psoralen photobiology are reviewed briefly. Several recent studies describing the incidence of skin cancer in UVA treated psoriasis cohorts are comparatively reviewed. In addition the impact of the analysis of mutations in the tumor suppressor gene, p53, are summarized. An unexpected mutation spectrum (very few PUVA type T-->A transversions and frequent UVB solar signature C-->T transitions) suggest that effects other than direct DNA photoadduct formation

may be at play. These analyses suggest that it may be possible to improve the therapeutic efficacy of PUVA by a careful evaluation of the mode of delivery. In this review the science behind PUVA is summarized. In addition, the incidence of skin cancer as a long term consequence of repeated treatments is surveyed. To relate clinical observations to molecular events, the nature of p53 mutations found in skin cancers from psoriasis patients is also analyzed. Finally some suggestions for improving the delivery of PUVA therapy are presented.

Gerdes, M. J. and S. H. Yuspa (2005). "The contribution of epidermal stem cells to skin cancer." Stem Cell Rev **1**(3): 225-31.

Tumors arising from the skin are of multiple phenotypes, with differing degrees of malignant potential. In mouse models of skin carcinogenesis, tumors of squamous phenotype are the most common; however, human disease indicates that multiple phenotypes may arise from a common pool of stem cells that are then influenced by epigenetic factors. The use of transgenic and knockout gene technologies with mice is unraveling some of the specific genes regulating fate determination in stem cells other than squamous lineage, including basal cell carcinoma and sebaceous adenomas. The following review examines the evidence for the stem cell origin of epidermal tumors and the contribution of some specific gene families toward stem cell fate decisions during epidermal tumor progression.

Girardi, M., E. Glusac, et al. (2003). "The distinct contributions of murine T cell receptor (TCR)gammadelta+ and TCRalphabeta+ T cells to different stages of chemically induced skin cancer." J Exp Med **198**(5): 747-55.

Epithelial tissues in which carcinomas develop often contain systemically derived T cell receptor (TCR)alphabeta+ cells and resident intraepithelial lymphocytes that are commonly enriched in TCRgammadelta+ cells. Recent studies have demonstrated that gammadelta cells protect the host against chemically induced cutaneous malignancy, but the role of alphabeta T cells has been enigmatic, with both protective and tumor-enhancing contributions being reported in different systems. This study aims to clarify the contributions of each T cell type to the regulation of squamous cell carcinoma induced in FVB mice by a two-stage regimen of 7,12-dimethylbenz[a]anthracene initiation followed by repetitive application of the tumor promoter 12-O-tetradecanoylphorbol 13-acetate. This protocol permits one to monitor the induction of papillomas and the progression of those papillomas to carcinomas. The results show that whereas gammadelta cells are strongly protective, the nonredundant contributions of alphabeta T cells to the host's protection against papillomas are more modest. Furthermore, at both high and low doses of carcinogens, alphabeta T cells can contribute to rather than inhibit the progression of papillomas to carcinomas. As is likely to be the case in humans, this study also shows that the contribution of T cells to tumor immunosurveillance is regulated by modifier genes.

Green, C. L. and P. A. Khavari (2004). "Targets for molecular therapy of skin cancer." Semin Cancer Biol **14**(1): 63-9.

Cancers of the skin encompass the first and second most common neoplasms in the United States, epidermal basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), respectively, as well as the melanocytic malignancy, malignant melanoma (MM). Recently identified alterations in the function of specific genes in these cancers provide new potential therapeutic targets. These alterations affect conserved regulators of cellular proliferation and viability, including the Sonic Hedgehog, Ras/Raf, ARF/p53, p16(INK4A)/CDK4/Rb and NF-kappaB pathways. New modalities designed to target these specific proteins may represent promising approaches to therapy of human skin cancers.

Greinert, R. (2009). "Skin cancer: new markers for better prevention." Pathobiology **76**(2): 64-81.

Skin cancer is the most frequent cancer in the white population worldwide. Incidence of basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and malignant melanoma (MM) is still increasing. This trend can be counteracted by means of primary and secondary prevention because the main risk factor for skin cancer - UV-radiation - is known, and, early detected, skin cancer can be cured successfully. For early detection of skin cancer suitable risk (group) markers have to be used to identify persons at risk. In order to increase the sensitivity and specificity of early detection efforts (screening programs) new molecular markers or biomarkers should be used in the future in the field of molecular epidemiology. In this review the skin cancer problem is summarized and the possible use of new biomarkers for skin cancer development, progression, metastasis and prognosis is discussed. The review focuses on results of gene expression profiling using array techniques and the new possibilities for the use of epigenetic biomarkers.

Grose, R., V. Fantl, et al. (2007). "The role of fibroblast growth factor receptor 2b in skin

homeostasis and cancer development." Embo J **26**(5): 1268-78.

The epithelial isoform of fibroblast growth factor receptor 2 (Fgfr2b) is essential for embryogenesis, and Fgfr2b-null mice die at birth. Using Cre-Lox transgenics to delete Fgfr2b in cells expressing keratin 5, we show that mice lacking epidermal Fgfr2b survive into adulthood but display striking abnormalities in hair and sebaceous gland development. Epidermal hyperthickening develops with age, and 10% of mutant mice develop spontaneous papillomas, demonstrating the role of Fgfr2b in post-natal skin development and in adult skin homeostasis. Mice lacking epithelial Fgfr2b show great sensitivity to chemical carcinogenic insult, displaying several oncogenic ha-ras mutations with dramatic development of papillomas and squamous cell carcinomas. Mutant mice have increased inflammation in the skin, with increased numbers of macrophages and gammadeltaT cells with abnormal morphology. Mutant skin shows several changes in gene expression, including enhanced expression of the pro-inflammatory cytokine interleukin 18 and decreased expression of Serpin a3b, a potential tumor suppressor. Thus we describe a novel role of Fgfr2b and provide the first evidence of a tyrosine kinase receptor playing a tumor suppressive role in the skin.

Grossman, D., J. M. McNiff, et al. (1999). "Expression of the apoptosis inhibitor, survivin, in nonmelanoma skin cancer and gene targeting in a keratinocyte cell line." Lab Invest **79**(9): 1121-6.

The recently described apoptosis inhibitor survivin is expressed in many human cancers, thus potentially contributing to disease progression and resistance to therapy. Its potential role in nonmelanoma skin cancer is unknown. By immunohistochemistry, survivin was expressed in 81% (17 of 21) of basal cell carcinomas (BCC) of both nodular and morpheaform subtypes, and in 92% (24 of 26) of cutaneous squamous cell carcinomas (SCC). Survivin was also expressed in 19 premalignant lesions of Bowen's disease (SCC in situ) and hypertrophic actinic keratosis (HAK), suggesting that its appearance occurs early during keratinocyte transformation. Survivin expression was detected by Western blotting in a model keratinocyte cell line, HaCat. Transfection of HaCat cells with green fluorescent protein (GFP)-conjugated survivin antisense or GFP-conjugated survivin dominant negative mutant (Cys84Ala) resulted in spontaneous apoptosis in the absence of other genotoxic stimuli. In GFP-conjugated survivin antisense transfectants, a decreased level of endogenous survivin was confirmed by flow cytometry. This was associated with a five-fold increase in the sub-G0/G1 fraction corresponding to apoptotic cells and a decrease in proliferating cells with 4N DNA content. These data demonstrate that apoptosis inhibition by survivin may participate in the onset and progression of both BCC and SCC, and suggest that therapeutic targeting of survivin may be beneficial in patients with recurrent or advanced disease.

Hall, J., D. R. English, et al. (1994). "DNA repair capacity as a risk factor for non-melanocytic skin cancer--a molecular epidemiological study." Int J Cancer **58**(2): 179-84.

Capacity to repair UV-induced DNA damage was studied by use of host cell reactivation assay in T lymphocytes isolated from 86 cases and 87 controls (aged 44-68 years) who were participants in a population-based case-control study of basal cell (BCC) or squamous cell (SCC) carcinoma of the skin in Geraldton, Western Australia. Lymphocytes were cultured and transfected with either control or UV-irradiated plasmids (254 nm, 350 J/m2) containing a reporter gene [the chloramphenicol-acetyltransferase (CAT) gene], and the repair capacity was determined by measuring CAT gene expression in protein extracts prepared from the transfected cells. DNA repair activity was 1.07 (95% confidence interval 0.94-1.26) times greater in BCC cases than in controls for each 350 J/m2 increment in UV dose to the plasmids, and 1.04 (95% confidence interval 0.85-1.26) times greater in SCC cases than in controls, though the differences were not statistically significant. DNA repair activity showed little association with age, sex and viability of the lymphocytes, though it was positively associated with their blastogenic rate ($p = 0.055$).

Halliday, G. M., N. S. Agar, et al. (2005). "UV-A fingerprint mutations in human skin cancer." Photochem Photobiol **81**(1): 3-8.

This review of our work, presented at the Photocarcinogenesis Symposium of the 14th International Congress on Photobiology, shows that UV-A causes a similar number of gene mutations as UV-B in human skin cancer. Areas of about 20 keratinocytes from solar keratoses and squamous cell carcinomas, which are benign and malignant skin cancers, respectively, were sampled by laser capture microdissection. Automated sequencing of the p53 gene was used to detect mutations in these tumor areas, and the cause of the mutations was attributed on the basis of previously published studies. UV-A and UV-B caused similar numbers of p53 gene mutations in both benign and malignant human skin tumors, with UV-B-induced mutations being restricted to the upper areas of the tumors and UV-A-induced mutations predominating at the basal layer.

Furthermore, each microdissected region within a tumor had distinct mutations showing that the skin tumors consisted of different clones of cells. This is not consistent with how human skin carcinogenesis is currently understood, and hypotheses to explain our data are presented. We propose that the UV-A waveband of sunlight is as important as UV-B in causing skin cancer in humans.

Halpern, A. C. and J. F. Altman (1999). "Genetic predisposition to skin cancer." Curr Opin Oncol **11**(2): 132-8.

Here we review recent insights in the genetics of skin cancer susceptibility as gleaned from studies of three hereditary syndromes: basal cell nevus syndrome, familial melanoma/dysplastic nevus syndrome, and xeroderma pigmentosum. We provide a brief synopsis of the recent findings related to these syndromes in an attempt to illustrate several emerging themes in the genetics of skin cancer. These themes include 1) the recent identification of multiple cancer susceptibility genes that occur in a myriad of cellular regulatory pathways; 2) the relative specificity of certain regulatory pathways to the development of specific types of cancer; and 3) the important role of DNA damage caused by ultraviolet radiation and defective DNA repair mechanisms in the development of skin cancer. We also review the implications of this knowledge to clinical practice relative to risk assessment, primary prevention, and therapy.

Han, J., G. A. Colditz, et al. (2007). "Manganese superoxide dismutase polymorphism and risk of skin cancer (United States)." Cancer Causes Control **18**(1): 79-89.

OBJECTIVE: We assessed whether the functional V16A polymorphism in the MnSOD gene is associated with skin cancer risk. METHODS: We conducted a nested case-control study (219 melanoma, 286 squamous cell carcinoma (SCC), and 300 basal cell carcinoma (BCC) cases, and 873 matched controls) within the Nurses' Health Study. Genotyping was performed by the 5' nuclease assay (TaqMan). We used logistic regression to model the association between the genotype and skin cancer risk. RESULTS AND CONCLUSIONS: Overall, there was no significant association between this polymorphism and the risk of each type of skin cancer. No significant interaction was observed between this polymorphism and sunburn history and constitutional susceptibility on skin cancer risk. For interactions between intakes of alpha-carotene and beta-carotene and the MnSOD polymorphism on SCC, the inverse association of intake of either carotene with SCC risk was limited to the Val carriers, whereas no association was observed among women with the AA genotype. We observed an interaction between total vitamin C intake and the MnSOD polymorphism on melanoma risk. No interaction was observed for the intakes of other carotenoids, vitamin E, and vitamin A. Further research is needed to confirm these possible associations.

Han, J., G. A. Colditz, et al. (2007). "Polymorphisms in the MTHFR and VDR genes and skin cancer risk." Carcinogenesis **28**(2): 390-7.

Folate and vitamin D have been shown to be influenced by ultraviolet (UV) radiation. UVA radiation can break down plasma folate, whereas vitamin D can be synthesized in UVB-exposed skin. Folate metabolism is involved in DNA synthesis and repair, and vitamin D processes anti-proliferative effects. The functions of both nutrients are implicated in skin carcinogenesis. We evaluated genetic polymorphisms in the methylenetetrahydrofolate reductase (MTHFR) gene (C677T and A1298C) and the vitamin D receptor (VDR) gene (Fok1, Bsm1 and Cdx2) with skin cancer risk in a nested case-control study within the Nurses' Health Study [219 melanoma, 286 squamous cell carcinoma (SCC), 300 basal cell carcinoma (BCC) and 873 controls]. No significant associations were observed for the two MTHFR polymorphisms on skin cancer risk. We observed an interaction between the C677T polymorphism and total folate intake on SCC risk (P, interaction=0.04); the highest risk was observed among women with TT genotype and low folate intake (OR=2.14; 95% CI=1.01-4.50). The VDR Bsm1 BB genotype was significantly associated with an increased SCC risk (OR=1.51; 95% CI=1.00-2.28). An interaction between the Bsm1 polymorphism and total vitamin D intake on SCC was observed, with the highest risk seen in women with the BB genotype and high vitamin D intake (OR=2.38; 95% CI=1.22-4.62) (P, interaction=0.08). This study suggests a possible role of the polymorphisms in MTHFR and VDR interacting with dietary intakes of folate and vitamin D in skin cancer development, especially for SCC. Due to a large number of comparisons and tests, the possible associations should be interpreted with caution and confirmed by other studies.

Han, J., G. A. Colditz, et al. (2005). "Genetic variation in XPD, sun exposure, and risk of skin cancer." Cancer Epidemiol Biomarkers Prev **14**(6): 1539-44.

The XPD gene is involved in the nucleotide excision repair pathway removing DNA photoproducts induced by UV radiation. Genetic variation in XPD may exert a subtle effect on DNA repair capacity. We assessed the associations between two common nonsynonymous polymorphisms (Asp312Asn and Lys751Gln) with skin cancer risk in

a nested case-control study within the Nurses' Health Study (219 melanoma, 286 squamous cell carcinoma, 300 basal cell carcinoma, and 874 controls) along with exploratory analysis on the haplotype structure of the XPD gene. There were inverse associations between the Lys751Gln and Asp312Asn polymorphisms and the risks of melanoma and squamous cell carcinoma. No association was observed between these two polymorphisms and basal cell carcinoma risk. We also observed that the association of the 751Gln allele with melanoma risk was modified by lifetime severe sunburns, cumulative sun exposure with a bathing suit, and constitutional susceptibility score (P for interaction = 0.03, 0.04, and 0.02 respectively). Similar interactions were also observed for the Asp312Asn. Our data suggest these two XPD nonsynonymous polymorphisms may be associated with skin cancer risk, especially for melanoma.

Han, J., G. A. Colditz, et al. (2004). "Polymorphisms in DNA double-strand break repair genes and skin cancer risk." Cancer Res **64**(9): 3009-13.

UV can cause a wide range of DNA lesions. UVA-induced oxidative DNA damage and blocked DNA replication by UVB-induced photoproducts can lead to double-strand breaks (DSBs). We selected 11 haplotype-tagging single nucleotide polymorphisms in three DSB repair genes XRCC2, XRCC3, and LigaseIV and evaluated their associations with skin cancer risk in a nested case-control study within the Nurses' Health Study [219 melanoma, 286 squamous cell carcinoma (SCC), 300 basal cell carcinoma (BCC), and 873 controls]. We observed that the XRCC3 18085T (241Met) allele and its associated haplotype were significantly inversely associated with the risks of SCC and BCC, whereas the XRCC3 4552C allele along with its associated haplotype and the XRCC2 30833A allele were significantly associated with increased BCC risk. The LigaseIV 4044T and 4062T alleles were associated with decreased BCC risk; two of four haplotypes were significantly associated with altered BCC risk. A trend toward decreased risk of nonmelanoma skin cancer was found in those harboring a greater number of putative low risk alleles (P for trend, 0.05 for SCC, <0.0001 for BCC). The main effects of these genotypes were essentially null for melanoma risk. This study provides evidence to suggest the role of the DSB repair pathway in skin cancer development, especially for BCC.

Han, J., D. G. Cox, et al. (2006). "The p53 codon 72 polymorphism, sunburns, and risk of skin cancer in US Caucasian women." Mol Carcinog **45**(9): 694-700.

The p53 gene is involved in the control of cell-cycle arrest and apoptosis. The germline Arg72Pro polymorphism alters the protein's biochemical functions, and may confer individual susceptibility to skin cancer. We evaluated the association of the Arg72Pro polymorphism with skin cancer risk among Caucasians in a nested case-control study within the Nurses' Health Study (NHS) (219 melanoma, 286 squamous cell carcinoma (SCC), and 300 basal cell carcinoma (BCC) and 874 controls). Compared to the Arg/Arg genotype, the Pro/Pro genotype had an OR of 1.57 (95%CI, 0.81-3.06) for melanoma risk, and an OR of 1.79 (95%CI, 1.01-3.17) for BCC risk. The positive association of the Pro allele with BCC risk was only limited to women with two or fewer lifetime sunburns (P, trend, 0.002; P, interaction, 0.02). No association was observed between the polymorphism and SCC risk. We also observed that the Pro allele was inversely associated with the risk of childhood sunburn among Caucasian participants pooled from four nested case-control studies within the NHS. This study suggests that the Arg72Pro polymorphism may play a role in skin carcinogenesis.

Han, J., S. E. Hankinson, et al. (2004). "Genetic variation in XRCC1, sun exposure, and risk of skin cancer." Br J Cancer **91**(8): 1604-9.

The XRCC1 gene is involved in the base excision repair pathway. We assessed the associations of polymorphisms and haplotypes in XRCC1 with skin cancer risk in a nested case-control study within the Nurses' Health Study (219 melanoma, 286 squamous cell carcinoma (SCC) and 300 basal cell carcinoma (BCC), and 873 controls). We genotyped four haplotype-tagging single-nucleotide polymorphisms (Arg194Trp, C26602T, Arg399Gln, and Gln632Gln). There was no significant difference in frequency distribution between cases and controls for any of the five inferred common haplotypes. We observed that the 399Gln allele was inversely associated with SCC risk. This inverse association was only seen among those who had five or more lifetime sunburns, those with a family history of skin cancer, and those in the highest tertile of cumulative sun exposure in a bathing suit, but not among those with low risk defined by these risk factors. We also observed a significant association of the carriage of 194Trp allele with increased SCC risk, which was modified by family history of skin cancer. These two polymorphisms were not associated with BCC or melanoma risk. Our data suggest that the Arg194Trp and Arg399Gln polymorphisms may be differently associated with skin cancer risk according to exposure dose and skin cancer type.

Han, J., P. Kraft, et al. (2006). "Melanocortin 1 receptor variants and skin cancer risk." Int J Cancer **119**(8): 1976-84.

Melanocortin 1 receptor (MC1R) gene variants are associated with red hair and fair skin color. We assessed the associations of common MC1R genotypes with the risks of 3 types of skin cancer simultaneously in a nested case-control study within the Nurses' Health Study (219 melanoma, 286 squamous cell carcinoma (SCC), and 300 basal cell carcinoma (BCC) cases, and 873 controls). We found that the 151Cys, 160Trp and 294His variants were significantly associated with red hair, fair skin color and childhood tanning tendency. The MC1R variants, especially the 151Cys variant, were associated with increased risks of the 3 types of skin cancer, after controlling for hair color, skin color and other skin cancer risk factors. Carriers of the 151Cys variant had an OR of 1.65 (95% CI, 1.04-2.59) for melanoma, 1.67 (1.12-2.49) for SCC and 1.56 (1.03-2.34) for BCC. Women with medium or olive skin color carrying 1 nonred hair color allele and 1 red hair color allele had the highest risk of melanoma. A similar interaction pattern was observed for red hair and carrying at least 1 red hair color allele on melanoma risk. We also observed that the 151Cys variant contributed additional melanoma risk among red-haired women. The information on MC1R status modestly improved the risk prediction; the increase was significant for melanoma and BCC (p, 0.004 and 0.05, respectively). These findings indicated that the effects of the MC1R variants on skin cancer risk were independent from self-reported phenotypic pigmentation.

Han, R., X. Peng, et al. (2002). "Gene gun-mediated intracutaneous vaccination with papillomavirus E7 gene delays cancer development of papillomavirus-induced skin papillomas on rabbits." Cancer Detect Prev **26**(6): 458-67.

High-risk human papillomavirus (HPV) E6 and E7 viral oncogenes are expressed in HPV-associated cancers, and thus represent tumor-specific antigens. We used the cottontail rabbit papillomavirus (CRPV) rabbit model to test whether vaccination with either the E6 or E7 genes alone could prevent or delay carcinoma development. CRPV-induced papillomas on 24 rabbits were allowed to grow for 3 months without any treatment intervention. An immunization protocol using gene gun-mediated intracutaneous administration of DNA plasmids encoding the E6 or the E7 gene or vector only, respectively was initiated at this time point. Carcinoma development was followed up to 24 months after virus infection. Within this period, five rabbits died due to other causes but without carcinoma; one from the vector control group, and two each from the E6- and E7-vaccinated groups. The remaining seven rabbits from the vector control group developed carcinoma within 7-17 months. The remaining six E6-vaccinated rabbits developed cancer within 8-15 months. There was no delay in cancer development for the E6-vaccinated rabbits compared to the vector-injected rabbits. Some delay in cancer development in the remaining E7-vaccinated rabbits was observed; one developed cancer at month 23 and a second was without cancer at month 24. In addition, some E7-vaccinated rabbits with primary skin carcinomas had fewer lung metastases (<2) compared to vector-vaccinated controls (20+). These results suggested that gene gun-mediated intracutaneous immunization with papillomavirus early gene E7 but not E6 delayed carcinoma development of papillomavirus-induced lesions.

Hannan, M. A., Y. Siddiqui, et al. (2001). "Evidence of DNA repair/processing defects in cultured skin fibroblasts from breast cancer patients." Cancer Res **61**(9): 3627-31.

Cultured skin fibroblasts from 14 breast cancer (BC) patients were compared with those from 8 healthy subjects and 4 ataxia-telangiectasia (A-T) cases for sensitivity to low dose-rate (0.007 Gy/min) gamma-irradiation assessed by a colony-forming assay and for postirradiation DNA synthesis inhibition determined by the method of [(3)H]thymidine incorporation. Fibroblasts from all but two BC patients exhibited moderately enhanced radiosensitivity in the colony-forming assay, occupying an intermediate position between the controls and the A-T cases. Fibroblasts from the radiosensitive BC patients also showed an intermediate response with respect to radio-induced DNA synthesis inhibition compared with those from controls and A-T cases. In a host cell reactivation assay using an irradiated herpes simplex virus for plaque-forming ability, the fibroblasts from 7 BC patients, used as host cells, resulted in a significantly reduced ($P < 0.0001$) recovery of the virus relative to the 8 control fibroblasts, suggesting a deficiency in DNA repair in the former. A number of the BC fibroblasts analyzed in an assay for potentially lethal damage repair confirmed the repair deficiency in the fibroblasts from the BC patients. Defects in DNA repair and/or DNA processing after exposure to genotoxic agents would lead to genomic instability and hence would be responsible for cancer predisposition. Our data suggest that most BC patients may carry various genes resulting in such defects, and additional studies on normal cells from a larger cohort of BC patients and their family members are warranted to establish a connection between mutations

or polymorphisms in specific DNA repair genes and susceptibility to breast cancer.

Harwood, C. A., J. M. McGregor, et al. (1999). "Human papillomavirus and the development of non-melanoma skin cancer." J Clin Pathol **52**(4): 249-53.

Human papillomaviruses (HPV) are increasingly recognised as important human carcinogens. The best established association with human malignancy is that of high-risk mucosal HPV types and anogenital cancer. HPV-induced transformation of anogenital epithelia has been the subject of intense research which has identified the cellular tumour suppressor gene products, p53 and pRB, as important targets for the viral oncoproteins E6 and E7 respectively. Certain HPV types are also strongly associated with the development of non-melanoma skin cancer in the inherited disorder epidermodysplasia verruciformis (EV). However, in contrast with anogenital malignancy the oncogenic mechanisms of EV-HPV types remain uncertain, and there appears to be a crucial additional requirement for ultraviolet radiation. Cutaneous HPV types in the general population are predominantly associated with benign viral warts, but a role in non-melanoma skin cancer has recently been postulated. Polymerase chain reaction based HPV detection techniques have shown a high prevalence of HPV DNA, particularly in skin cancers from immunosuppressed patients and to a lesser extent in malignancies from otherwise immunocompetent individuals. No particular HPV type has yet emerged as predominant, and the role of HPV in cutaneous malignancy is unclear at present. It remains to be established whether HPV plays an active or purely a passenger role in the evolution of non-melanoma skin cancer.

Higashi, Y., T. Kanekura, et al. (2000). "Enhanced expression of cyclooxygenase (COX)-2 in human skin epidermal cancer cells: evidence for growth suppression by inhibiting COX-2 expression." Int J Cancer **86**(5): 667-71.

Cyclooxygenase (COX)-2 is one of the rate-limiting enzymes in the conversion of arachidonic acid to prostaglandins and other eicosanoids. Recent studies have shown enhanced expression of COX-2 in cancer cells of several tissues. We investigated the expression of COX-2 and prostaglandin (PG) E((2)) production in two human skin epidermal cancer cell lines: cutaneous squamous cell carcinoma, HSC-5, and eccrine carcinoma, EcCa. Both COX-2 expression and PGE((2)) production were significantly enhanced in cancer cell lines compared with the non-tumorigenic human keratinocyte cell line, HaCaT. In order to determine the role of COX-2 in the proliferation of HSC-5 and EcCa, the growth of untreated cells and cells transfected with COX-2 antisense oligonucleotide was compared using the MTT assay. Transfection with the antisense oligonucleotide suppressed COX-2 protein expression and significantly inhibited cell growth. The effect of a selective inhibitor of COX-2, NS398, was compared with the effect of the antisense oligonucleotide in order to see whether COX-2 expression and prostaglandins have selective effects on cell growth. COX-2 expression was unchanged by NS398 treatment, whereas NS398 inhibited cell growth to a certain extent. The degree of growth inhibition was greater with the antisense oligonucleotide than with NS398. Our findings indicate that COX-2 protein expression is enhanced in skin epidermal cancer cells and that COX-2 plays a pivotal role in regulating cell growth. Furthermore, inhibition of COX-2 expression had a more significant effect on growth suppression than inhibition of COX-2 catalytic activity, suggesting the existence of two different signal pathways via COX-2 in regulating cell growth.

Hill, L. L., A. Ouhtit, et al. (1999). "Fas ligand: a sensor for DNA damage critical in skin cancer etiology." Science **285**(5429): 898-900.

DNA-damaged cells can either repair the DNA or be eliminated through a homeostatic control mechanism termed "cellular proofreading." Elimination of DNA-damaged cells after ultraviolet radiation (UVR) through sunburn cell (apoptotic keratinocyte) formation is thought to be pivotal for the removal of precancerous skin cells. Sunburn cell formation was found to be dependent on Fas ligand (FasL), a pro-apoptotic protein induced by DNA damage. Chronic exposure to UVR caused 14 of 20 (70 percent) FasL-deficient mice and 1 of 20 (5 percent) wild-type mice to accumulate p53 mutations in the epidermis. Thus, FasL-mediated apoptosis is important for skin homeostasis, suggesting that the dysregulation of Fas-FasL interactions may be central to the development of skin cancer.

Holmberg, E., B. L. Rozell, et al. (1996). "Differential allele loss on chromosome 9q22.3 in human non-melanoma skin cancer." Br J Cancer **74**(2): 246-50.

Familial predisposition to basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin are apparent in the autosomal dominant syndromes naevoid basal cell carcinoma syndrome (NBCCS) and multiple self-healing squamous epitheliomata (MSSE) respectively. The gene responsible for NBCCS has been proposed to be a tumour-suppressor gene and is mapped to the same 2 Mb interval on 9q22.3 as the MSSE gene ESS1. In an attempt to further map the NBCCS gene, we have examined loss of heterozygosity (LOH) in 16 sporadic

BCCs and two familial BCCs using microsatellite markers located within the candidate gene region. The overall frequency of LOH observed was 67% in the BCCs and partial or interstitial deletions were found in eight tumours, with the highest LOH frequency at markers D9S280, D9S287 and D9S180. To determine if the same genomic region also shows frequent LOH in tumours with a squamous phenotype, we have examined 11 SCCs, four actinic keratoses and 13 cases of Bowen's disease for LOH at 9q22.3. An overall LOH frequency of 50% was observed at D9S180, and occurred in all types of squamous tumours. In contrast, a much lower LOH frequency of only 6% was found at the D9S287 locus. Our observation of different patterns of LOH at 9q22.3 in sporadic BCCs and SCCs implies that more than one tumour-suppressor gene might be located in this genomic region.

Hoot, K. E., J. Lighthall, et al. (2008). "Keratinocyte-specific Smad2 ablation results in increased epithelial-mesenchymal transition during skin cancer formation and progression." J Clin Invest **118**(8): 2722-32.

TGF-beta and its signaling mediators, Smad2, -3, and -4, are involved with tumor suppression and promotion functions. Smad4-/- mouse epidermis develops spontaneous skin squamous cell carcinomas (SCCs), and Smad3-/- mice are resistant to carcinogen-induced skin cancer; however, the role of Smad2 in skin carcinogenesis has not been explored. In the present study, we found that Smad2 and Smad4, but not Smad3, were frequently lost in human SCCs. Mice with keratinocyte-specific Smad2 deletion exhibited accelerated formation and malignant progression of chemically induced skin tumors compared with WT mice. Consistent with the loss of Smad2 in poorly differentiated human SCCs, Smad2-/- tumors were poorly differentiated and underwent epithelial-mesenchymal transition (EMT) prior to spontaneous Smad4 loss. Reduced E-cadherin and activation of its transcriptional repressor Snail were also found in Smad2-/- mouse epidermis and occurred more frequently in Smad2-negative human SCCs than in Smad2-positive SCCs. Knocking down Snail abrogated Smad2 loss-associated EMT, suggesting that Snail upregulation is a major mediator of Smad2 loss-associated EMT. Furthermore, Smad2 loss led to a significant increase in Smad4 binding to the Snail promoter, and knocking down either Smad3 or Smad4 in keratinocytes abrogated Smad2 loss-associated Snail overexpression. Our data suggest that enhanced Smad3/Smad4-mediated Snail transcription contributed to Smad2 loss-associated EMT during skin carcinogenesis.

Hsu, S., H. Qin, et al. (2007). "Expression of caspase-14 reduces tumorigenicity of skin cancer cells." In Vivo **21**(2): 279-83.

BACKGROUND: The green tea polyphenol (-)-epigallocatechin-3-gallate (EGCG) possesses anti-carcinogenic properties and was found to induce terminal differentiation in epidermal keratinocytes. Caspase-14, a member of the caspase family associated with epithelial cell differentiation, planned cell death, and barrier formation, is induced by EGCG in normal human epidermal keratinocytes but not in cancer cells. MATERIALS AND METHODS: A human epidermoid cancer cell line, A431, was co-transfected with a caspase-14-expressing pCMV vector and a GFP/neo-etpressingpCMVvector. Cell growth and tumorigenicity of the stable transfectant were determined in comparison to cells transfected with the control GFP/neo-expressing pCMV vector. RESULTS: Expression of exogenous caspase-14 led to growth inhibition and reduced the tumorigenicity of A431 cells. CONCLUSION: Pending future studies, caspase-14 could be used as a novel approach to skin cancer therapy via gene delivery systems.

Hudson, T. S., D. K. Hartle, et al. (2007). "Inhibition of prostate cancer growth by muscadine grape skin extract and resveratrol through distinct mechanisms." Cancer Res **67**(17): 8396-405.

The phytochemical resveratrol contained in red grapes has been shown to inhibit prostate cancer cell growth, in part, through its antioxidant activity. Muscadine grapes contain unique phytochemical constituents compared with other grapes and are potentially a source for novel compounds with antitumor activities. We compared the antitumor activities of muscadine grape skin extract (MSKE), which we show contains no resveratrol, with that of resveratrol using primary cultures of normal prostate epithelial cells (PrEC) and the prostate cancer cell lines RWPE-1, WPE1-NA22, WPE1-NB14, and WPE1-NB26, representing different stages of prostate cancer progression. MSKE significantly inhibited tumor cell growth in all transformed prostate cancer cell lines but not PrEC cells. Prostate tumor cell lines, but not PrEC cells, exhibited high rates of apoptosis in response to MSKE through targeting of the phosphatidylinositol 3-kinase-Akt and mitogen-activated protein kinase survival pathways. The reduction in Akt activity by MSKE is mediated through a reduction in Akt transcription, enhanced proteosome degradation of Akt, and altered levels of DJ-1, a known regulator of PTEN. In contrast to MSKE, resveratrol did not induce apoptosis in this model but arrested cells at the G(1)-S phase transition of the cell cycle associated with increased expression of p21 and decreased expression of cyclin D1 and

cyclin-dependent kinase 4 proteins. These results show that MSKE and resveratrol target distinct pathways to inhibit prostate cancer cell growth in this system and that the unique properties of MSKE suggest that it may be an important source for further development of chemopreventive or therapeutic agents against prostate cancer.

Hussain, I., S. ul Rehman, et al. (2009). "Mutational spectrum of conserved regions of TP53 and PTEN genes in Kangri cancer (of the skin) in the Kashmiri population." Mutat Res **676**(1-2): 5-10.

Kangri cancer is a unique, thermally induced squamous cell carcinoma (SCC) of the skin that develops due to persistent use of a Kangri (a brazier) by the Kashmiri people to combat the cold temperature during winter. Unlike classical UV-induced SCC of the skin, Kangri cancer appears on the legs and abdomen. Its common features are erythematous patches, recurrence and metastasis. In the absence of any molecular etiology, we made a preliminary attempt to estimate the nature and frequency of mutations in the TP53 and PTEN genes in Kangri cancer patients from Kashmir. PCR-SSCP analysis followed by direct sequencing revealed that TP53 mutations account for 40% (12/30) of sporadic Kangri cancer patients and that PTEN mutations account for only 6.6% (2/30). There were 16 mutations in TP53 exons 5 and 7, found in 12 patients. They consisted of 11 substitutions (7 transitions, 3 transversions and 1 double-base) and 5 insertions. The 11 substitutions represent 8 distinct missense mutations, 3 of which were silent mutations. The mutations detected in the PTEN gene consisted of one insertion and one C>T transition. This high percentage of TP53 mutations (especially A>G) showed a statistically significant association with age and positive lymph node status. Our results indicate that TP53 is a predominant target of chronic hyperthermia in the development of Kangri cancer in the moderate risk Kashmiri population. The differences in the TP53 mutation spectrum of UV-induced SCC of the skin and Kangri cancer are probably due to the nature of the respective environmental carcinogens. The study also suggests that TP53 may function as a potential molecular marker and prognostic tool, at least in a subset of sporadic Kangri tumors.

Hussein, M. R. (2005). "Ultraviolet radiation and skin cancer: molecular mechanisms." J Cutan Pathol **32**(3): 191-205.

Every living organism on the surface of the earth is exposed to the ultraviolet (UV) fraction of the sunlight. This electromagnetic energy has both life-giving and life-endangering effects. UV radiation can damage DNA and thus mutagenize several genes involved in the development of the skin cancer. The presence of typical signature of UV-induced mutations on these genes indicates that the ultraviolet-B part of sunlight is responsible for the evolution of cutaneous carcinogenesis. During this process, variable alterations of the oncogenic, tumor-suppressive, and cell-cycle control signaling pathways occur. These pathways include (a) mutated PTCH (in the mitogenic Sonic Hedgehog pathway) and mutated p53 tumor-suppressor gene in basal cell carcinomas, (b) an activated mitogenic ras pathway and mutated p53 in squamous cell carcinomas, and (c) an activated ras pathway, inactive p16, and p53 tumor suppressors in melanomas. This review presents background information about the skin optics, UV radiation, and molecular events involved in photocarcinogenesis.

Ichihashi, M., N. U. Ahmed, et al. (2000). "Preventive effect of antioxidant on ultraviolet-induced skin cancer in mice." J Dermatol Sci **23 Suppl 1**: S45-50.

Reactive oxygen species (ROS) have been shown to be responsible for inducing DNA damage after ultraviolet radiation (UV). Antioxidant, vitamin E and epigallocatechin gallate extracted from green tea, applied topically to the skin, delayed the onset of UV-induced skin cancer in mice. Since olive oil is reported to have a potent antioxidative effect in in vitro system, we asked whether, topical use of olive oil reduces the number and delays the onset of UV-induced skin cancer in mice. We found that super virgin olive oil painted immediately after UVB radiation significantly delayed the onset and reduced the number of skin cancer, but pretreatment of super virgin olive oil and pre- and/or post treatment by regular olive oil neither retarded nor reduced skin cancer formation in UV-irradiated mice. Further, 8-hydroxy-deoxyguanosine (8-OHdG) formation in mice epidermis was apparently reduced by super virgin olive oil painted immediately after UV radiation, although cyclobutane pyrimidine dimers and (6-4) photoproducts were not reduced by olive oil treatment. Our results suggest that daily topical use of super virgin olive oil after sun bathing may delay and reduce UV-induced skin cancer development in human skin, possibly by decreasing ROS-induced 8-OHdG which is responsible for gene mutation.

Ichikawa, M., H. Nakane, et al. (2000). "Decreased UV sensitivity, mismatch repair activity and abnormal cell cycle checkpoints in skin cancer cell lines derived from UVB-irradiated XPA-deficient mice." Mutat Res **459**(4): 285-98.

Xeroderma pigmentosum group A gene (XPA)-deficient mice are defective in nucleotide excision repair (NER) and are therefore highly sensitive to ultraviolet (UV)-induced skin

carcinogenesis. We established cell lines from skin cancers of UVB-irradiated XPA-deficient mice to investigate the phenotypic changes occurring during skin carcinogenesis. As anticipated, the skin cancer cell lines were devoid of NER activity but were less sensitive to killing by UV-irradiation than the XPA(-/-) fibroblast cell line. The lines were also more resistant to 6-thioguanine (6-TG) than XPA(-/-) and XPA(+/+) fibroblasts, which was suggestive of a mismatch repair (MMR) defect. Indeed, in vitro mismatch binding and MMR activity were impaired in several of these cell lines. Moreover, these cell lines displayed cell cycle checkpoint derangements following UV-irradiation and 6-TG exposure. The above findings suggest that MMR downregulation may help cells escape killing by UVB, as was seen previously for methylating agents and cisplatin, and thus that MMR deficient clones are selected for during the tumorigenic transformation of XPA(-/-) cells.

Inga, A., G. Scott, et al. (1998). "Ultraviolet-light induced p53 mutational spectrum in yeast is indistinguishable from p53 mutations in human skin cancer." Carcinogenesis **19**(5): 741-6.

Ultraviolet (UV) light has been associated with the development of human non-melanoma skin cancers (NMSC). Such cancers often exhibit mutations in the p53 tumour suppressor gene. In order to determine the UV-induced p53 mutation spectrum, a yeast expression vector that harbours a human wild-type p53 cDNA was UV-irradiated in vitro and transfected into a yeast strain that contained the ADE2 gene regulated by a p53-responsive promoter. Forty-five mutant clones contained 51 mutations. Seven mutations were tandem base pair substitutions, four of which being CC-->TT, hallmark mutations of UV mutagenesis. Eighty percent (41/51) of the mutations were single or non-tandem base pair substitutions, the majority of which (27/41) were C-->T transitions. Ninety-five percent of such mutations occurred at dipyrimidine sites. Through a rigorous statistical test, the UV-induced p53 mutation spectrum appears to differ significantly ($P < 0.008$) from the one induced by the antineoplastic drug chloroethyl-cyclohexyl-nitrosourea, and to be indistinguishable from the one observed in NMSC ($P = 0.4$). These results demonstrate that the assay allows the determination of carcinogen-specific p53 mutation fingerprints and represents a new tool for molecular epidemiology.

Jackson, S., C. Harwood, et al. (2000). "Role of Bak in UV-induced apoptosis in skin cancer and abrogation by HPV E6 proteins." Genes Dev **14**(23): 3065-73.

Ultraviolet B (UVB) damage is recognized as the most important etiological factor in the development of skin cancer. Human papillomaviruses (HPV) have also been implicated in the disease, although the mechanism of action of these viruses remains unknown. We present evidence here that Bak protein is involved in signaling apoptosis in the skin in response to UVB damage, and that cutaneous HPV E6 proteins target and abrogate Bak function by promoting its proteolytic degradation both in vitro and in regenerated epithelium. Additionally, HPV positive skin cancers had undetectable levels of Bak in contrast to HPV negative cancers, which expressed Bak. This study supports a link between the virus and UVB in the induction of HPV-associated skin cancer and reveals a survival mechanism of virally infected cells.

Jans, J., G. A. Garinis, et al. (2006). "Differential role of basal keratinocytes in UV-induced immunosuppression and skin cancer." Mol Cell Biol **26**(22): 8515-26.

Cyclobutane pyrimidine dimers (CPDs) and 6-4 photoproducts (6-4PPs) comprise major UV-induced photolesions. If left unrepaired, these lesions can induce mutations and skin cancer, which is facilitated by UV-induced immunosuppression. Yet the contribution of lesion and cell type specificity to the harmful biological effects of UV exposure remains currently unclear. Using a series of photolyase-transgenic mice to ubiquitously remove either CPDs or 6-4PPs from all cells in the mouse skin or selectively from basal keratinocytes, we show that the majority of UV-induced acute effects to require the presence of CPDs in basal keratinocytes in the mouse skin. At the fundamental level of gene expression, CPDs induce the expression of genes associated with repair and recombinational processing of DNA damage, as well as apoptosis and a response to stress. At the organismal level, photolyase-mediated removal of CPDs, but not 6-4PPs, from the genome of only basal keratinocytes substantially diminishes the incidence of skin tumors; however, it does not affect the UVB-mediated immunosuppression. Taken together, these findings reveal a differential role of basal keratinocytes in these processes, providing novel insights into the skin's acute and chronic responses to UV in a lesion- and cell-type-specific manner.

Jans, J., W. Schul, et al. (2005). "Powerful skin cancer protection by a CPD-photolyase transgene." Curr Biol **15**(2): 105-15.

BACKGROUND: The high and steadily increasing incidence of ultraviolet-B (UV-B)-induced skin cancer is a problem recognized worldwide. UV introduces different types of damage into the DNA, notably cyclobutane pyrimidine dimers (CPDs) and (6-4) photoproducts (6-4PPs). If unrepaired, these

photolesions can give rise to cell death, mutation induction, and onset of carcinogenic events, but the relative contribution of CPDs and 6-4PPs to these biological consequences of UV exposure is hardly known. Because placental mammals have undergone an evolutionary loss of photolyases, repair enzymes that directly split CPDs and 6-4PPs into the respective monomers in a light-dependent and lesion-specific manner, they can only repair UV-induced DNA damage by the elaborate nucleotide excision repair pathway. RESULTS: To assess the relative contribution of CPDs and 6-4PPs to the detrimental effects of UV light, we generated transgenic mice that ubiquitously express CPD-photolyase, 6-4PP-photolyase, or both, thereby allowing rapid light-dependent repair of CPDs and/or 6-4PPs in the skin. We show that the vast majority of (semi)acute responses in the UV-exposed skin (i.e., sunburn, apoptosis, hyperplasia, and mutation induction) can be ascribed to CPDs. Moreover, CPD-photolyase mice, in contrast to 6-4PP-photolyase mice, exhibit superior resistance to sunlight-induced tumorigenesis. CONCLUSIONS: Our data unequivocally identify CPDs as the principal cause of nonmelanoma skin cancer and provide genetic evidence that CPD-photolyase enzymes can be employed as effective tools to combat skin cancer.

Jiang, W., H. N. Ananthaswamy, et al. (1999). "p53 protects against skin cancer induction by UV-B radiation." Oncogene **18**(29): 4247-53.

To assess the role of the p53 tumor suppressor gene in skin carcinogenesis by UV radiation, mice constitutively lacking one or both copies of the functional p53 gene were compared to wild-type mice for their susceptibility to UV carcinogenesis. Heterozygous mice showed greatly increased susceptibility to skin cancer induction, and homozygous p53 knockout mice were even more susceptible. Accelerated tumor development in the heterozygotes was not associated with loss of the remaining wild-type allele of p53, as reported for tumors induced by other carcinogens, but in many cases was associated with UV-induced mutations in p53. Tumors arose on the ears and dorsal skin of mice of all three genotypes, and homozygous knockout mice also developed ocular tumors, mainly melanomas. Skin tumors in the p53 knockout mice were predominately squamous cell carcinomas and were associated with premalignant lesions resembling actinic keratoses, whereas those in the heterozygous and wild-type mice were mainly sarcomas. These results demonstrate the importance of p53 in protecting against UV-induced cancers, particularly in the eye and epidermis.

Kanjilal, S., S. S. Strom, et al. (1995). "p53 mutations in nonmelanoma skin cancer of the head and neck: molecular evidence for field cancerization." Cancer Res **55**(16): 3604-9.

Multiple and distinct p53 mutations were detected by DNA sequence analysis in tumor and adjacent nonmalignant skin samples from eight patients with nonmelanoma skin cancer of the head and neck, providing unambiguous evidence for field cancerization. The mutations consisted of C-->T transitions at dipyrimidine sequences (30% of all single base substitutions), T-->C transitions (47%), and G-->T transversions (12%), suggesting that other carcinogens may act along with UV radiation in the development of nonmelanoma skin cancer. Patient interviews revealed that, in addition to substantial exposure to solar UV radiation, most had a history of smoking and were exposed to carcinogens from industrial or agricultural sources. These data show that extensive molecular epidemiological investigations are necessary to elucidate risk factors associated with the disease in localities where patients often report substantial exposure to environmental carcinogens.

Kassem, A., K. Technau, et al. (2009). "Merkel cell polyomavirus sequences are frequently detected in nonmelanoma skin cancer of immunosuppressed patients." Int J Cancer **125**(2): 356-61.

Recently, a new human polyoma virus has been identified in Merkel cell carcinomas (MCC). MCC is a highly aggressive neuroendocrine nonmelanoma skin cancer (NMSC) associated with immunosuppression. Clonal integration of this virus which was termed Merkel cell polyoma virus (MCPyV) was reported in a number of MCC. Squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are also NMSC and are the most frequent cancers in the setting of immunosuppression. A unique group of 56 NMSC from 11 immunosuppressed patients and 147 NMSC of 125 immunocompetent patients was tested for MCPyV by DNA PCR, targeting the Large T Antigen and the structural Viral Protein 1. NMSC included SCC, BCC and Bowen's disease (BD). In addition, normal skin and 89 colorectal cancers were tested. MCPyV specific sequences were significantly more frequently found in NMSC of immunosuppressed patients compared to immunocompetent patients ($p < 0.001$). In particular BD and BCC revealed a significant increased association of MCPyV of immunosuppressed patients ($p = 0.002$ and $p = 0.006$). Forty-seven of 147 (32%) sporadic NMSC were MCPyV positive. Interestingly, 37.5% (36/96) of sporadic BCC of immunocompetent patients were MCPyV positive. No MCPyV was detected within normal skin and only 3 out of 89 of additionally tested

colorectal cancers were MCPyV positive. Our data show that MCPyV is a frequently reactivated virus in immunocompromized patients. How MCPyV contributes to the pathogenesis of NMSC, i.e., BD, SCC and BCC, in immunosuppressed patients and in addition, potentially to the pathogenesis of a subset of sporadic BCC needs further investigations.

Kemp, C. J. (2005). "Multistep skin cancer in mice as a model to study the evolution of cancer cells." Semin Cancer Biol **15**(6): 460-73.

Although much of cancer research relies on Nowell's clonal evolution hypothesis as a conceptual framework, large gaps remain in understanding how tumors develop. The multistage skin cancer model in mice provides continuing insight on fundamental aspects of tumor evolution. In this model, mutation of the oncogene Hras is frequently the initiating event while mutation of the tumor suppressor p53 is a late event, associated with malignant progression. Recent evidence demonstrates that intracellular signaling from the initial Hras mutation leads directly to the activation of p53, creating selective pressure in favor of cells with mutant p53. Thus, selection for subsequent mutations is mechanistically linked to the initial mutation, explaining the preferred order of mutational events observed. Analysis of this model also reveals that a diverse array of signals can selectively impair or enhance clonal expansion of Ras mutant cells into a visible neoplasm. These modifiers can be genetic, physiological, or environmental and are often highly specific to tumor cells. This indicates that tumor cells have an inherent reduced capacity to buffer against perturbations. Reduced buffering may play an important role in both tumor evolution and therapy response and may be a hallmark of cancer cells.

Kennedy, C., A. Naipal, et al. (2002). "MICA gene polymorphism is not associated with an increased risk for skin cancer." J Invest Dermatol **118**(4): 686-91.

The MICA gene encodes for major histocompatibility complex class I chain-related proteins (MIC), which belong to a recently identified new family of nonclassical major histocompatibility complex molecules. The general structure of the MICA molecule resembles that of major histocompatibility complex class I molecules. MIC molecules are considered to be stress-induced antigens that are recognized by cytotoxic T cells and natural killer cells, which play an important role in the surveillance of transformed infected and damaged cells. Associations of major histocompatibility complex class I molecules with skin cancer have been described before. To evaluate the possible association of MICA gene polymorphism with the risk for nonmelanoma skin cancer we evaluated 153 cases with squamous cell carcinoma, 261 cases with basal cell carcinoma, 111 controls with malignant melanoma, and 247 controls without a history of skin cancer. Five distinct MICA alleles A4, A5, A6, A9, and A5.1 were studied. As the MICA 5.1 variant gene contains a four-nucleotide insertion that causes a stop codon in the trans membrane region, the resulting truncated MICA molecule does not reside on the cellular membrane. In the case of individuals who are homozygous for MICA 5.1 this results in cells that are naked for the MICA molecule. We therefore specifically addressed the possible association between MICA 5.1 homozygosity and skin cancer, as these individuals are expected to be at the highest risk for skin cancer if the MICA gene plays a role in skin carcinogenesis. Viral proteins may serve as antigens for recognition of skin cancer by the immune system. Human papillomavirus is the most likely candidate virus to be involved in the carcinogenesis of cutaneous squamous cell carcinoma. Hence, we also assessed the association between MICA polymorphism and squamous cell carcinoma in human-papillomavirus-positive and human-papillomavirus-negative individuals as identified by the presence of human papillomavirus DNA in hairs plucked from their eyebrows. Our analyses did not reveal any significant differences regarding the MICA allele frequencies between cases and controls. Also homozygotes and heterozygotes for the MICA 5.1 variant gene were not at an increased risk for skin cancer compared to individuals without this variant gene and infection with human papillomavirus did not materially influence these findings. The same group of cases and controls was large enough to show an association between melanocortin 1 receptor gene polymorphism and skin cancer and to reasonably exclude an association between p53 codon 72 polymorphism and skin cancer. Therefore, we conclude that an association between MICA gene polymorphism and nonmelanoma skin cancer is not likely.

Kerkela, E., R. Ala-Aho, et al. (2000). "Expression of human macrophage metalloelastase (MMP-12) by tumor cells in skin cancer." J Invest Dermatol **114**(6): 1113-9.

Matrix metalloproteinases play an essential role in tumor growth and invasion. Different matrix metalloproteinases are often expressed in cancers with distinct patterns. To investigate the role of human macrophage metalloelastase (MMP-12) in epidermal tumors, we studied human macrophage metalloelastase mRNA and protein expression in malignant squamous cell and basal cell carcinomas, and in premalignant Bowen's disease. Human

macrophage metalloelastase was detected in 11 of 17 squamous cell carcinomas in epithelial cancer cells, whereas macrophages were positive in 15 of 17 samples. In basal cell carcinomas, human macrophage metalloelastase was more often found in macrophages (seven of 19) than in cancer cells (four of 19). Human macrophage metalloelastase mRNA was also detected in three cell lines derived from squamous cell carcinomas of the head and neck and in transformed HaCaT cells, whereas premalignant tumors and primary keratinocytes were negative for human macrophage metalloelastase mRNA. Western analysis revealed human macrophage metalloelastase protein in squamous cell carcinoma cells. Our results show that human macrophage metalloelastase can be expressed in vivo and in vitro by transformed epithelial cells and indicate that the level of human macrophage metalloelastase expression correlates with epithelial dedifferentiation and histologic aggressiveness.

Khavari, P. A. (2006). "Modelling cancer in human skin tissue." Nat Rev Cancer **6**(4): 270-80.

The capacity to induce neoplasia in human tissue in the laboratory has recently provided a new platform for cancer research. Malignant conversion can be achieved in vivo by expressing genes of interest in human tissue that has been regenerated on immune-deficient mice. Induction of cancer in regenerated human skin recapitulates the three-dimensional architecture, tissue polarity, basement membrane structure, extracellular matrix, oncogene signalling and therapeutic target proteins found in intact human skin in vivo. Human-tissue cancer models therefore provide an opportunity to elucidate fundamental cancer mechanisms, to assess the oncogenic potency of mutations associated with specific human cancers and to develop new cancer therapies.

Kondoh, M., M. Ueda, et al. (1994). "Siblings with xeroderma pigmentosum complementation group A with different skin cancer development: importance of sun protection at an early age." J Am Acad Dermatol **31**(6): 993-6.

BACKGROUND: For patients with xeroderma pigmentosum (XP), strict protection from UV light exposure is the only way to prevent and retard skin cancer formation. OBJECTIVE: Our purpose was to learn how the timing of sun protection influences the clinical findings in patients with XP. METHODS: We studied two siblings with XP group A (XPA) who showed a significant difference in the age at onset of skin cancer development and in neurologic abnormalities. RESULTS: The elder sister had had her first basal cell carcinoma (BCC) at 13 years of age and had had multiple BCCs by 25 years of age. Her younger sister had her first BCC at 23 years of age. Neurologic impairment of the younger sister was much milder. The elder sister started strict sun protection at 4 years of age, whereas the younger began at 2 years of age. Analysis of the XPA complementing gene revealed that both patients had the identical mutation. CONCLUSION: In patients with XP the earlier sun protection begins the later skin cancer develops. Neurologic deterioration may also be reduced by earlier sun protection.

Kowalczyk, M. C., Z. Walaszek, et al. (2009). "Differential effects of several phytochemicals and their derivatives on murine keratinocytes in vitro and in vivo: implications for skin cancer prevention." Carcinogenesis **30**(6): 1008-15.

The purpose of our study was to investigate in vitro the potential cancer preventive properties of several phytochemicals, i.e. grape seed extract (GSE), resveratrol (RES), ursolic acid (URA), ellagic acid (ELA), lycopene and N-acetyl-L-cysteine (NAC) to define the mechanisms by which these compounds may inhibit murine skin carcinogenesis. We measured quenching of peroxyl, superoxide and hydroxyl radicals by these phytochemicals. We also used adenosine triphosphate (ATP) bioluminescence, Caspase-Glo 3/7 and P450-Glo (CYP1A1 and CYP1B1) assays to study antiproliferative, proapoptotic and CYP-inhibiting effects of the phytochemicals. We next determined their effects on a 4 week inflammatory hyperplasia assay using 7,12-dimethylbenz[a]anthracene-induced murine skin carcinogenesis model to further understand their mechanism of action. Three murine keratinocyte cell lines, i.e. non-tumorigenic (3PC), papilloma-derived (MT1/2) and squamous cell carcinoma-derived (Ca3/7) cell lines, were used in in vitro assays. We have found that GSE, ELA and RES are potent scavengers of peroxyl and superoxide radicals. Statistically significant effects on activities of caspase-3 and -7 were observed only after GSE and URA treatments. All tested compounds protected cells from hydrogen peroxide-induced DNA damage. Using a short-term complete carcinogenesis assay, we have found that all selected compounds caused marked decreases of epidermal thickness and (except RES) reduced percentages of mice with mutation in codon 61 of Ha-ras oncogene. In conclusion, differential effects of tested phytochemicals on events and processes critical for the growth inhibition of keratinocytes in vitro and in vivo indicate that combinations of tested compounds may, in the future, better counteract both tumor initiation and tumor promotion/progression.

Krahn, G., U. Leiter, et al. (2001). "Coexpression patterns of EGFR, HER2, HER3 and HER4 in non-melanoma skin cancer." Eur J Cancer **37**(2): 251-9.

The receptor tyrosine kinases (RTKs) epidermal growth factor receptor (EGFR), HER2, HER3 and HER4 are involved in the pathogenesis of multiple human malignant neoplasias. However, their role in the carcinogenesis of basal cell carcinomas (BCC) and squamous cell carcinomas (SCC) remains to be elucidated. In order to further define the role of these RTKs, 56 human skin tissue samples of normal skin, BCC and SCC were studied by conventional and differential and quantitative reverse transcriptase-polymerase chain reaction (rtPCR). EGFR and HER3 were predominantly expressed in the BCCs and SCCs, while HER2 was ubiquitously expressed. HER4 was not expressed in any sample. Since in vitro studies have provided compelling evidence that heterodimer formation of these receptors are associated with different signal transduction processes, coexpression patterns might be decisive for the induction and maintenance of a malignant phenotype. These results confirm this concept: isolated HER2 expression and EGFR/HER2 were predominantly found in normal skin, while HER2/HER3 and the triple expression of EGFR/HER2/HER3 were seen more frequently in the BCCs and SCCs compared with normal skin (50% and 40% compared with 26%, respectively). The activation of HER3, in addition to EGFR and HER2, might therefore be associated with the malignant phenotype. However, due to the small numbers in this study, further confirmation of the patterns is needed.

Krahn, G., U. Leiter, et al. (2001). "UVB-induced decrease of p16/CDKN2A expression in skin cancer patients." Pigment Cell Res **14**(3): 201-5.

The lack of p16 expression has been shown in cultured melanoma cells, however contradictory evidence for p16 expression in melanoma tissues exist. Ultraviolet (UV) C and UVB have been shown to affect p16 expression, which impairs cell cycle regulation in vitro and in vivo. In this study, p16/CDKN2A gene expression was determined by reverse transcription polymerase chain reaction in seven skin cancer patients, in one dysplastic nevus patient and in seven healthy individuals, prior to UVB exposure and at various times after application of one minimal erythema dose (MED). Five of the seven skin cancer patients showed a down-regulation of p16/CDKN2A expression after UVB exposure, while controls remained unaltered. The UVB-induced decline of p16/CDKN2A in skin cancer patients might offer new insights into photocarcinogenesis. The putative sequence of events could start with a down-regulation of p16/CDKN2A expression, which would lead to impaired cell cycle regulation. Altered expression patterns of p16/CDKN2A following UVB exposure could be of value for identifying people with an increased risk of UV-induced skin cancer.

Kruse, R. and T. Ruzicka (2004). "DNA mismatch repair and the significance of a sebaceous skin tumor for visceral cancer prevention." Trends Mol Med **10**(3): 136-41.

DNA mismatch repair is a postreplicative DNA repair cascade ensuring genomic integrity. Inactivating germline mutations in DNA mismatch repair genes are responsible for hereditary non-polyposis colorectal carcinoma syndrome (HNPCC), which predisposes to various types of visceral cancer. Most associated tumors exhibit high-grade microsatellite instability. Some patients develop skin tumors of the sebaceous glands. This combined occurrence is known as Muir-Torre syndrome, which has a high probability of an underlying DNA mismatch repair defect. This is also true for individuals selected solely on the basis of sebaceous neoplasias, tumors with the highest frequency of high-grade microsatellite instability. This article focuses on the recent advances in molecular diagnostics for the detection of DNA mismatch repair defects in patients with sebaceous neoplasias, and the potential significance for the secondary prevention of visceral cancer in these patients.

Laing, M. E., E. Kay, et al. (2007). "Genetic factors associated with skin cancer in renal transplant patients." Photodermatol Photoimmunol Photomed **23**(2-3): 62-7.

BACKGROUND: Non-melanoma skin cancer represents a significant cause of morbidity and mortality among renal transplant recipients. Established risk factors that increase susceptibility to skin cancer after transplantation include skin type, sun exposure and level of immunosuppression. METHODS: A comprehensive literature review was carried out to discuss relevant genetic polymorphism for the development of skin cancer in organ transplant recipients. These include genetic polymorphisms in glutathione S-transferase, interleukin-10, retinoblastoma and p53 genes. We also discuss genetic polymorphisms in the folate pathway, melanocortin 1 receptor and vitamin D receptor recently discovered in our group. RESULTS: No single factor is causative in cutaneous carcinogenesis in transplant recipients. Interactions of some of the above mechanisms with known environmental factors lead to increased risk. CONCLUSION: Polymorphisms in methylenetetrahydrofolate reductase are potentially correctable with folic acid supplementation; however, further evaluation is required in adequately powered prospective clinical

trials. Avoidance of known oncogenic environmental factors and genetic risk evaluation may improve outcomes in transplant patients.

Lambert, P. F., H. Pan, et al. (1993). "Epidermal cancer associated with expression of human papillomavirus type 16 E6 and E7 oncogenes in the skin of transgenic mice." Proc Natl Acad Sci U S A **90**(12): 5583-7.

Certain "high-risk" anogenital human papillomaviruses (HPVs) have been associated with the majority of human cervical carcinomas. In these cancers, two papillomaviral genes, E6 and E7, are commonly expressed. In this study we provide evidence that expression of the E6 and E7 genes from the high-risk HPV-16 in the skin of transgenic mice potentiated the development of preneoplastic lesions, and a high percentage of these epidermal lesions subsequently developed into locally invasive cancers. High levels of E6/E7 expression were found in these tumors relative to the preneoplastic lesions, and expression was localized to the proliferating, poorly differentiated epidermal cells. Also, the p53 and Rb genes were found to be intact, not mutationally inactivated, in representative skin tumors. These findings demonstrate that the E6 and E7 genes from a papillomavirus etiologically associated with human cervical cancer can contribute to the development of epidermal cancers in an animal model.

Lawrence, N. J., L. Song, et al. (2009). "Topical thymidine dinucleotide application protects against UVB-induced skin cancer in mice with DNA repair gene (Ercc1)-deficient skin." DNA Repair (Amst) **8**(5): 664-71.

Topical application of thymidine dinucleotides (pTpT) provides some protection against the effects of UV on the skin, however, many details of the protective mechanism have yet to be elucidated. We have used mice with an epidermis-specific knockout for the nucleotide excision repair gene, Ercc1, to investigate the mechanisms of protection. pTpT offered no protection against the pronounced UV-induced short-term erythema and skin thickening responses that are characteristic of DNA repair-deficient skin. It also had no effect on UV-induced apoptosis in Ercc1-deficient cultured keratinocytes. However, in these short-term experiments in both skin and keratinocyte culture pTpT did cause a slight reduction in proliferation. pTpT application during a chronic UV irradiation protocol provided some protection from UVB-induced skin carcinogenesis in epidermis-specific Ercc1 knockout mice. The median tumour free survival time was increased in the pTpT-treated group and treated animals had fewer tumours. In addition, pTpT-treated animals developed fewer large inwardly growing skin lesions than untreated animals. Furthermore, the proliferation response was reduced in chronically irradiated, non-lesional pTpT-treated skin. We conclude that cancer protection by pTpT in our mice is not modulated by an upregulation of DNA repair, as protection appears to be independent of a functional nucleotide excision repair pathway. We hypothesise instead that protection by pTpT is due to a reduction in epidermal proliferation.

Leffell, D. J. (2000). "The scientific basis of skin cancer." J Am Acad Dermatol **42**(1 Pt 2): 18-22.

BACKGROUND: Mutations in tumor suppressor gene p53 are very common in many human cancers. They are present in more than 90% of squamous cell carcinomas (SCCs) and are usually found in actinic keratoses (AKs). Data demonstrate a strong relationship between the early effects of ultraviolet radiation (UVR) on p53 in skin and the development of AK and SCC. OBJECTIVE: The purpose of this article is to review specific data about the p53 tumor suppressor gene, UVR, and their interaction to cause AKs. METHODS: The published, peer-reviewed literature is reviewed and a published proposal for the mechanism for UVR-induced carcinogenesis is explained. RESULTS: The specific effect of UVR on the p53 tumor suppressor gene, including its impact on apoptosis, in humans, and in animals, suggests a cause-effect relationship between UVR and the earliest mutations seen in AKs. CONCLUSION: AKs result from UVR in a process by which UVR mutates a known tumor suppressor gene (p53). It is likely that the mutated cells expand preferentially in a clonal fashion at the expense of the normal surrounding keratinocytes to develop into a clinical lesion of AK.

Letarte, S., M. Y. Brusniak, et al. (2008). "Differential Plasma Glycoproteome of p19 Skin Cancer Mouse Model Using the Corra Label-Free LC-MS Proteomics Platform." Clin Proteomics **4**(3-4): 105.

A proof-of-concept demonstration of the use of label-free quantitative glycoproteomics for biomarker discovery workflow is presented here, using a mouse model for skin cancer as an example. Blood plasma was collected from 10 control mice, and 10 mice having a mutation in the p19(ARF) gene, conferring them high propensity to develop skin cancer after carcinogen exposure. We enriched for N-glycosylated plasma proteins, ultimately generating deglycosylated forms of the modified tryptic peptides for liquid chromatography mass spectrometry (LC-MS) analyses. LC-MS runs for each sample were then performed with a view to identifying proteins that were differentially abundant between the two mouse

populations. We then used a recently developed computational framework, Corra, to perform peak picking and alignment, and to compute the statistical significance of any observed changes in individual peptide abundances. Once determined, the most discriminating peptide features were then fragmented and identified by tandem mass spectrometry with the use of inclusion lists. We next assessed the identified proteins to see if there were sets of proteins indicative of specific biological processes that correlate with the presence of disease, and specifically cancer, according to their functional annotations. As expected for such sick animals, many of the proteins identified were related to host immune response. However, a significant number of proteins also directly associated with processes linked to cancer development, including proteins related to the cell cycle, localisation, trasport, and cell death. Additional analysis of the same samples in profiling mode, and in triplicate, confirmed that replicate MS analysis of the same plasma sample generated less variation than that observed between plasma samples from different individuals, demonstrating that the reproducibility of the LC-MS platform was sufficient for this application. These results thus show that an LC-MS-based workflow can be a useful tool for the generation of candidate proteins of interest as part of a disease biomarker discovery effort.

Lin, C. C., M. C. Yen, et al. (2008). "Delivery of noncarrier naked DNA vaccine into the skin by supersonic flow induces a polarized T helper type 1 immune response to cancer." J Gene Med **10**(6): 679-89.

BACKGROUND: DNA vaccine is a new and powerful approach to generate immunological responses against infectious disease and cancer. The T helper type (Th)1 immune response is usually required for generating effective anti-tumor responses. A microparticulate bombardment system can induce an immune response using very low amounts of DNA. Using nozzle aerodynamics, a low pressure gene gun has been developed to decrease the noise associated with high pressure gene guns. Particles are propelled by supersonic flow through this novel nozzle. To test whether this gun could inoculate a DNA vaccine that stimulates an anti-tumor Th1 immune response, we examined the effect of direct delivery of naked DNA (i.e. without any carrier) on the anti-tumor immune response of mice. METHODS: The luciferase reporter plasmid DNA was delivered using a low-pressure biolistic device and expressed in C3H/HeN, BALB/c, and C57BL/6 mice. RESULTS: Plasmid DNA expression was mainly in the epidermis. Noncarrier naked neu DNA vaccine and gold particle-coated neu DNA vaccine (at 1 microg per mouse) had similar anti-tumor effects in C3H mice. However, cytokine profile examination showed the Th1-bias of the response induced by naked DNA vaccine and the Th2-bias of the response induced by coated DNA vaccine. CONCLUSIONS: A shift in the immune response to favour enhanced tumor rejection can be achieved by skin delivery of naked DNA vaccine.

Lin, S. L., D. C. Chang, et al. (2008). "Mir-302 reprograms human skin cancer cells into a pluripotent ES-cell-like state." Rna **14**(10): 2115-24.

Renewal of stem cells differs from cancer cell growth in self-controlled cell division. The mir-302 microRNA (miRNA) family (mir-302s) is expressed most abundantly in slow-growing human embryonic stem (ES) cells, and quickly decreases after cell differentiation and proliferation. Therefore, mir-302s was investigated as one of the key factors essential for maintenance of ES cell renewal and pluripotency in this study. The Pol-II-based intronic miRNA expression system was used to transgenically transfect the mir-302s into several human cancer cell lines. The mir-302-transfected cells, namely, miRNA-induced pluripotent stem (mirPS) cells, not only expressed many key ES cell markers, such as Oct3/4, SSEA-3, SSEA-4 ,Sox2, and Nanog, but also had a highly demethylated genome similar to a reprogrammed zygotic genome. Microarray analyses further revealed that genome-wide gene expression patterns between the mirPS and human ES H1 and H9 cells shared over 86% similarity. Using molecular guidance in vitro, these mirPS cells could differentiate into distinct tissue cell types, such as neuron-, chondrocyte-, fibroblast-, and spermatogonia-like primordial cells. Based on these findings, we conclude that mir-302s not only function to reprogram cancer cells into an ES-like pluripotent state but also to maintain this state under a feeder-free cultural condition, which may offer a great opportunity for therapeutic intervention.

Lira, M. G., S. Mazzola, et al. (2007). "Association of functional gene variants in the regulatory regions of COX-2 gene (PTGS2) with nonmelanoma skin cancer after organ transplantation." Br J Dermatol **157**(1): 49-57.

BACKGROUND: Overexpression of cyclooxygenase-2 (COX-2), resulting in excessive prostaglandin production, has been observed in human epidermal keratinocytes after ultraviolet B injury, in squamous cell skin carcinoma (SCC), in actinic keratoses, and in the early stages of carcinogenesis in a wide variety of tissues. The dysregulation of COX-2 expression can in part be due to functional changes affecting regulatory elements in the promoter or 3' untranslated region (UTR) of the gene. Two common

polymorphisms (-765G-->C, and -1195A-->G) in the promoter region of the COX-2 gene (now PTGS2), and one common polymorphism in the 3' UTR (8473T-->C) have been described, and reported as associated with various malignancies. OBJECTIVES: To determine if common known polymorphisms in the regulatory region of the COX-2 gene (PTGS2) can be associated with nonmelanoma skin cancer (NMSC) predisposition after organ transplantation, to evaluate if cancer risks are associated with specific COX-2 gene (PTGS2) haplotypes containing these polymorphisms, and to identify possible new genetic polymorphisms in the proximal 5' or 3' regulatory regions of the gene associated with disease. METHODS: The frequency of the three polymorphisms was determined in 240 Northern Italian transplant recipient patients (107 cases and 133 controls) with polymerase chain reaction-restriction fragment length polymorphism analysis. The proximal 5' and 3' regulatory regions of the gene were screened by heteroduplex analysis. RESULTS: Stratification by age at transplant and type of tumours [SCC or basal cell carcinoma (BCC)] demonstrated that allele -765C represented a protective factor in BCC cases undergoing transplantation before 50 years of age (CC + CG vs. GG, Fisher exact test P = 0.003). One rare polymorphism, -62C-->G, was detected in the 5' flanking region. The allele frequency of -62G was 0.019, and no difference in genotype between cases and controls was observed. No other variants were found, suggesting that sequence variations in these regions are not likely to contribute to NMSC risk in this population. Haplotype analysis showed that the haplotype containing all major alleles represents a protective factor in patients with SCC undergoing transplantation after 50 years of age [P = 0.009; OR = 0.37 (0.18-0.79)] and that variant -1195A-->G may represent a risk factor in this subgroup of patients [P = 0.01; OR = 4.77 (1.47-16.41)]. Haplotype analysis in patients with BCC revealed that variant -765C might be a protective factor in patients undergoing transplantation before 50 years of age. Variant 8473T-->C, located in the 3' UTR region of the gene, showed no association with NMSC risk after transplantation. CONCLUSIONS: COX-2 common variants -765G-->C and -1195A-->G appear to be associated with risk of NMSC, although in different ways in the SCC and BCC subgroups, indicating that environmental and genetic risk factors may play different roles in the outcome leading to these two phenotypes.

Lira, M. G., L. Provezza, et al. (2006). "Glutathione S-transferase and CYP1A1 gene polymorphisms and non-melanoma skin cancer risk in Italian transplanted patients." Exp Dermatol **15**(12): 958-65.

Solid organ transplant recipients are at higher risk of non-melanoma skin cancer (NMSC), especially basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). Genetic alterations in the production of detoxifying enzymes such as glutathione S-transferase (GST) and CYP1A1 may enhance this risk. We investigated the frequency of GST genotypes (GSTM1, GSTM3, GSTT1 and GSTP1) and CYP1A1 in 239 transplant recipients: 107 cases with NMSC and 132 controls free from NMSC matched for type of transplanted organ, duration of transplantation, sex and age. Allele GSTP1*A was associated with a higher risk of NMSC [odds ratio (OR) 1.7 (1.1-2.5); P = 0.017]. Homozygosity for allele GSTP1 Val(105) was lower in cases [OR 0.3 (0.1-0.8); P = 0.012], especially in patients with SCC [OR 0.1 (0.0-0.7); P = 0.012]. A higher risk of BCC was found in patients with GSTM1 null/null [null/null versus A + B, OR 3.1 (1.4-6.8); P = 0.003]. Analysis of allelism and interaction between allelic variants showed significant association between combined GSTM1 and CYP1A1 Val(462) genotypes, where individuals homozygous for the risk allele GSTM1 null and carrying also the allele CYP1A1 Val(462), show a higher risk of developing NMSC [OR 4.5 (1.1-21.4); P = 0.03], especially SCC [OR 6.5 (1.4-34.4); P = 0.01]. GSTP1 polymorphisms are associated with both BCC and SCC risk. GSTM1 polymorphisms seem to be involved in BCC risk, while GSTM1 null/null genotype combined with CYP1A1 allele Val(462) are associated with a higher risk for SCC, indicating that allelism and/or interactions between allelic variants at other loci may also influence the risk of NMSC, particularly SCC.

Liu, B., X. Xia, et al. (2008). "IKKalpha is required to maintain skin homeostasis and prevent skin cancer." Cancer Cell **14**(3): 212-25.

It has long been known that excessive mitotic activity due to H-Ras can block keratinocyte differentiation and cause skin cancer. It is not clear whether there are any innate surveillants that are able to ensure that keratinocytes undergo terminal differentiation, preventing the disease. IKKalpha induces keratinocyte terminal differentiation, and its downregulation promotes skin tumor development. However, its intrinsic function in skin cancer is unknown. Here, we found that mice with IKKalpha deletion in keratinocytes develop a thickened epidermis and spontaneous squamous cell-like carcinomas. Inactivation of epidermal growth factor receptor (EGFR) or reintroduction of IKKalpha inhibits excessive mitosis, induces terminal differentiation, and prevents skin cancer through

repressing an EGFR-driven autocrine loop. Thus, IKKalpha serves as an innate surveillant.

Luscombe, C. J., M. E. French, et al. (2001). "Outcome in prostate cancer associations with skin type and polymorphism in pigmentation-related genes." Carcinogenesis **22**(9): 1343-7.

Epidemiological studies have suggested that UV exerts a protective effect on prostate cancer. Accordingly, we determined, in 210 prostate cancer cases, whether parameters of exposure, skin type and polymorphism in MC1R, VDR and TYR were associated with the outcome parameters, histological grade, clinical stage and presence of bone metastases. We used logistic regression analysis, with correction for age and metastases, stage and grade in the models, to determine if the frequencies of individual factors were different in the patient groups. The development of metastases was not associated with UV exposure parameters. Paradoxically, patients with skin type 1 were at significantly reduced risk [P = 0.027, odds ratio (OR) 0.17, 95% CI 0.03-0.82] of developing metastases compared with cases with skin type 4. MC1R Val92/Val92 and VDR ff were associated with increased risk of metastases (ORs 4.30 and 4.98, respectively). Further, cumulative exposure (P = 0.005, OR 0.85/year) and increasing proportion of outdoor occupation (P = 0.001, OR 0.84/unit) were associated with reduced risk of advanced stage tumours. Skin types, MC1R or VDR genotypes were not significantly associated with advanced stage. None of the exposure parameters, skin types or genotypes were associated with tumour grade. While MC1R Val92/Val92 and VDR ff were only associated with bone metastases, TYR genotypes were associated with each of the outcome parameters. Thus, in logistic regression models that included age, but not advanced stage and high grade histology, TYR A1A2 was significantly associated with reduced risk of metastases (P = 0.033, OR 0.41). Similarly, in models that included age but not the other outcome parameters, associations between TYR A2A2 and high-grade and advanced stage were significant (P = 0.040, OR 0.41) or approached significance (P = 0.052, OR 0.44), respectively. These data indicate for the first time that pigmentation response to UV is associated with outcome in prostate cancer.

Ma, C., K. M. Quesnelle, et al. (2009). "Characterization CSMD1 in a large set of primary lung, head and neck, breast and skin cancer tissues." Cancer Biol Ther **8**(10): 907-16.

The Cub and Sushi Multiple Domains-1 (CSMD1) is a tumor suppressor gene on 8p23.2, where allelic loss is both frequent and associated with poor prognosis in head and neck squamous cell carcinoma (HNSCC). To understand the extent of CSMD1 aberrations in vivo, we characterized 184 primary tumors from the head and neck, lung, breast and skin for gene copy number and analyzed expression in our HNSCCs and lung squamous cell carcinomas (SCCs). We detected loss of CSMD1 in a large proportion of HNSCCs (50%), lung (46%) and breast cancers (55%), and to a lesser extent in cutaneous SCCs (29%) and basal cell carcinomas (BCCs, 17%) using array-based comparative genomic hybridization (aCGH). Studying the region more closely with quantitative real-time PCR (qPCR), the loss of CSMD1 increased to 80% in HNSCCs and 93% in lung SCCs. CSMD1 expression was decreased in tumors compared to adjacent benign tissue (65%, 13/20) and was likely due to gene loss in 45% of cases (9/20). We also identified truncated transcripts lacking exons due to DNA copy number loss (30%, 5/17) or aberrant splicing (24%, 4/17). We show loss of CSMD1 in primary HNSCC tissues, and document for the first time that CSMD1 is lost in breast, lung and cutaneous SCCs. We also show that deletions of CSMD1 and aberrant splicing contribute to altered CSMD1 function in vivo.

Mahler, K. L., J. L. Fleming, et al. (2008). "Sequence divergence of Mus spretus and Mus musculus across a skin cancer susceptibility locus." BMC Genomics **9**: 626.

BACKGROUND: Mus spretus diverged from Mus musculus over one million years ago. These mice are genetically and phenotypically divergent. Despite the value of utilizing M. musculus and M. spretus for quantitative trait locus (QTL) mapping, relatively little genomic information on M. spretus exists, and most of the available sequence and polymorphic data is for one strain of M. spretus, Spret/Ei. In previous work, we mapped fifteen loci for skin cancer susceptibility using four different M. spretus by M. musculus F1 backcrosses. One locus, skin tumor susceptibility 5 (Skts5) on chromosome 12, shows strong linkage in one cross. RESULTS: To identify potential candidate genes for Skts5, we sequenced 65 named and unnamed genes and coding elements mapping to the peak linkage area in outbred spretus, Spret/EiJ, FVB/NJ, and NIH/Ola. We identified polymorphisms in 62 of 65 genes including 122 amino acid substitutions. To look for polymorphisms consistent with the linkage data, we sequenced exons with amino acid polymorphisms in two additional M. spretus strains and one additional M. musculus strain generating 40.1 kb of sequence data. Eight candidate variants were identified that fit with the linkage data. To determine the degree of variation across M. spretus, we conducted phylogenetic analyses. The relatedness of the M.

spretus strains at this locus is consistent with the proximity of region of ascertainment of the ancestral mice. CONCLUSION: Our analyses suggest that, if Skts5 on chromosome 12 is representative of other regions in the genome, then published genomic data for Spret/EiJ are likely to be of high utility for genomic studies in other M. spretus strains.

Marks, F., G. Furstenberger, et al. (2003). "Mouse skin as a model for cancer chemoprevention by nonsteroidal anti-inflammatory drugs." Recent Results Cancer Res **163**: 46-57; discussion 264-6.

The mouse skin model of multistage carcinogenesis has demonstrated that cancer results from a synergism between genotoxic and nongenotoxic factors. The former induce irreversible genetic alterations, whereas the latter promote tumor development by favoring the clonal outgrowth of the genetically altered cells. While therapeutic gene repair is a still unrealized dream, tumor promotion provides an attractive target for cancer prevention. A key event in epithelial tumor development is an aberrant constitutive overexpression of cyclooxygenase-2 (COX-2), being detectable already in premalignant lesions and leading to an overproduction of prostaglandins. In the mouse skin model, prostaglandin F2alpha has been identified as an endogenous tumor promoter. The well-established chemopreventive effect of nonsteroidal anti-inflammatory drugs seems to be mainly due to COX-2 inhibition. Targeted transgenic overexpression of COX-2 in mouse epidermis induces a preneoplastic phenotype and renders the tissue extremely sensitive to genotoxic carcinogens; i.e., for the induction of skin tumor development, tumor promoter treatment can be omitted in those animals. It is concluded that COX-2 acts as an endogenous tumor promoter and that its overexpression represents a first order risk factor for cancer development. Conversely, specific COX-2 inhibitors rank among the most promising agents for cancer chemoprevention.

Marshall, S. E., C. Bordea, et al. (2000). "Glutathione S-transferase polymorphisms and skin cancer after renal transplantation." Kidney Int **58**(5): 2186-93.

BACKGROUND: Susceptibility to skin cancer after transplantation is multifactorial, and risk factors include skin type, sun exposure, and level of immunosuppression. A major mechanism of carcinogenesis is ultraviolet radiation-induced free radical damage, and genetically determined ability to metabolize free radicals may also predispose to skin cancer. The glutathione S-transferase enzymes play a major role in limiting the toxic effects of reactive oxygen species, and this study was designed to determine whether polymorphisms in these enzymes are associated with skin cancers in renal transplant recipients. METHODS: Two hundred twenty-two long-term survivors of renal transplantation were examined for polymorphisms in the GSTM1, GSTT1, and GSTP1 genes, using a unified polymerase chain reaction with sequence specific primers (PCR-SSP) genotyping method. RESULTS: The GSTP1*C allele was associated with the development of squamous cell carcinomas (SCCs; P = 0.01). No associations of the GSTM1 null genotype or the GSTT1 null genotype were identified, and the development of basal cell carcinomas was not associated with any GST polymorphism studied. CONCLUSIONS: These results indicate that genetic variation in enzymes involved in free radical metabolism in the skin are associated with the development of skin cancer. While all renal transplant recipients should be advised to protect themselves from the sun, the identification of transplant patients with a genetic predisposition to skin tumors may permit the targeting of preventative and early intervention strategies to high-risk individuals.

Marshall, S. E., C. Bordea, et al. (2000). "p53 codon 72 polymorphism and susceptibility to skin cancer after renal transplantation." Transplantation **69**(5): 994-6.

BACKGROUND: Infection with human papillomavirus (HPV) is an important risk factor for the development of skin cancer after renal transplantation. It has recently been suggested that degradation of the tumor suppressor gene p53 is an important mechanism for human papillomavirus-induced carcinogenesis. A common genomic polymorphism occurs at codon 72 of the p53 gene, and in vitro the codon 72Arg variant appears to be particularly susceptible to degradation. METHODS: To test the hypothesis that this polymorphism predisposes to the development of human papillomavirus-associated tumors, we studied p53 codon 72 genotype in 222 long-term survivors of renal transplantation, of whom 55 had developed at least one skin tumor. RESULTS: No differences in allele or genotype frequency were detected between individuals who had or had not developed skin tumors after transplantation, or any subgroup thereof. CONCLUSIONS: The p53 codon 72Arginine allele does not confer susceptibility to the development of skin tumors after renal transplantation.

Martin, J., F. J. Duncan, et al. (2009). "Macrophage migration inhibitory factor (MIF) plays a critical role in pathogenesis of ultraviolet-B (UVB) -induced nonmelanoma skin cancer (NMSC)." Faseb J **23**(3): 720-30.

Mounting evidence suggests that macrophage migration inhibitory factor (MIF) may serve as an important link between chronic inflammation and cancer development. The proinflammatory and proangiogenic activities of MIF position it as a potentially important player in the development and progression of nonmelanoma skin cancer (NMSC). To assess the role of MIF in the development and progression of NMSC, we exposed MIF(-/-) BALB/c mice to acute and chronic ultraviolet B (UVB) irradiation. Our studies demonstrate that MIF(-/-) BALB/c mice have a significantly diminished acute inflammatory response to UVB exposure compared to wild-type mice, as measured by myeloperoxidase activity, dermal neutrophil infiltration, and edematous response. Relative to wild-type mice, MIF(-/-) mice also show significantly lower vascular endothelial growth factor (VEGF) concentrations in whole skin and significantly lower 8-oxo-dG adduct concentrations in epidermal DNA following UVB exposure. Furthermore, MIF(-/-) mice showed significant increases in p53 activity, epidermal thickness, and epidermal cell proliferation following acute UVB insult. In response to chronic UVB exposure, MIF(-/-) mice showed a 45% reduction in tumor incidence, significantly less angiogenesis, and delayed tumor progression when compared to their wild-type counterparts. These data indicate that MIF plays an important role in UVB-induced NMSC development and progression.

Martin, K. R., C. Trempus, et al. (2001). "Dietary N-acetyl-L-cysteine modulates benzo[a]pyrene-induced skin tumors in cancer-prone p53 haploinsufficient Tg.AC (v-Ha-ras) mice." Carcinogenesis **22**(9): 1373-8.

Epidemiologic studies support the protective role of dietary antioxidants in preventing cancer. However, emerging evidence from clinical trials and laboratory data suggest that in some cases individual antioxidant supplements may actually exacerbate carcinogenesis. Our goal was to explore these paradoxical activities in a rodent model that possesses genotypic characteristics of human cancers. We selected the p53 haploinsufficient Tg.AC (v-Ha-ras) mouse as a model, because it contains an activated, carcinogeninducible ras oncogene and an inactivated p53 tumor suppressor gene, which are frequent genetic alterations in human cancers. These mice develop chemically induced benign and malignant skin tumors rapidly which can easily be quantified. Mice were fed basal diets with or without 3% N-acetyl-L-cysteine (NAC), a well-recognized antioxidant, prior to, during and after topical application of the carcinogen benzo[a]pyrene (64 microg/mouse) applied twice per week for 7 weeks. Tumor incidence exceeded 90% for both groups, and NAC did not reduce tumor latency. Mice fed NAC displayed a 43% reduction ($P < 0.05$) in tumor multiplicity and delayed the appearance of lesions ($P < 0.05$). Dietary NAC also significantly ($P < 0.05$) improved group survival by 5 weeks. Total tumor yields were reduced in both dietary groups but malignant spindle cell tumors (SCT) increased by 25% in NAC-fed mice. The v-Ha-ras oncogene and p53 protein products were clearly co-expressed in both benign and malignant lesions from both dietary groups. In summary, dietary supplementation with NAC was chemopreventive, but the marginal increase in SCT suggests a paradoxical effect.

Massimi, P., M. Thomas, et al. (2008). "Comparative transforming potential of different human papillomaviruses associated with non-melanoma skin cancer." Virology **371**(2): 374-9.

It is well established that high-risk human papillomaviruses (HPVs) that infect mucosal epithelia are the causative agents of cervical cancer. In contrast, the association of cutaneo-tropic HPV types with the development of non-melanoma skin cancer (NMSC) is less well defined. In this study, we have analysed the in vitro transforming potential of various cutaneous HPV types. Using oncogene cooperation assays with activated ras, we have shown that diverse cutaneous types, including 12, 14, 15, 24, 36 and 49, have significant transforming potential. Interestingly, most of this activity appears to be encoded by the E6 gene product. In contrast, the common HPV-10 exhibits no significant transforming potential in these assays. This difference may be a reflection of different patterns of cellular localization, with transforming E6s being nuclear and non-transforming being cytoplasmic. These results provide molecular support for a role of these viruses in the development of certain human malignancies.

Matsumura, Y., A. M. Moodycliffe, et al. (2005). "Inverse relationship between increased apoptosis and decreased skin cancer in UV-irradiated CD1d-/- mice." Photochem Photobiol **81**(1): 46-51.

We previously demonstrated that CD1d knockout mice were resistant to ultraviolet (UV)-induced immunosuppression. Because immune suppression is a critical factor in the development of UV-induced skin cancers, we investigated the response of wild type (WT) and CD1d-/- mice to UV carcinogenesis. We found that although 100% of WT mice developed skin tumors after 45 weeks of UV irradiation, only 60% of CD1d-/- mice developed skin tumors. To investigate the mechanisms involved in the resistance of CD1d-/- mice to UV-induced carcinogenesis, we determined the time course and

kinetics of keratinocyte cell death after UV irradiation. After acute UV exposure, the terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end-labeling (TUNEL)-positive keratinocytes were eliminated from the skin of WT mice by 72 h post-UV, but they still persisted until 96 h in CD1d-/- mice. The kinetics of p53 protein expression closely followed the kinetics of apoptotic cell death. Chronic UV irradiation resulted in induction of a significantly higher number of apoptotic keratinocytes in CD1d-/- than WT mice. In addition, epidermis and dermis from chronically UV-irradiated CD1d-/- mice harbored significantly fewer p53 mutations than WT mice. These results indicate that the resistance of CD1d-/- mice to UV carcinogenesis may be due to increased cell death and elimination of keratinocytes and fibroblasts containing DNA damage and p53 mutations.

Matta, J. L., J. L. Villa, et al. (2003). "DNA repair and nonmelanoma skin cancer in Puerto Rican populations." J Am Acad Dermatol **49**(3): 433-9.

BACKGROUND: UV radiation is a risk factor for nonmelanoma skin cancer (NMSC). The relation between DNA damage and oncogenesis suggests that diminished DNA repair capacity (DRC) is involved in tumorigenesis. OBJECTIVE: The purpose of this study was to test the hypothesis that a low DRC is a susceptibility factor for the development of NMSC in Puerto Rico. METHODS: A case-control retrospective clinical study was done to compare the age-adjusted DRC in participants with and without NMSC. DRC was measured using a host cell reactivation assay with a luciferase reporter gene irradiated with UV light and transfected into human peripheral lymphocytes. An epidemiologic questionnaire was used to solicit risk factors. RESULTS: The mean (+/-2 SE) DRC of 177 control patients without skin cancer was 8.6% +/- 0.7. Participants (280) with NMSC had a 42% lower DRC (5.0% +/- 0.3). CONCLUSION: A low DRC is a susceptibility factor for NMSC.

McGregor, J. M., R. J. Berkhout, et al. (1997). "p53 mutations implicate sunlight in post-transplant skin cancer irrespective of human papillomavirus status." Oncogene **15**(14): 1737-40.

Mutations in p53 were detected in 11/23 (48%) of non melanoma skin cancers in renal allograft recipients and in 5/8 (63%) of sporadic tumours from immune competent patients. 9/12 (75%) of mutations in transplant patients and all 5 mutations in non transplant tumours were consistent with damage caused by ultraviolet (u.v.) irradiation. DNA sequences, predominantly of the epidermodysplasia verruciformis (EV) subgroup, were detected in 9/23 (39%) of transplant tumours and in 2/8 (25%) of eight non-transplant tumours. There was no relationship between HPV status and p53 mutation, HPV DNA being present in 5/16 (31%) of tumours with p53 mutation and 6/15 (40%) of tumours lacking p53 mutation. These data are consistent with an important role for sunlight in the development of post-transplant skin cancer, and with limited functional data suggesting that E6 proteins of the cutaneous and EV-related papillomaviruses do not target p53 for ubiquitin-mediated degradation.

McGregor, J. M., A. Farthing, et al. (1994). "Posttransplant skin cancer: a possible role for p53 gene mutation but not for oncogenic human papillomaviruses." J Am Acad Dermatol **30**(5 Pt 1): 701-6.

BACKGROUND: Loss of p53 tumor suppressor function is a critical step in the development of diverse malignancies, including skin cancers in nonimmunosuppressed patients where UV-specific p53 gene mutations have been identified. In tumors associated with human papillomavirus (HPV), such as cervical carcinoma, p53 may be inactivated instead by binding to a viral oncoprotein. OBJECTIVE: Our purpose was to examine the hypothesis that HPV may play an analogous role in the development of posttransplant skin cancer. METHODS: p53 Immunoreactivity, suggestive of p53 gene mutation, was examined by immunocytochemistry. Oncogenic HPV DNA was detected by polymerase chain reaction. RESULTS: Comparable p53 immunoreactivity was seen in skin tumors from both transplant and nontransplant patients. HPV DNA was not demonstrated in any tumor specimen. CONCLUSION: Our data do not implicate oncogenic HPV in posttransplant skin cancer. p53 Gene mutation, rather than HPV-induced p53 degradation, may be more significant in the development of these tumors.

McGregor, J. M., C. C. Yu, et al. (1992). "Aberrant expression of p53 tumour-suppressor protein in non-melanoma skin cancer." Br J Dermatol **127**(5): 463-9.

Expression of the cellular p53 tumour-suppressor protein was examined in 78 epidermal tumours, including basal and squamous cell carcinomas, keratoacanthomas, solar keratoses, Bowen's disease and viral warts. An immunohistochemical study was employed using the antibody CM-1, raised against recombinant human p53 protein. Positive staining for p53, not detectable in normal cells because wild-type p53 is rapidly degraded, reflects abnormal stabilization of p53 protein, and in many cases suggests p53 gene mutation. p53 immunoreactivity was not observed in

normal skin or in viral warts. In contrast, positive staining for CM-1 was seen throughout the tumour in the majority of basal and squamous cell carcinomas and in Bowen's disease. Immunoreactivity to p53 was also observed in the majority of keratoacanthomas and solar keratoses, but was confirmed to areas of dysplastic basal epithelium. This study demonstrates that accumulation of p53 protein, suggestive in many cases of p53 gene mutation and hence loss of tumour-suppressor function, may occur as an important early step in the development of diverse epidermal cancers.

Meira, L. B., D. L. Cheo, et al. (2002). "Mice defective in the mismatch repair gene Msh2 show increased predisposition to UVB radiation-induced skin cancer." DNA Repair (Amst) **1**(11): 929-34.

Mice defective in the mismatch repair (MMR) gene Msh2 manifest an enhanced predisposition to skin cancer associated with exposure to UVB radiation. This predisposition is further heightened if the mice are additionally defective for the nucleotide excision repair gene Xpc. To test the hypothesis that the predisposition of Msh2 mutant mice to skin cancer reflects a mutator phenotype associated with increased proliferation of skin cells following exposure to UV radiation, Msh2 mutant mice were exposed to the tumor promoter TPA. Such mice showed a robust proliferative response in the skin, but did not manifest evidence of dysplasia or neoplasia. We conclude that the predisposition of Msh2 mice to UVB radiation-induced skin cancer reflects an interaction between the processes of mismatch repair and some other excision repair mode, the exact nature of which remains to be established.

Melnikova, V. O. and H. N. Ananthaswamy (2005). "Cellular and molecular events leading to the development of skin cancer." Mutat Res **571**(1-2): 91-106.

The transition from a normal cell to a neoplastic cell is a complex process and involves both genetic and epigenetic changes. The process of carcinogenesis begins when the DNA is damaged, which then leads to a cascade of events leading to the development of a tumor. Ultraviolet (UV) radiation causes DNA damage, inflammation, erythema, sunburn, immunosuppression, photoaging, gene mutations, and skin cancer. Upon DNA damage, the p53 tumor suppressor protein undergoes phosphorylation and translocation to the nucleus and aids in DNA repair or causes apoptosis. Excessive UV exposure overwhelms DNA repair mechanisms leading to induction of p53 mutations and loss of Fas-FasL interaction. Keratinocytes carrying p53 mutations acquire a growth advantage by virtue of their increased resistance to apoptosis. Thus, resistance to cell death is a key event in photocarcinogenesis and conversely, elimination of cells containing excessive UV-induced DNA damage is a key step in protecting against skin cancer development. Apoptosis-resistant keratinocytes undergo clonal expansion that eventually leads to formation of actinic keratoses and squamous cell carcinomas. In this article, we will review some of the cellular and molecular mechanisms involved in initiation and progression of UV-induced skin cancer.

Melnikova, V. O., A. Pacifico, et al. (2005). "Fate of UVB-induced p53 mutations in SKH-hr1 mouse skin after discontinuation of irradiation: relationship to skin cancer development." Oncogene **24**(47): 7055-63.

Chronic exposure to ultraviolet (UV) radiation causes skin cancer in humans and mice. We have previously shown that in hairless SKH-hr1 mice, UVB-induced p53 mutations arise very early, well before tumor development. In this study, we investigated whether discontinuation of UVB exposure before the onset of skin tumors results in the disappearance of p53 mutations in the skin of hairless SKH-hr1 mice. Irradiation of mice at a dose of 2.5 kJ/m2 three times a week for 8 weeks induced p53 mutations in the epidermal keratinocytes of 100% of the mice. UVB irradiation was discontinued after 8 weeks, but p53 mutations at most hotspot codons were still present even 22 weeks later. During that period, the percent of mice carrying p53(V154A/R155C), p53(H175H/H176Y), and p53R275C mutant alleles remained at or near 100%, whereas the percentage of mice with p53R270C mutation decreased by 45%. As expected, discontinuation of UVB after 8 weeks resulted in a delay in tumor development. A 100% of tumors carried p53(V154A/R155C) mutant alleles, 76% carried p53(H175H/H176Y) mutants, and 24 and 19% carried p53R270C and p53R275C mutants, respectively. These results suggest that different UVB-induced p53 mutants may provide different survival advantages to keratinocytes in the absence of further UVB exposure and that skin cancer development can be delayed but not prevented by avoidance of further exposure to UVB radiation.

Milchgrub, S., Wistuba, II, et al. (2000). "Molecular identification of metastatic cancer to the skin using laser capture microdissection: a case report." Cancer **88**(4): 749-54.

BACKGROUND: In the current study the authors report a 57-year-old woman with a scalp tumor and cervical lymphadenopathy who had a previously resected duodenal carcinoid. Histologic and immunophenotypic characteristics of the duodenal carcinoid differed from those of the scalp

and cervical lymph node tumors, prompting the use of molecular methodologies to make the diagnosis. METHODS: Paraffin embedded tissues from the duodenal carcinoid, scalp, and lymph node tumors were dissected using microscopic visualization and laser capture microdissection. DNA was extracted and polymerase chain reaction (PCR) was performed to evaluate loss of heterozygosity and microsatellite alterations using primers flanking 22 polymorphic microsatellite markers from 9 chromosomal regions, including genes associated with MEN-1 (11q), CDKN2 (9p), p53 (17p), and bronchial carcinoid (3p). Microdissected lymphocytes from the three tissues were used as source of constitutional DNA (controls). RESULTS: Fourteen of the 22 markers were informative (heterozygous in control lymphocytes). A marker on 3p12 showed loss of the same parental allele in the three tumors. A different marker on 3p14.2 showed an identical shifted band in the three tumors indicative of a common microsatellite alteration. CONCLUSIONS: The shared molecular abnormalities among the three tumors indicated a common clonal origin, leading to a diagnosis of primary duodenal carcinoid with clear cell metastases to the scalp and cervical lymph nodes. These findings led to radiation therapy and immunotherapy rather than chemotherapy. This case illustrates the novel application of laser capture microdissection combined with PCR-based analyses of genomic markers for the identification of the origin of metastatic disease.

Molho-Pessach, V. and M. Lotem (2007). "Viral carcinogenesis in skin cancer." Curr Probl Dermatol **35**: 39-51.

The skin is an organ in which direct contact with viruses, solar UV irradiation and increased susceptibility to immune suppression gather to support viral tumorigenesis. Viruses transform keratinocytes by activation of cancer-promoting genes. Viral proteins may directly act as oncogenes that drive cells to proliferate or generate inflammatory responses and cause regeneration of injured cells that eventually lead to malignant transformation. Accelerated viral carcinogenesis is observed in the immune-deficient host. Decreased T-cell reactivity and lower number of antigen-presenting cells in the skin assist in viral escape and emergence of skin tumors. Three pathogenic human viruses associated with skin neoplasms are described: human papilloma virus (HPV), Kaposi's sarcoma (KS)-associated herpesvirus and human T-cell leukemia virus type 1. HPV was linked to squamous cell carcinoma (SCC) of the skin after its role in SCC of the cervix has been discovered. In the rare autosomal recessive epidermodysplasia verruciformis, an increased susceptibility to specific HPV strains initially results in widespread wart infection and later in life in the development of SCC over the sun-exposed skin. The role of HPV in nonmelanoma skin cancer of immune competent hosts is more difficult to prove. The discovery of human herpesvirus 8 as the causative pathogen of KS was made following the AIDS epidemic, and its role in all clinical variants of this tumor was confirmed. KS-associated herpesvirus exerts its tumorigenic effect through a wide repertoire of genes that regulate angiogenesis, inflammation, and cell cycle. Human T-cell leukemia virus type 1 causes adult T-cell leukemia and is often associated with skin eruptions that share common features with cutaneous T-cell lymphoma. In summary, studies of oncogenic viruses shed light on molecular mechanisms leading to tumor formation and aid in recognition of new pathways of carcinogenesis.

Mollenhauer, J., M. Deichmann, et al. (2003). "Frequent downregulation of DMBT1 and galectin-3 in epithelial skin cancer." Int J Cancer **105**(2): 149-57.

DMBT1 and galectin-3 are potential interacting proteins with presumably complex roles in tumorigenesis. While at present a variety of mechanisms are discussed for DMBT1 and its participation in cancer, galectin-3 is commonly known to exert tumor-promoting effects. However, in vitro studies in a rodent system have suggested that DMBT1/galectin-3 interaction in the ECM triggers epithelial differentiation, which would point to tumor-suppressive properties. To improve the understanding of DMBT1/galectin-3 action in cancer, we carried out studies in skin cancer of different origins. Mutational analyses of DMBT1 identified a missense mutation in 1 of 13 melanoma cell lines. It led to an exchange of an evolutionary conserved proline residue for serine and located within the second CUB domain of DMBT1. Immunohistochemical analyses demonstrated absence of DMBT1/galectin-3 expression from melanocytes but induction of DMBT1 expression in 1 of 8 nevi and 1 of 11 melanomas and of galectin-3 expression in 3 of 8 nevi and 4 of 8 melanomas. These data suggest that DMBT1 and galectin-3 are unlikely to act as classical tumor suppressors in melanomas. DMBT1 and galectin-3 appear to be secreted to the ECM by epithelial cells within the epidermis and the hair follicle. Compared to the flanking normal epidermis, skin tumors of epithelial origin frequently displayed downregulation of DMBT1 (18 of 19 cases) and galectin-3 (12 of 12 cases). Thus, loss of DMBT1/galectin-3 expression may play a role in the genesis of epithelial skin cancer. This would support the view that galectin-3 can exert tumor-suppressive effects in certain scenarios, and DMBT1/galectin-3-

mediated differentiation represents a candidate mechanism for this effect.

Montesano, R., P. Hainaut, et al. (1997). "The use of biomarkers to study pathogenesis and mechanisms of cancer: oesophagus and skin cancer as models." IARC Sci Publ(142): 291-301.

Recent advances in molecular biology have made it possible to use genetic alterations associated with cancer as biomarkers to study the pathogenesis and mechanisms of cancer. However, the lessons that can be drawn from the analysis of alterations in a particular cancer gene are extremely dependent upon the biological context in which they arise. In this article, we discuss the biological significance of alterations in the p53 tumour suppressor gene in cancers of the oesophagus and of the skin. In both tissues, different forms of cancer occur at high frequency (squamous-cell carcinoma and adenocarcinoma in the oesophagus; squamous-cell carcinoma, basal-cell carcinoma and melanoma in the skin). We show that specific patterns of p53 alteration occur in these various cancers and that analysis of these alterations is useful to make inferences about the etiopathogenesis of cancers of the oesophagus and of the skin.

Montonen, O., S. Ezer, et al. (1998). "Expression of the anhidrotic ectodermal dysplasia gene is reduced in skin cancer coinciding with reduced E-cadherin." Exp Dermatol **7**(4): 168-74.

X-linked anhidrotic ectodermal dysplasia (EDA) is characterized by defects in the development of hair, teeth, and sweat glands. We have recently cloned the gene for EDA by positional cloning. The EDA gene encodes a transmembrane protein with a putative role in epithelial mesenchymal interactions. Since EDA could play a role in cell-cell or cell-matrix adhesion, acantholytic skin diseases and several types of non-invasive and invasive skin cancers were studied using in situ hybridization. Because of the observation that the promoter region of the EDA gene contains a binding site for LEF-1, which is involved in the signaling through E-cadherin/beta catenin complex, we compared the expression of EDA with immunolocalization for E-cadherin (E-CD). EDA expression during hair growth cycle, in benign adnexal tumors, and neuroectoderm-derived nevus cells was also examined. Our findings indicate that EDA expression is less abundant in malignant tumors, including basal and squamous cell carcinomas and melanoma, and in acantholytic keratinocytes compared to normal epidermis. The reduction in expression also coincides with diminished E-CD staining in all malignant cell types and in acantholytic cells. Our results suggest that EDA protein functions in the regulation of epithelial cell contacts and that it may be associated with the E-CD signaling pathway.

Nagano, T., M. Kunisada, et al. (2008). "Involvement of interleukin-10 promoter polymorphisms in nonmelanoma skin cancers-a case study in non-Caucasian skin cancer patients." Photochem Photobiol **84**(1): 63-6.

Interleukin 10 (IL-10) is a potent immunosuppressive cytokine, therefore elevated IL-10 expression has been implicated in inhibition of antitumor immune response. IL-10 gene promoter polymorphism has been shown to be involved in susceptibility to skin cancers, but there has been no report focusing on susceptibility to skin cancers among non-Caucasian populations. We enrolled 129 patients with skin cancers and 50 age- and sex-matched healthy controls between April 2004 and March 2007. Genomic DNA was extracted from patients' blood samples and IL-10 promoter polymorphisms were identified using polymerase chain reaction-restriction fragment length polymorphism or direct sequencing. The distribution of the frequency of allele or haplotype of IL-10 gene promoter in Japanese was quite different from that of Europeans. No significant differences could be demonstrated in the frequency of allele or haplotype of IL-10 gene promoter between the patient group and the control group. However, the frequency of the low-IL-10 expression haplotype was significantly high in Bowen's disease subgroup. The frequency of low expression IL-10 promoter genotype was significantly less ($P = 0.009$, $chi(2) = 6.74$) in the group of nonmelanoma skin cancer generated on sun-exposed areas in comparison with that on covered areas. Our results indicated that low expression haplotype of IL-10 in Bowen's disease may inhibit the escape of tumor cells from immune surveillance, resulting in suppression of tumor growth and tumor invasion to the dermis. Moreover, high IL-10-expressing haplotype of IL-10 promoter may be a risk factor for photocarcinogenesis.

Nakazawa, H., D. English, et al. (1994). "UV and skin cancer: specific p53 gene mutation in normal skin as a biologically relevant exposure measurement." Proc Natl Acad Sci U S A **91**(1): 360-4.

Many human skin tumors contain mutated p53 genes that probably result from UV exposure. To investigate the link between UV exposure and p53 gene mutation, we developed two methods to detect presumptive UV-specific p53 gene mutations in UV-exposed normal skin. The methods are based on mutant allele-specific PCRs and ligase chain reactions and designed to detect CC to TT mutations at codons 245 and 247/248, using 10 micrograms of DNA

samples. These specific mutations in the p53 gene have been reported in skin tumors. CC to TT mutations in the p53 gene were detected in cultured human skin cells only after UV irradiation, and the mutation frequency increased with increasing UV dose. Seventeen of 23 samples of normal skin from sun-exposed sites (74%) on Australian skin cancer patients contained CC to TT mutations in one or both of codons 245 and 247/248 of the p53 gene, and only 1 of 20 samples from non-sun-exposed sites (5%) harbored the mutation. None of 15 biopsies of normal skin from non-sun-exposed or intermittently exposed sites on volunteers living in France carried such mutations. Our results suggest that specific p53 gene mutations associated with human skin cancer are induced in normal skin by solar UV radiation. Measurement of these mutations may be useful as a biologically relevant measure of UV exposure in humans and as a possible predictor of risk for skin cancer.

Nan, H., T. Niu, et al. (2008). "Missense polymorphisms in matrix metalloproteinase genes and skin cancer risk." Cancer Epidemiol Biomarkers Prev **17**(12): 3551-7.

Matrix metalloproteinases (MMP) degrade various components of the extracellular matrix, and their overexpression has been implicated in tumor progression. Nonsynonymous single nucleotide polymorphisms (SNPs) lead to amino acid substitutions that can alter the function of the encoded protein. We evaluated the associations of six nonsynonymous SNPs in the MMP3, MMP8, and MMP9 genes with skin cancer risk in a nested case-control study of Caucasians within the Nurses' Health Study among 218 melanoma cases, 285 squamous cell carcinoma (SCC) cases, 300 basal cell carcinoma (BCC) cases, and 870 normal controls. We observed that the MMP9 Arg668Gln polymorphism was significantly associated with a decreased risk of SCC. Compared with the Arg/Arg group, the multivariate odds ratio was 0.67 (95% confidence interval, 0.47-0.97) for the Arg/Gln group and 0.21 (95% confidence interval, 0.05-0.97) for the Gln/Gln group (P(trend) = 0.004). We did not observe any association of this SNP with the risks of melanoma and basal cell carcinoma. No associations were found for other SNPs with skin cancer risk. This study provides evidence for the contribution of the MMP9 Arg668Gln to SCC development.

Nelson, H. H., B. Christensen, et al. (2005). "The XPC poly-AT polymorphism in non-melanoma skin cancer." Cancer Lett **222**(2): 205-9.

Signature UV-DNA lesions, cyclobutane dimers and 6-4 photoproducts, are repaired via the nucleotide excision repair pathway. NER may be subdivided into transcription-coupled repair and global genome repair, and the XPC protein is specific to this latter repair pathway recognizing helix distorting lesions and initiating their repair. Inactivating XPC mutations are associated with xeroderma pigmentosa and an extremely high risk of skin cancer. A common polymorphism in intron 9 of the XPC gene has been associated with both reduced repair of UV-DNA damage (using the host-cell reactivation assay) and increased risk of squamous cell head and neck cancer. Here, we have tested the hypothesis that the XPC PAT+ polymorphism is associated with non-melanoma skin cancer using a population-based case control study of skin cancer in New Hampshire (n=1917). Overall, there was a modest decreased risk of squamous cell carcinoma (SCC) among those with the homozygous variant PAT+/+ genotype (OR 0.8, 95% CI 0.5-1.1) that was most evident among tanners (OR 0.4, 95% CI 0.1-1.1), however, these trends failed to reach statistical significance. There was no association of the PAT+/+ genotype and basal cell carcinoma (OR 1.0, 95% CO 0.7-1.3), however there was a modest, non-statistically significant, decreased risk among those with the heterozygous genotype (OR 0.8, 95% CI 0.7-1.1). We did not detect gene environment interactions for either SCC or BCC between the XPC PAT genotype and average hours of UV exposure per week, painful sunburn history, nor ionizing radiation therapy. These results suggest that the XPC PAT+polymorphism does not play a major role in non-melanoma skin cancer, but that it may slightly modify the risk of SCC among individuals with a phenotype which results in low UV-DNA adduct burdens. These results require further confirmation.

Nelson, H. H., K. T. Kelsey, et al. (2002). "The XRCC1 Arg399Gln polymorphism, sunburn, and non-melanoma skin cancer: evidence of gene-environment interaction." Cancer Res **62**(1): 152-5.

XRCC1, a protein directly involved in the repair of DNA base damage, contains at least three common polymorphisms. One of these, the codon 399 arg-->gln variant, has been associated with several cancer-related biomarkers, suggesting it may have functional significance in exposure-induced cancers. However, results from case-control studies have yielded conflicting results. We investigated the XRCC1 arg399gln polymorphism and its interaction with carcinogen exposure in a large, population-based case-control study of non-melanoma skin cancer. Cases were derived from an incident survey of all newly diagnosed non-melanoma skin cancer in New Hampshire, and controls were population based and frequency matched to cases on age and sex (n =

1176). Exposure information was derived from a detailed interviewer-administered questionnaire, and XRCC1 genotype was determined from blood-derived DNA using a PCR-RFLP method. Overall, the XRCC1 homozygous variant gln399gln genotype was related to a significantly reduced risk of both basal cell [BCC; odds ratio (OR) 0.7, 95% confidence interval 0.4-1.0] and squamous cell carcinoma (SCC; OR 0.6, 95% confidence interval 0.3-0.9). There was no significant gene-environment interaction of the variant XRCC1 genotype and a history of therapeutic X-ray exposure. However, there was a statistically significant multiplicative interaction of XRCC1 genotype and lifetime number of sunburns in SCC [likelihood ratio test (2 d.f.), $P < 0.02$]. Although the absolute risk of SCC associated with sunburns was similar across genotypes, the relative risk of SCC associated with painful sunburn history was significantly higher for homozygous variants than wild types (OR 6.8 for gln399gln and 1.5 for arg399arg). In summary, our data show that the homozygous XRCC1 variant (gln399gln) is associated with a lower risk of non-melanoma skin cancer and suggest that the etiology of sunburn-related SCC may be significantly different by XRCC1 genotype. These data, using the classic skin carcinogenesis model, provide new insight on the role of the XRCC1 399 polymorphism in neoplasia and may help explain the conflicting results relating this polymorphism to cancer risk at various sites.

Nielsen, K., C. Ingvar, et al. (2004). "Melanoma and nonmelanoma skin cancer in patients with multiple tumours--evidence for new syndromes in a population-based study." Br J Dermatol **150**(3): 531-6.

BACKGROUND: The hypotheses that Swedish patients with four or more primary tumours [including at least one cutaneous malignant melanoma (CMM)] harbour an increased number of CDKN2A (formerly p16) germline mutations, and that this group of patients show a predisposition to other tumours, e.g. nonmelanoma skin cancer (NMSC), were studied descriptively. So far the mutation 113insArg explains all CDKN2A-associated CMM in ethnic Swedes. OBJECTIVES: All patients with four or more primary tumours, of which at least one was a CMM, from the Southern Swedish Regional Tumour Registry, between 1958 and 1999, were included in this study. METHODS: Forty-four patients were found and subdivided into three groups according to having multiple CMM (group A) or single CMM +/- NMSC (groups B and C). Screening for the presence of the Swedish founder mutation 113insArg in blood or in tissue blocks was performed. RESULTS: Patients in group A were younger at the time of the first CMM diagnosis than patients in group B and group C. The 113insArg mutation was found in four of 44 patients (9%), three with multiple CMM. In group C (n = 14) no founder mutation was evident, while in group B (n = 15) one mutation carrier was found. Nonmutation carriers with multiple CMM (group A) also had a predilection for meningiomas and neurinomas (four patients) or multiple NMSC (three patients). In group B CMM were especially associated with adenocarcinomas but in group C CMM were associated with multiple NMSC. CONCLUSION: The association between meningiomas and neurinomas (no acoustic neurinoma was seen) might indicate a new syndrome. Patients in groups B and C may harbour unknown genetic defects, which could interact with different environmental risk factors.

Nindl, I., T. Meyer, et al. (2004). "Human papillomavirus and overexpression of P16INK4a in nonmelanoma skin cancer." Dermatol Surg **30**(3): 409-14.

BACKGROUND: P16INK4a overexpression has been identified as a specific biomarker in high-risk human papillomavirus (HPV)-infected cervical (pre)cancer lesions. OBJECTIVE: To evaluate the overexpression of this cyclin-dependent kinase inhibitor in skin tumors depending on HPV infections, we analyzed normal skin, benign skin disease, and skin cancer specimens. METHODS: Biopsies of 23 patients with normal histology (3), psoriasis (2), verrucae vulgaris (2), actinic keratoses (5), squamous cell carcinoma (SCC) in situ (3), Bowen's carcinoma (1), and SCC (7) were analyzed. Specimens of 23 patients were immunostained using the monoclonal antibody E6H4 specific for p16INK4a. HPV status was assessed by a polymerase chain reaction (PCR) system to detect all currently known HPV types. MY (MY09/MY11 and MYN9/MYN10)-, CP (CP65/CP70 and CP66/CP69)-nested PCR, and three single PCR methods CN1, CN3, and CN4 were used in a first step, and HPV typing was performed by restriction fragment length polymorphism analysis. Only beta-globin-positive patients were included in this study. RESULTS: HPV DNA was detected in all actinic keratoses, SCC in situ, Bowen's carcinoma, and SCC, in 50% (one of two) of verrucae vulgaris, in 66% (two of three) of normal skin, and in none of two psoriasis. P16INK4a expression was not detected in normal skin, psoriasis, and verrucae vulgares. Overexpression of p16INK4a was detected in a subset of dysplastic cells (10% to 80%) of all skin (pre)cancer lesions such as actinic keratoses, SCC in situ, Bowen's carcinoma, and SCC infected with HPV independent of sun exposure. CONCLUSION: P16INK4a appears to be overexpressed in a portion of dysplastic cells from actinic keratoses and SCC.

Further studies to examine the association of HPV infection and the overexpression of p16INK4a are warranted.

Nogues, M. R., M. Giralt, et al. (2002). "Parameters related to oxygen free radicals in human skin: a study comparing healthy epidermis and skin cancer tissue." J Invest Dermatol **119**(3): 645-52.

In vitro studies with tumor cells have demonstrated that oxygen free radicals are involved in the development of skin cancers and that variations in the body's defense mechanisms can modify the course of the disease. To assess the validity of this hypothesis in spontaneous tumors, we determined glutathione S-transferase, superoxide dismutase, reduced and oxidized glutathione, and thiobarbituric acid reactive substances in healthy whole skin (n = 95), dermis (n = 73), and epidermis (n = 69). The values were compared with those obtained in three types of skin cancer: basal cell carcinoma (n = 16), squamous cell carcinoma (n = 6), and melanoma (n = 33). In healthy skin, glutathione S-transferase, superoxide dismutase, reduced glutathione, and oxidized glutathione were higher in epidermis than in dermis, whereas thiobarbituric acid reactive substances were higher in dermis than in epidermis; whole skin had intermediate values. These results suggest that there is an induction of some anti-oxygen free radicals mechanisms in epidermis as a result of increased oxygen free radicals production. Glutathione S-transferase and thiobarbituric acid reactive substances were higher in all types of tumor than in healthy epidermis but oxidized glutathione was lower. Reduced glutathione and superoxide dismutase activity were lower in basal cell carcinoma and squamous cell carcinoma samples. Glutathione S-transferase increased, whereas superoxide dismutase and thiobarbituric acid reactive substances decreased in melanoma samples in direct relation to the Clark levels. Higher glutathione S-transferase activity, particularly in the most invasive forms of melanoma, indicates that this type of cancer is more malignant. Similarly, a decrease in superoxide dismutase activity can also encourage progression of the tumor. These results are in accord with those from tumor cell cultures and could suggest new strategies (gene therapy) for managing skin cancer.

Nomura, T., H. Nakajima, et al. (1997). "Induction of cancer, actinic keratosis, and specific p53 mutations by UVB light in human skin maintained in severe combined immunodeficient mice." Cancer Res **57**(11): 2081-4.

To study the mechanism and risk of human skin cancer from solar light, we exposed human skin transplanted to severe combined immunodeficient mice to daily doses of UVB for periods of approximately 2 years. We have succeeded for the first time in inducing cancer and solar (actinic) keratosis in human skin by UVB. Of 18 normal skins exposed to doses of 7.3 x 10(5) to 1.8 x 10(6) J/m2, 14 actinic keratoses (77.8%) and 3 squamous cell carcinomas (16.7%) developed, whereas neither actinic keratosis nor cancer was observed in 15 human skins not exposed to UVB. Each human skin showed a different susceptibility, and skins sensitive for actinic keratosis were also sensitive for cancer induction. Among p53 mutations at various sites, mutation at codon 242 (C TGC --> C CGC; Cys --> Arg) was specifically observed in both skin cancers and actinic keratoses. Furthermore, double or triple mutations were induced in all UVB-induced skin cancers and in three of eight actinic keratoses. Most of the mutations (17 of 20) occurred at dipyrimidine sites.

O'Connor, D. P., E. W. Kay, et al. (2001). "p53 codon 72 polymorphism and human papillomavirus associated skin cancer." J Clin Pathol **54**(7): 539-42.

BACKGROUND/AIMS: Non-melanoma skin cancers frequently harbour multiple human papillomavirus (HPV) types. A recent report suggests that a polymorphism of the p53 tumour suppressor gene that results in the substitution of a proline residue with an arginine residue at position 72 of the p53 protein might act as a risk factor in HPV associated malignancies. This study aimed to determine the following: (1) the relation between HPV infection and the development of cutaneous squamous cell carcinoma (SCC), and (2) whether there is a correlation between p53 codon 72 polymorphism and the development of SCC. METHODS: Blood samples were taken from 55 patients with skin cancer (both renal transplant recipients and immunocompetent patients with skin cancer) and 115 ethnically matched volunteers. A polymerase chain reaction based assay was used to determine p53 codon 72 genotypes. In addition, 49 benign and malignant lesions from 34 of the patients with skin cancer and 20 normal human skin samples from 20 of the control volunteers were examined for HPV. RESULTS: The proportions of p53 codon 72 genotypes found were 78% arginine homozygous, 2% proline homozygous, and 20% heterozygous among patients with skin cancer and 79% arginine homozygous, 3.5% proline homozygous, and 17.5% heterozygous among the control population. Statistical analysis showed no significant differences in the distribution of the two p53 isoforms between the patients with skin cancer and the control population. The predominant viral types detected in both the patients and the control group were EV associated HPVs, although the incidence was lower in normal skin samples than in malignant lesions or viral warts.

CONCLUSIONS: These results suggest that in a Celtic population there is no correlation between the presence of HPV, the p53 codon 72 arginine polymorphism, and the development of skin cancer.

O'Connor, D. P., E. W. Kay, et al. (2001). "Altered p53 expression in benign and malignant skin lesions from renal transplant recipients and immunocompetent patients with skin cancer: correlation with human papillomaviruses?" Diagn Mol Pathol **10**(3): 190-9.

Renal transplant recipients are prone to numerous benign and malignant skin lesions. Previous work in the authors' laboratory has determined that the human papillomavirus may be the viral aetiology of these skin lesions. The p53 tumor-suppressor gene is the most frequently mutated gene in a wide range of human cancers. Here the authors describe an immunohistochemical study to evaluate the expression of p53 in benign and malignant skin lesions from renal transplant recipients and immunocompetent patients with skin cancer. The effect of p53 mutations on the expression patterns observed were examined by polymerase chain reaction-single strand conformation polymorphism analysis and direct cycle sequencing. The expression of the p53-regulated cyclin-dependant kinase inhibitor p21Waf1/Cip1 and Mdm2 was also examined in p53-positive cells. The expression of p53 in benign and malignant lesions was found to be markedly different. p53 was expressed in only 40% (6/15) of viral warts analyzed. The expression was confined to the basal layer both in the lesion and in adjacent normal skin, and the level of expression was low and only in a small number of cells (<10%). Of the cutaneous squamous cell carcinomas analyzed, 60% (9/15) showed p53 expression. Two different patterns of expression were observed. Basal layer expression in both the invasive tumor and adjacent normal skin was observed in 50% of the p53-positive squamous cell carcinomas; in the remaining 50%, p53 was expressed diffusely throughout the invasive tumor and in the basal layer of adjacent normal skin. The level of expression was high and in a large number of cells. Polymerase chain reaction-single strand conformation polymorphism analysis revealed that only one of the squamous cell carcinomas expressing p53 harbored a p53 mutation and that the accumulated p53 in the remaining tumors was wild type. No Mdm2 or p21Waf1/Cip1 expression was detected in the p53-positive squamous cell carcinomas, indicating that although the accumulated p53 is stable, it does not function effectively as a transcriptional activator. This represents a novel p53 phenotype in cutaneous squamous cell carcinoma. In addition, no correlation was seen between the presence and absence of human papillomavirus and p53 expression.

O'Grady, A., C. Dunne, et al. (2007). "Differential expression of matrix metalloproteinase (MMP)-2, MMP-9 and tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2 in non-melanoma skin cancer: implications for tumour progression." Histopathology **51**(6): 793-804.

AIMS: To investigate the expression of matrix metalloproteinase (MMP)-2, MMP-9, and tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2 in non-melanoma skin cancer (NMSC) and to compare their expression between different tumour types and with clinicopathological factors. METHODS AND RESULTS: A study of 11 normal skin, 29 Bowen's disease (BD), 40 squamous cell carcinoma (SCC) and 38 basal cell carcinoma (BCC) samples for MMP-2, MMP-9, TIMP-1 and TIMP-2 expression was carried out using immunohistochemistry and in situ hybridization. The expression of all metalloproteinases was greater in tumours than in normal skin. MMP-2 and MMP-9 expression was more extensive in the stroma of SCC than of BCC or BD. TIMP-1 expression was greater in the stroma of BCC than of SCC or BD and TIMP-2 expression was greater in the stroma of SCC than of BD. There was a correlation between increased metalloproteinase expression and depth of lesion (MMP-2 and TIMP-2), inflammation (MMP-2, MMP-9, TIMP-1 and TIMP-2) and microvessel density (MMP-2, MMP-9 and TIMP-2). CONCLUSIONS: MMP-2, MMP-9, TIMP-1 and TIMP-2 play an important role in the pathogenesis of non-melanoma skin cancer, but differ significantly in their expression levels between the tumour types examined. The immunoexpression of these proteins may be useful indicators of cutaneous cancer invasion and progression.

Ohmen, J. D., R. L. Moy, et al. (1994). "Selective accumulation of T cells according to T-cell receptor V beta gene usage in skin cancer." J Invest Dermatol **103**(6): 751-7.

To investigate whether specific T-cell populations are overrepresented in tumor-infiltrating lymphocytes (TIL) in skin cancer, we determined the T-cell receptor (TCR) diversity in biopsy specimens of basal cell carcinoma and squamous cell carcinoma. Immunostaining of tissue sections indicated that the majority of T cells expressed alpha beta TCRs. To assess diversity of the TCR beta chain, RNA was isolated directly from the tumor specimens and peripheral blood mononuclear cells (PBMC) from the same patient, cDNA was synthesized, and variable (V) beta chain gene usage was determined by the

polymerase chain reaction (PCR). In each basal cell (n = 11) and squamous cell (n = 7) carcinoma studied, several V beta families were overrepresented in TIL versus PBMC, in that they accounted for greater than 5% of the repertoire in TIL and were at least 2% higher in TIL than in PBMC. The predominant V beta gene segments overrepresented in TIL generally differed from individual to individual. Simultaneous comparison of the V beta repertoire of TIL to that of uninvolved skin and PBMC from the same individual revealed preferential expression of V beta families within the TIL in three of five basal cell and four of four squamous cell carcinomas. Again, the predominant V beta s differed from individual to individual. Comparison of the TCR repertoire in uninvolved skin versus PBMC did indicate that some V beta families were overexpressed in the resident T-cell compartment in skin, although the overrepresented families were not constant from individual to individual. These data indicate the selective concentration of T cells bearing specific alpha beta TCRs in the local immune response to basal cell and squamous cell carcinomas.

Oka, A., H. Hayashi, et al. (2003). "Localization of a non-melanoma skin cancer susceptibility region within the major histocompatibility complex by association analysis using microsatellite markers." Tissue Antigens **61**(3): 203-10.

The major histocompatibility complex (MHC) is known to have a role in the development of non-melanoma skin cancer (NMSC), although the genes and mechanisms involved have yet to be determined. To identify the susceptibility locus for NMSC within the MHC, we used a collection of well-defined polymorphic microsatellite markers from the Human leucocyte antigen (HLA) region for an association analysis of 150 cases with NMSC and 200 healthy controls selected from the Busselton population in Western Australia. High-resolution mapping was undertaken using a total of 40 highly polymorphic markers located at regular intervals across the HLA region (3.6Mb). Polymerase chain reaction (PCR) analysis was initially performed on pooled DNA markers to detect those markers that showed different allele profiles. Statistically significant differences in allelic frequencies (differentiating alleles) were found between cases and controls at three polymorphic microsatellite loci within a 470-kb genomic susceptibility region ranging between 6 kb centromeric of the HLA-B gene and intron 5 of the DDR gene. Interestingly, this genome region corresponded completely with the psoriasis-susceptibility locus. The three differentiating alleles and another four markers outside the susceptibility region were then PCR tested by individual genotyping of cases and controls. The newly identified susceptibility locus for NMSC within the MHC was found to be significantly different between the cases and controls by comparisons of allele frequencies at the three differentiating loci estimated from DNA pools and then confirmed by individual genotyping. This is the first study using high density microsatellite markers to localize a NMSC susceptibility region within the human genome.

Paolino, D., D. Cosco, et al. (2008). "Innovative bola-surfactant niosomes as topical delivery systems of 5-fluorouracil for the treatment of skin cancer." Int J Pharm **353**(1-2): 233-42.

An innovative niosomal system made up of alpha,omega-hexadecyl-bis-(1-aza-18-crown-6) (Bola), Span 80 and cholesterol (2:5:2 molar ratio) was proposed as a topical delivery system for 5-fluorouracil (5-FU), largely used in the treatment of different forms of skin cancers. Bola-niosomes showed a mean size of approximately 400 nm, which were reduced to approximately 200 nm by a sonication procedure with a polydispersion index value of 0.1. Bola-niosomes showed a loading capacity of approximately 40% with respect to the amount of 5-FU added during the preparation. 5-FU-loaded bola-niosomes were tested on SKMEL-28 (human melanoma) and HaCaT (non-melanoma skin cancer with a specific mutations in the p53 tumor suppressor gene) to assess the cytotoxic activity with respect to the free drug. 5-FU-loaded bola-niosomes showed an improvement of the cytotoxic effect with respect to the free drug. Confocal laser scanning microscopy studies were carried out to evaluate both the extent and the time-dependent bola-niosome-cell interaction. The percutaneous permeation of 5-FU-loaded niosomes was evaluated by using human stratum corneum and epidermis membranes. Bola-niosomes provided an increase of the drug penetration of 8- and 4-folds with respect to a drug aqueous solution and to a mixture of empty bola-niosomes with a drug aqueous solution.

Peissel, B., D. Zaffaroni, et al. (2001). "Use of intercross outbred mice and single nucleotide polymorphisms to map skin cancer modifier loci." Mamm Genome **12**(4): 291-4.

Car-R and Car-S outbred mouse lines, phenotypically selected for resistance and susceptibility to skin carcinogenesis respectively, show significant linkage disequilibrium (LD) at genetic markers mapping on chromosomal regions where skin cancer modifier loci (Skts3, Skts1, and Psl1 on Chrs 5, 7, and 9 respectively) have been mapped in standard crosses. Analysis of these regions for genetic linkage with skin cancer phenotypes in 245

(Car-R x Car-S)F2 intercross mice, by using single nucleotide polymorphisms (SNPs), revealed significant linkage at a possible allelic form of the Skts1 locus, whose mapping region was shortened to a <5.5-cM interval near the Tyr locus. The Car-derived Skts1 locus was linked with papilloma multiplicity and latency by a recessive inheritance of the susceptibility allele. Putative loci on Chr 5 (Skts3) and 9 (Psl1) showed no significant linkage. These results point to the important role of the Stks1 locus in mouse skin tumorigenesis in independent crosses. The shortened Skts1 mapping region should facilitate the identification of candidate genes.

Pendas, A. M., A. R. Folgueras, et al. (2004). "Diet-induced obesity and reduced skin cancer susceptibility in matrix metalloproteinase 19-deficient mice." Mol Cell Biol **24**(12): 5304-13.

Matrix metalloproteinase 19 (MMP-19) is a member of the MMP family of endopeptidases that, in contrast to most MMPs, is widely expressed in human tissues under normal quiescent conditions. MMP-19 has been found to be associated with ovulation and angiogenic processes and is deregulated in diverse pathological conditions such as rheumatoid arthritis and cancer. To gain further insights into the in vivo functions of this protease, we have generated mutant mice deficient in Mmp19. These mice are viable and fertile and do not display any obvious abnormalities. However, Mmp19-null mice develop a diet-induced obesity due to adipocyte hypertrophy and exhibit decreased susceptibility to skin tumors induced by chemical carcinogens. Based on these results, we suggest that this enzyme plays an in vivo role in some of the tissue remodeling events associated with adipogenesis, as well as in pathological processes such as tumor progression.

Peritz, A. E. and F. P. Gasparro (1999). "Psoriasis, PUVA, and skin cancer--molecular epidemiology: the curious question of T-->A transversions." J Investig Dermatol Symp Proc **4**(1): 11-6.

Photochemotherapy with 8-methoxypsoralen and long wavelength ultraviolet radiation (PUVA) is commonly used to treat psoriasis and vitiligo. These vastly different diseases respond to the therapy by different mechanisms even though the immediate effects of the therapy - photoadduct formation - is the same for both. Because psoriasis is not cured by PUVA, patients receive many treatments over their lifetime and develop a significant risk for the development of skin cancers (primarily squamous cell carcinomas). In this review the basic aspects of psoralen photobiology are reviewed briefly. In addition the impact of the analysis of mutations in the tumor suppressor gene, p53, are summarized. An unexpected mutation spectrum (very few T-->A transversions and frequent UVB signature C-->T transitions) suggest that effects other than direct DNA photoadduct formation may be at play. The roles of reactive oxygen species-induced base changes as well as other clastogenic factors are discussed. This analysis suggests that it may be possible to improve the therapeutic efficacy of PUVA by a careful evaluation of the mode of delivery.

Pfister, H. (1992). "Human papillomaviruses and skin cancer." Semin Cancer Biol **3**(5): 263-71.

Human papillomavirus (HPV)-induced skin warts are classically benign lesions. However an association between specific HPV types and skin cancer becomes obvious in epidermodysplasia verruciformis (EV). The analysis of this disease suggests that lesions infected with HPV types 5 and 8 carry a high risk of developing squamous cell carcinomas. The oncogenes of EV-viruses appear to be E6 and E2, rather than E7. The 'high risk' EV-viruses, HPV 5, 8, and 47, differ from related HPV types in the transforming activity of the E6 gene and in the density of positive transcription control elements in the non-coding region (NCR) of the genome. The extrachromosomal viral DNA in cancers may show deletions affecting regulatory sequences. EV-specific lesions occasionally occur in immunosuppressed patients and HPV 5 or 8 persist in some of the skin cancers to which these patients are prone. DNAs of HPV 2, 16, 34, or 41 were identified in few premalignant and malignant skin tumors of the general population.

Purdie, K. J., J. Pennington, et al. (1999). "The promoter of a novel human papillomavirus (HPV77) associated with skin cancer displays UV responsiveness, which is mediated through a consensus p53 binding sequence." Embo J **18**(19): 5359-69.

An aetiological role has been proposed for human papillomavirus (HPV) in skin carcinogenesis within the immunosuppressed patient population. To examine this possibility, we have focused on an HPV type that, to date, has been identified only in the cutaneous lesions of renal transplant recipients despite a high degree of sequence homology with other HPVs commonly found in warts in the general population. We report that the non-coding region of this virus, HPV type 77, contains a consensus binding site for the tumour suppressor protein p53, and we show by gel-retardation analysis that this sequence does indeed bind p53. Furthermore, using reporter gene assays, we demonstrate that HPV77 promoter activity is stimulated by UV radiation and that this response is mediated through the p53 binding site. This is the first

report of a p53-dependent positive response element within a viral genome. Our results suggest a possible novel mechanism by which specific types of HPV might act as cofactors with UV radiation in cutaneous transformation.

Qi, M., D. Chen, et al. (2002). "n-6 Polyunsaturated fatty acids increase skin but not cervical cancer in human papillomavirus 16 transgenic mice." Cancer Res **62**(2): 433-6.

Using a mouse with transgenes for the highly oncogenic human papillomavirus type 16, we asked whether a diet high in fat, namely, the n-6 polyunsaturated fatty acid linoleic acid, would influence the development of skin or cervical cancer. Virgin female keratin 14-human papillomavirus 16 transgenic mice were fed control diet or diet with 20% corn oil. The effect of these diets was compared in mice implanted or not implanted with 0.125 mg/60 day release of estradiol. More precancers and cancers of the skin developed faster in mice fed the high-fat diet. Estrogen had no effect on the development of skin cancers. In contrast, estrogen was necessary for the development of cervical cancer, and a high-fat diet had no effect on the development of cervical cancer.

Queille, S., C. Drougard, et al. (2001). "Effects of XPD mutations on ultraviolet-induced apoptosis in relation to skin cancer-proneness in repair-deficient syndromes." J Invest Dermatol **117**(5): 1162-70.

To understand the relationship between DNA repair, apoptosis, transcription, and cancer-proneness, we have studied the apoptotic response and the recovery of RNA synthesis following ultraviolet C and ultraviolet B irradiation in nucleotide excision repair deficient diploid fibroblasts from the cancer-prone xeroderma pigmentosum (XP) syndrome patients and the non-cancer-prone trichothiodystrophy (TTD) patients. Analysis of four XPD and four TTD/XPD fibroblast strains presenting different mutations on the XPD gene has shown that XPD cells are more sensitive to ultraviolet-induced apoptosis than TTD/XPD cells, and this response seems to be modulated by the type and the location of the mutation on the XPD gene. Moreover, the other xeroderma pigmentosum fibroblast strains analyzed (groups A and C) are more sensitive to undergo apoptosis after ultraviolet irradiation than normal human fibroblasts, showing that the cancer-proneness of xeroderma pigmentosum patients is not due to a deficiency in the ultraviolet-induced apoptotic response. We have also found that cells from transcription-coupled repair deficient XPA, XPD, TTD/XPD, and Cockayne's syndrome patients undergo apoptosis at lower ultraviolet doses than transcription-coupled repair proficient cells (normal human fibroblasts and XPC), indicating that blockage of RNA polymerase II at unrepaired lesions on the transcribed strand is the trigger. Moreover, XPD and XPA cells are more sensitive to ultraviolet-induced apoptosis than trichothiodystrophy and Cockayne's syndrome fibroblasts, suggesting that both cyclobutane pyrimidine dimers and pyrimidine 6-4 pyrimidone on the transcribed strand trigger apoptosis. Finally, we show that apoptosis is directly proportional to the level of inhibition of transcription, which depends on the density of ultraviolet-induced lesions occurring on transcribed sequences.

Queille, S., L. Luron, et al. (2007). "Analysis of skin cancer risk factors in immunosuppressed renal transplant patients shows high levels of UV-specific tandem CC to TT mutations of the p53 gene." Carcinogenesis **28**(3): 724-31.

Immunosuppressed renal transplant recipients (RTRs) are predisposed to non-melanoma skin cancers (NMSCs), predominantly squamous cell carcinomas (SCCs). We have analyzed skin lesions from RTRs with aggressive tumors for p53 gene modifications, the presence of Human Papillomas Virus (HPV) DNA in relation to the p53 codon 72 genotype and polymorphisms of the XPD repair gene. We detected 24 p53 mutations in 15/25 (60%) NMSCs, 1 deletion and 23 base substitutions, the majority (78%) being UV-specific C to T transitions at bipyrimidine sites. Importantly, 35% (6/17) are tandem mutations, including 4 UV signature CC to TT transitions possibly linked to modulated DNA repair caused by the immunosuppressive drug cyclosporin A (CsA). We found 8 p53 mutations in 7/17 (41%) precancerous actinic keratosis (AK), suggesting that p53 mutations are early events in RTR skin carcinogenesis. Immunohistochemical analysis shows a good correlation between p53 accumulation and mutations. HPV DNA was detected in 78% of skin lesions (60% Basal Cell Carcinomas, 82%AK and 79% SCCs). Thus, immunosuppression has increased the risk of infections by HPVs, predominantly epidermodysplasia verruciformis, speculated to play a role in skin cancer development. No association is found between HPV status and p53 mutation. Moreover, p53 codon 72 or frequencies of three XPD genotypes of RTRs are comparable with control populations. The p53 mutation spectrum, presenting a high level of CC to TT mutations, shows that the UV component of sunlight is the major risk factor and modulated DNA repair by immunosuppressive drug treatment may be significant in the skin carcinogenesis of RTRs.

Quinn, A. G., E. Healy, et al. (1995). "Microsatellite instability in human non-melanoma and melanoma skin cancer." J Invest Dermatol **104**(3): 309-12.

Microsatellite instability secondary to replication errors (RER), characterized by length changes at repetitive loci scattered throughout the genome, is a recently recognized genetic mechanism important in the development of some human cancers. Although RER has been reported in sebaceous gland tumors from patients with the Muir-Torre syndrome, the frequency of RER in human non-melanoma and melanoma skin cancers is not known. In this study, we investigated the importance of RER in human skin carcinogenesis. RER was identified in three of four actinic keratoses from a patient belonging to a kindred with documented Muir-Torre syndrome, which indicates that defective DNA replication may contribute to skin cancer development in such patients. Examination of a series of tumors from patients without Muir-Torre, including 137 skin cancers (47 basal cell carcinomas, 49 squamous cell carcinomas, and 41 primary malignant melanomas), 19 actinic keratoses, and 20 cases of Bowen's disease, using 10 or more microsatellite markers, identified repeat-sequence instability in less than 5% of the tumors studied. In six of the eight tumors, the sole change was an alteration 2 base pairs in length at a single locus. One patient with a squamous cell carcinoma showed changes at multiple loci suggesting defective mismatch repair. Although the low frequency of RER found in this study of a large series of human skin tumors suggests that this phenomenon is uncommon in patients with skin cancer, the identification of RER at multiple loci in two patients suggests that error-prone replication may be important in skin cancer development in some individuals.

Ramsay, H. M., P. N. Harden, et al. (2001). "Polymorphisms in glutathione S-transferases are associated with altered risk of nonmelanoma skin cancer in renal transplant recipients: a preliminary analysis." J Invest Dermatol **117**(2): 251-5.

Non-melanoma skin cancer (NMSC) represents a significant cause of morbidity and mortality among renal transplant recipients, with tumors behaving more aggressively than those in nontransplant patients. Not all immunosuppressed patients develop NMSC, however, and in those that do, the rate of accrual and numbers of lesions vary considerably. Though ultraviolet light is critical, it is unlikely that this alone explains the observed phenotypic diversity, suggesting the possible involvement of genetic factors. Furthermore, although twin studies in nontransplant patients with NMSC suggest a low genetic component, several genes associated with susceptibility and outcome in these patients have been identified. Thus, having previously shown that polymorphism in members of the glutathione S-transferase (GST) supergene family is associated with altered NMSC risk in nontransplant patients, we examined allelism in GSTM1, GSTP1, GSTM3, and GSTT1 in 183 renal transplant recipients. GSTM1 null was associated with increased squamous cell carcinoma (SCC) risk ($p = 0.042$, OR = 3.1). This remained significant after correction for age, gender, and ultraviolet light exposure ($p = 0.012$, OR = 8.4) and was particularly strong in patients with higher ultraviolet light exposure (e.g., sunbathing score > 3, $p = 0.003$, OR = 11.5) and in smokers ($p = 0.021$, OR = 4.8). Analysis of the interaction between GSTM1 null and sunbathing score showed that the two factors were synergistic and individuals with both risk parameters demonstrated a shorter time from transplantation to development of the first SCC ($p = 0.012$, hazard ratio = 7.1). GSTP1*Ile homozygotes developed larger numbers of SCC ($p = 0.002$, rate ratio = 7.6), particularly those with lower ultraviolet light exposure and cigarette consumption. GSTM3 and GSTT1 also demonstrated significant associations, though some genotype frequencies were low. These preliminary data suggest that genetic factors mediating protection against oxidative stress are important in NMSC development in immunosuppressed patients and may be useful in identifying high-risk individuals.

Rass, K. and J. Reichrath (2008). "UV damage and DNA repair in malignant melanoma and nonmelanoma skin cancer." Adv Exp Med Biol **624**: 162-78.

Exposition of the skin with solar ultraviolet radiation (UV) is the main cause of skin cancer development. The consistently increasing incidences of melanocytic and nonmelanocytic skin tumors are believed to be at least in part associated with recreational sun exposure. Epidemiological data indicate that excessive or cumulative sunlight exposition takes place years and decades before the resulting malignancies arise. The most important defense mechanisms that protect human skin against UV radiation involve melanin synthesis and active repair mechanisms. DNA is the major target of direct or indirect UV-induced cellular damage. Low pigmentation capacity in white Caucasians and rare congenital defects in DNA repair are mainly responsible for protection failures. The important function of nucleotide excision DNA repair (NER) to protect against skin cancer becomes obvious by the rare genetic disease xeroderma pigmentosum, in which diverse NER genes are mutated. In animal models, it has been demonstrated that UVB is more effective to induce skin cancer than UVA. UV-

induced DNA photoproducts are able to cause specific mutations (UV-signature) in susceptible genes for squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). In SCC development, UV-signature mutations in the p513 tumor suppressor gene are the most common event, as precancerous lesions reveal approximately 80% and SCCs > 90% UV-specific p53 mutations. Mutations in Hedgehog pathway related genes, especially PTCH1, are well known to represent the most significant pathogenic event in BCC. However, specific UV-induced mutations can be found only in approximately 50% of sporadic BCCs. Thus, cumulative UVB radiation can not be considered to be the single etiologic risk factor for BCC development. During the last decades, experimental animal models, including genetically engineered mice, the Xiphophorus hybrid fish, the south american oppossum and human skin xenografts, have further elucidated the important role of the DNA repair system in the multi-step process of UV-induced melanomagenesis. An increasing body of evidence now indicates that nucleotide excision repair is not the only DNA repair pathway that is involved in UV-induced tumorigenesis of melanoma and nonmelanoma skin cancer. An interesting new perspective in DNA damage and repair research lies in the participation of mammalian mismatch repair (MMR) in UV damage correction. As MMR enzyme hMSH2 displays a p53 target gene, is induced by UVB radiation and is involved in NER pathways, studies have now been initiated to elucidate the physiological and pathophysiological role of MMR in malignant melanoma and nonmelanoma skin cancer development.

Rees, J. L. and E. Healy (1997). "Melanocortin receptors, red hair, and skin cancer." J Investig Dermatol Symp Proc **2**(1): 94-8.

Cutaneous pigmentation is a major determinant of the cutaneous response to ultraviolet radiation, and consequently of the risk of developing skin cancer. Over the past 10 years, several genes involved in melanogenesis have been identified, including the melanocortin 1 receptor gene. Recent work on the melanocortin 1 receptor suggests that it is a key player in determining whether eumelanin or pheomelanin is predominantly produced both in vitro and in vivo. In the mouse, variants of this receptor, which differ in their ability to activate adenylyl cyclase, are associated with different coat colors. In humans, melanocortin 1 receptor variants are associated with red hair and fair skin, and work in progress from our laboratory suggests that certain melanocortin 1 receptor variants may preferentially be associated with hair color rather than skin type. In addition, melanocortin 1 receptor variants are a risk factor, possibly independent of skin type, for melanoma susceptibility.

Ren, Z. P., A. Ahmadian, et al. (1997). "Benign clonal keratinocyte patches with p53 mutations show no genetic link to synchronous squamous cell precancer or cancer in human skin." Am J Pathol **150**(5): 1791-803.

Ultraviolet light, which is the major etiology of human skin cancer, will cause mutations in the p53 gene. We and others have found that such mutations occur in more than one-half of non-melanoma squamous cell cancer and precancer. Immunostaining for p53 has disclosed a characteristic compact pattern not only in cancer/precancer but also in areas of microscopically normal epidermis termed p53 patches. By microdissection, sequence analysis of the p53 gene, and analysis of loss of heterozygosity (LOH) at the site of this gene, we have now extended previous data to ascertain whether these p53 patches are precursors of simultaneously present squamous cell cancer or its morphologically recognized precancerous stages (dysplasia, carcinoma in situ). In none of 11 instances with co-existence of a p53 patch with dysplasia or in situ or invasive cancer were the mutations identical. We conclude that p53 patches, estimated to be approximately 100,000 times as common as dysplasia, have a very small or even no precancerous potential. Their common presence demonstrates that human epidermis contains a large number of p53 mutations apparently without detrimental effect. The only result of the mutation may be a clandestine benign clonal keratinocyte proliferation. The importance of p53 mutations for such benign cell multiplication on one band and malignant transformation on the other is unclear. Although the spectrum, type, and multiplicity of mutations were similar in both types of proliferative responses, there was a clear difference with respect to LOH. No LOH was found in 17 p53 patches. By contrast 11 of 30 precancers/cancers had LOH.

Ren, Z. P., F. Ponten, et al. (1996). "Two distinct p53 immunohistochemical patterns in human squamous-cell skin cancer, precursors and normal epidermis." Int J Cancer **69**(3): 174-9.

Specimens of squamous-cell neoplasms (81 invasive cancers, 36 in situ cancers, 70 dysplasias, 5 keratoacanthomas, 19 papillomas) and normal skin were immunostained with p53 antibody. Nuclear accumulation of p53 was visualized as following 2 distinct patterns: dispersed or compact. The former is interpreted as a reversible reaction to sunlight, whereas the latter, after microdissection and sequencing of DNA, has been shown to reflect clonal multiplication of keratinocytes with mutated p53. The

dispersed pattern was diffusely distributed and usually only involved a small proportion of epidermal cells. The compact pattern was characterized as a contiguous area of homogeneously stained cells sharply demarcated from its surroundings. It involved patches of normal epidermis or large areas of dysplastic or malignant squamous epithelium. Immature cells were always stained, whereas immunoreactivity was variably present in differentiating keratinocytes. Dispersed patterns occurred in 94.7% of strongly UV-exposed skin (mainly face) and to a lesser extent in less exposed parts of the body. It showed no correlation to the age of the individual. About two-thirds of biopsies from individuals over age 50 displayed compact patterns in sun-exposed, otherwise normal, epidermis. About 65% of pre-malignant and malignant squamous-cell neoplasms had a compact pattern. The presence of p53 immunoreactivity as a compact pattern supports the idea that mutations of the p53 gene are early events in the sequence from dysplasia to invasive squamous-cell cancer of the skin. Also, even in the absence of cellular atypia, patches of epidermal cells can accumulate p53 in a way that is indistinguishable from that of cancer and pre-cancer.

Rodriguez-Villanueva, J. and T. J. McDonnell (1995). "Induction of apoptotic cell death in non-melanoma skin cancer by interferon-alpha." Int J Cancer **61**(1): 110-4.

Interferon-alpha (IFN-alpha) is a cytokine that is effective in the treatment of a variety of cancers, including non-melanoma skin cancers. The biologic responses of cells to IFN-alpha are pleiotropic and include growth suppression and immunomodulation. The potential direct effects of IFN-alpha on tumor cell populations are incompletely characterized. Our findings indicate that IFN-alpha can directly induce apoptosis (programmed cell death) in sensitive squamous cell skin cancer cell lines. Cell lines resistant to the cytotoxic effects of IFN-alpha showed no evidence of apoptosis induction. Transfection of IFN-alpha-sensitive cell lines with a bcl-2 expression vector conferred partial resistance to cell death induction by IFN-alpha. Our results indicate that the clinical efficacy of IFN-alpha may, in part, be related to the ability of this cytokine to induce apoptosis.

Romer, J., C. Pyke, et al. (2001). "Cancer cell expression of urokinase-type plasminogen activator receptor mRNA in squamous cell carcinomas of the skin." J Invest Dermatol **116**(3): 353-8.

In this study we have used in situ hybridization with radiolabeled antisense RNA probes to examine the expression of mRNA for urokinase-type plasminogen activator and its receptor in histologic samples of squamous cell (n = 7) and basal cell (n = 7) carcinomas of the skin. Messenger RNA for both urokinase-type plasminogen activator and its receptor were expressed in all of the squamous cell carcinomas, but could not be detected in the basal cell carcinomas. In all of the seven squamous cell carcinomas a signal for urokinase-type plasminogen activator receptor mRNA was detected focally in well-differentiated cancer cells surrounding keratinized pearls, and in four specimens urokinase-type plasminogen activator receptor mRNA was in addition expressed by cancer cells at the edge of invasively growing strands of tumor. Urokinase-type plasminogen activator mRNA expression was found in virtually all the cancer cells of the squamous cell carcinomas, and importantly we found, by hybridizations for urokinase-type plasminogen activator and its receptor mRNA on adjacent sections of squamous cell carcinomas, that it was exactly the invading cancer cells that simultaneously expressed both these components required for plasmin-mediated proteolysis at the cell surface. We have previously shown that both urokinase-type plasminogen activator and its receptor mRNA are expressed by the leading-edge keratinocytes in regenerating epidermis during mouse skin wound healing, and that wound healing is impaired in mice made deficient in plasminogen by targeted gene disruption. We propose that there are similarities between the mechanisms of generation and regulation of extracellular proteolysis during skin re-epithelialization and squamous cell carcinoma invasion. The ability of the squamous carcinoma cells to mimic the "invasive" phenotype of re-epithelializing keratinocytes may be one of the factors that make squamous cell carcinomas more aggressive tumors than basal cell carcinomas.

Runger, T. M., I. Vergilis, et al. (2005). "How disruption of cell cycle regulating genes might predispose to sun-induced skin cancer." Cell Cycle **4**(5): 643-5.

The Ink4a/Arf (CDKN2a) locus encodes two proteins that regulate two of the most important tumor suppressor pathways represented by p53 and Rb.(1) Loss of either p16(INK4a) or p19(ARF) was recently reported to reduce the ability of mouse cells to repair UV-induced DNA damage and to induce a UV-mutator phenotype. This observation was independent of cell cycle effects incurred by either p16(INK4a) and/or p19(ARF) loss, as it was demonstrable in unirradiated cells using UV-treated DNA. We suggest that this might explain why germ line mutations of INK4a/ARF predispose mainly to malignant melanoma, a UV-induced skin cancer, and provides a molecular explanation for the link between

melanomagenesis and impaired DNA repair. It also further demonstrates that regulation of cell cycle check points and DNA repair in response to genomic insults, such as ultraviolet irradiation are intricately interwoven processes. Differences in the apoptotic response to ultraviolet light between melanocytes and keratinocytes might explain why INK4a/ARF mutations predispose to malignant melanoma, but not to keratinocyte-derived skin cancers.

Saran, A., D. Zaffaroni, et al. (2002). "Inhibition of both skin and lung tumorigenesis by Car-R mouse-derived cancer modifier loci." Int J Cancer **97**(5): 580-3.

The Car-R outbred mouse line was phenotypically selected for high resistance to two-stage skin tumorigenesis. In the present study we tested the hypothesis that a subset of genetic loci responsible for resistance to skin tumorigenesis of Car-R mice might also inhibit lung tumorigenesis. Skin and lung tumorigenesis were induced in groups of Car-R, SWR/J, (SWR/JxCar-R)F1 and SWR/Jx(SWR/JxCar-R) backcross mice by i.p. urethane initiation and skin TPA promotion. Car-R mice showed a much lower susceptibility to both skin and lung tumorigenesis as compared to SWR/J mice, which are susceptible to both lung and skin tumorigenesis. The Car-R-inherited genome significantly inhibited both skin and lung cancer development in the F1 progeny of Car-R with SWR/J mice. In the backcross population, skin and lung tumor phenotypes showed a statistically significant correlation, indicating that a subset of the cancer resistance alleles, which segregated in the Car-R line during selection for resistance to skin carcinogenesis, provides resistance to both skin and lung tumorigenesis.

Saul, A. N., T. M. Oberyszyn, et al. (2005). "Chronic stress and susceptibility to skin cancer." J Natl Cancer Inst **97**(23): 1760-7.

BACKGROUND: Studies have shown that chronic stress or UV radiation independently suppress immunity. Given their increasing prevalence, it is important to understand whether and how chronic stress and UV radiation may act together to increase susceptibility to disease. Therefore, we investigated potential mediators of a stress-induced increase in emergence and progression of UV-induced squamous cell carcinoma. METHODS: SKH1 mice susceptible to UV-induced tumors were unexposed (naive, n = 4) or exposed (n = 16) to 2240 J/m2 of UVB radiation three times a week for 10 weeks. Half of the UVB-exposed mice were left nonstressed (i.e., they remained in their home cages) and the other half were chronically stressed (i.e., restrained during weeks 4-6). UV-induced tumors were measured weekly from week 11 through week 34, blood was collected at week 34, and tissues were collected at week 35. mRNA expression of interleukin (IL)-12p40, interferon (IFN)-gamma, IL-4, IL-10, CD3epsilon, and CCL27/CTACK, the skin T cell-homing chemokine, in dorsal skin was quantified using real-time polymerase chain reaction. CD4+, CD8+, and CD25+ leukocytes were counted using immunohistochemistry and flow cytometry. All statistical tests were two-sided. RESULTS: Stressed mice had a shorter median time to first tumor (15 versus 16.5 weeks, difference = 1.5 weeks, 95% confidence interval [CI] = -3.0 to 3.3 weeks; P = .03) and reached 50% incidence earlier than controls (15 weeks versus 21 weeks). Stressed mice also had lower IFN-gamma (mean = 0.03 versus mean = 0.07, difference = 0.04, 95% CI = 0.004 to 0.073; P = .02), CCL27/CTACK (mean = 101 versus mean = 142, difference = 41, 95% CI = 8.1 to 74.4; P = .03), and CD3epsilon (mean = 0.18 versus mean = 0.36, difference = 0.18, 95% CI = 0.06 to 0.30; P = .007) gene expression and lower numbers of infiltrating CD4+ cells (mean = 9.40 versus mean = 13.7, difference = 4.3, 95% CI = 2.36 to 6.32; P = .008) than nonstressed mice. In addition, stressed mice had more regulatory/suppressor CD25+ cells infiltrating tumors and more CD4+ CD25+ cells in circulation (mean = 0.36 versus mean = 0.17, difference = 0.19, 95% CI = 0.005 to 0.38; P = .03) than nonstressed mice. CONCLUSIONS: Chronic stress increased susceptibility to UV-induced squamous cell carcinoma in this mouse model by suppressing type 1 cytokines and protective T cells and increasing regulatory/suppressor T cell numbers.

Saunders, N., A. Dicker, et al. (1999). "Histone deacetylase inhibitors as potential anti-skin cancer agents." Cancer Res **59**(2): 399-404.

The regulation of squamous differentiation is a tightly regulated process involving transcriptional repression and activation. Previous studies have established that squamous carcinoma cell lines inappropriately regulate the transcription of genes important to the control of squamous differentiation. Histone deactylase inhibitors such as trichostatin A (TSA) and butyrate disrupt normal chromatin structure and cause alterations in gene expression/regulation. For these reasons, we examined the effects of both butyrate and TSA on the growth and differentiation of human keratinocytes or squamous carcinoma cells in tissue culture. We found that treatment of keratinocytes or squamous carcinoma cells with butyrate induced a reversible growth arrest. TSA, on the other hand, induced an irreversible growth arrest in both keratinocytes and

squamous carcinoma cells. The growth arrest of keratinocytes induced by TSA or butyrate was accompanied by a reduction in the mRNA levels for proliferation gene cdk1 and an induction of the mRNA for the differentiation-specific transglutaminase type I gene (TG1). In contrast, the squamous carcinoma cells had decreased cdk1 and TG1 mRNA in response to TSA or butyrate. Both of these agents produced transient increases in the acetylation of histone H4 in keratinocytes and squamous carcinoma cells. These data indicated that TSA may have potential as a topical treatment for epidermal malignancies.

Saurat, J. H. (2001). "Skin, sun, and vitamin A: from aging to cancer." J Dermatol **28**(11): 595-8.

Human epidermis contains significant amounts of Vitamin A, the enzymes responsible for its metabolism toward either storage or activation, the binding proteins for its protection and specific transport, and the nuclear receptors involved in the vitamin A-induced gene-activity modulation. This complex system may be drastically altered upon ultraviolet light exposure because vitamin A absorbs in the UVB range. We have conducted a series of experiments in order to analyse the effects of UV exposure on the epidermal stores of endogenous vitamin A (retinol and retinyl esters), the activity of enzymes and binding proteins, and some biological parameters such as apoptosis transcription factors expression (cJun) and thymine dimers. Current data indicate that the vitamin A system is a direct target of both UVB and UVA and participates in an adaptive response to UV exposure. The physiological role of this adaptive response to acute and chronic sun exposure should be further analysed. Interfering with this UV-induced vitamin A deficiency is a new concept for the prevention of skin cancer and aging.

Sauter, E. R., A. J. Klein-Szanto, et al. (1998). "Ultraviolet B-induced squamous epithelial and melanocytic cell changes in a xenograft model of cancer development in human skin." Mol Carcinog **23**(3): 168-74.

We previously demonstrated that precancers (actinic keratoses and dysplasias) and squamous cell carcinomas (SCCs) develop in one quarter of human neonatal foreskins grafted onto recombinase-activating gene-1-knockout mice treated once with 7,12-dimethylbenz[a]anthracene (DMBA) followed by chronic intermediate-range ultraviolet (UV) B light irradiation. The goals of this study were to determine if a longer UVB exposure followed by further observation would increase the number of precancers and invasive cancers and to evaluate whether this model results in changes in p53 expression and cell proliferation similar to those seen in sun-damaged normal skin, actinic keratoses, and SCCs. The treatment consisted of a single dose of DMBA followed by 500 J/m2 UVB radiation administered three times weekly for at least 5 mo. Histologic changes (cysts, hyperplasias, precancers, and/or invasive cancers) were seen in 24 of 25 treated xenografts but not in controls. Ten of 25 grafts (40%) had two or more histological changes, and two human SCCs developed. After seven or more months of UV exposure and a total time from DMBA treatment to killing of 12-18 mo, 83% (15 of 18) of specimens developed squamous precancer or SCC of human origin, and 44% (eight of 18) developed melanocytic hyperplasia or melanoma. The change from moderate dysplasias to SCC required longer UV exposure (median, 11 mo), and 5 mo more observation than did the development of mild dysplasias (median UV exposure, 7 mo; median DMBA to death time, 12 mo). There was a direct correlation between both p53 expression and cell proliferation and the degree of histologic alteration both in squamous epithelial and melanocytic cells.

Sikkink, S. K., I. Rehman, et al. (1997). "Deletion mapping of chromosome 3p and 13q and preliminary analysis of the FHIT gene in human nonmelanoma skin cancer." J Invest Dermatol **109**(6): 801-5.

Loss of heterozygosity of chromosomes 3p and 13q occurs frequently in human cutaneous squamous cell neoplasms, suggesting the presence of one or more tumor suppressor genes on these chromosome arms that may be involved in the pathogenesis of this tumor type. To date there is no clear evidence in cutaneous tumors where these putative genes are located. In this study we have analyzed 20 squamous cell neoplasms that show allelic loss at chromosome 13q, and 22 squamous cell neoplasms that show allelic loss at chromosome 3p, in an attempt to define the smallest area of deletion. One commonly deleted region was identified on chromosome 13 that centred around 13q13, and two commonly deleted regions were identified on chromosome 3 that mapped to 3p24-pter and 3p12-p14.1. Our findings suggest the presence of at least one tumor suppressor gene on chromosome 13 and two tumor suppressor genes on chromosome 3p that may be involved in the progression of these neoplasms. Deletions within the Fragile Histidine Triad gene, located at 3p14.2, have been reported in several tumors, leading to the suggestion that this gene is involved in tumor development. To evaluate the role of the Fragile Histidine Triad gene in nonmelanoma skin cancer, we have used reverse transcriptase polymerase chain reaction analysis to screen for deletions in 16 tumors (five basal cell

carcinomas, five squamous cell carcinomas, five actinic keratoses, and one case of Bowen's disease) and HaCaT and A431 cell lines. A normal transcript was found to be expressed in 14 of 16 tumors and both cell lines. This suggests that the Fragile Histidine Triad gene is not a common target for deletion in Bowen's disease and the cell lines HaCaT and A431.

Simon, J. C., K. H. Heider, et al. (1996). "Expression of CD44 isoforms in human skin cancer." Eur J Cancer **32A**(8): 1394-400.

In animal models, isoforms of CD44 (CD44v) containing sequences encoded by one or several of ten different exons (v1-v10) contribute to tumour metastasis. In certain human cancers, CD44v6 expression is associated with poor prognosis. This paper examines CD44v expression in skin carcinogenesis and skin cancer metastasis. CD44v expression was studied in basal cell carcinoma (BCC), squamous cell carcinoma (SCC), primary malignant melanoma (PMM), metastases of MM (MMM), benign melanocytic naevi (BMN) and normal skin (NS) by immunohistochemistry and reverse transcript polymerase chain reaction (RT-PCR). BCC, SCC and NS expressed several CD44v, including v6, albeit in different distributions and intensities. PMM, MMM and BMN expressed isoforms containing v7/8 and v10, but failed to express epitopes encoded by v5 or v6. Thus, different CD44 isoforms are found in human skin cancers and are modulated during carcinogenesis. However, we did not observe a correlation of CD44v6 expression with metastatic potential.

Soehnge, H., A. Ouhtit, et al. (1997). "Mechanisms of induction of skin cancer by UV radiation." Front Biosci **2**: d538-51.

Ultraviolet (UV) radiation is the carcinogenic factor in sunlight; damage to skin cells from repeated exposure can lead to the development of cancer. UV radiation has been mainly implicated as the cause of non-melanoma skin cancer, although some role for UV in malignant melanoma has been suggested. The induction of skin cancer is mainly caused by the accumulation of mutations caused by UV damage. Cellular mechanisms exist to repair the DNA damage, or to induce apoptosis to remove severely damaged cells; however, the additive effects of mutations in genes involved in these mechanisms, or in control of the cell cycle, can lead to abnormal cell proliferation and tumor development. The molecular events in the induction of skin cancer are being actively investigated, and recent research has added to the understanding of the roles of tumor suppressor and oncogenes in skin cancer. UV radiation has been shown to induce the expression of the p53 tumor suppressor gene, and is known to produce "signature" mutations in p53 in human and mouse skin cancers and in the tumor suppressor gene patched in human basal cell carcinoma. The role of UV radiation in suppression of immune surveillance in the skin, which is an important protection against skin tumor development, is also being investigated. The knowledge gained will help to better understand the ways in which skin cancer arises from UV exposure, which will in turn allow development of better methods of treatment and prevention.

Sommerer, C., W. Hartschuh, et al. (2008). "Pharmacodynamic immune monitoring of NFAT-regulated genes predicts skin cancer in elderly long-term renal transplant recipients." Clin Transplant **22**(5): 549-54.

INTRODUCTION: Among elderly allograft recipients non-melanoma skin cancer (NMSC) is the most common malignancy. We have previously shown that malignancies are associated with a higher intensity of ciclosporin A (CsA)-induced immunosuppression. METHOD: Fifty-five long-term elderly renal transplant patients with a stable transplant function had regular skin examinations. The expression of the nuclear factor of activated T cells (NFAT)-regulated genes (interleukin-2, granulocyte-macrophage colony stimulating-factor, interferon-gamma) was determined by real-time PCR at CsA trough levels and two h after oral intake. RESULTS: The CsA dose was 2.0 mg/kg (0.95-3.50), with CsA trough level (C0) level 97 microg/L (33-157) and CsA two-h level (C2) 538 microg/L (350-1228). NMSC was diagnosed in 14/55 patients (25.4%). A total of 85.7% of allograft recipients with NMSC were male ($p < 0.005$). Age, time after transplantation, CsA dose, CsA C0 and C2 level were comparable in both groups. NFAT-regulated gene expression was signficantly lower in patients with skin cancer compared with patients without skin cancer [4.94% (0.91-13.4) vs. 11.6% (3.3-40.8), $p < 0.001$). CONCLUSION: The unproportional high incidence of NMSC in elderly long-term kidney-transplanted patients correlates with a lower NFAT-regulated gene expression which is a surrogate biomarker for a higher degree of functional immunosuppression. Further studies are required to determine whether the reduction of CsA with an increased NFAT-regulated gene expression is associated with a lower NMSC incidence.

Srivastava, S., Y. A. Tong, et al. (1992). "Detection of both mutant and wild-type p53 protein in normal skin fibroblasts and demonstration of a shared 'second hit' on p53 in diverse tumors from a cancer-prone family with Li-Fraumeni syndrome." Oncogene **7**(5): 987-91.

Germline transmission of mutant p53 gene in cancer-prone families with Li-Fraumeni syndrome has

revealed a new role for p53 in the genetic predisposition to cancer. The studies reported here focus on the analysis of the expression of normal and mutant p53 RNA and protein in germline configuration and demonstrate that normal skin fibroblasts derived from members of a family with Li-Fraumeni syndrome express mutant p53Gly----Asp(245) protein and RNA at levels similar to the wild-type p53. Thus, these fibroblasts represent a unique biological system in which endogenous promoters are utilized for the expression of both mutant and normal p53. We have further extended the earlier observations on the analysis of mutant p53 with a limited number of tumors derived from individuals with Li-Fraumeni syndrome. Tumors arising from two different germ layers in four individuals in a single family clearly exhibited the loss of the wild-type allele and the retention of the mutant allele observed in the normal skin fibroblasts derived from the same individuals. These observations further support the notion that germline p53 mutation plays a key role in the tumorigenesis of individuals with Li-Fraumeni syndrome.

Stander, S. and T. Schwarz (2005). "Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is expressed in normal skin and cutaneous inflammatory diseases, but not in chronically UV-exposed skin and non-melanoma skin cancer." Am J Dermatopathol **27**(2): 116-21.

Tumor necrosis factor-related apoptosis inducing ligand (TRAIL) is a member of the tumor necrosis factor family that preferentially induces apoptosis in transformed but not normal cells and that is constitutively expressed in many organs including the skin. In addition to its therapeutic potential, TRAIL might act as a natural guardian eliminating transformed cells at an early stage. Ultraviolet (UV) radiation is not only a potent carcinogen because of its mutagenic effects but also because of its capacity to paralyze natural protection mechanisms, including the tumor suppressor gene p53. Therefore, we studied the effect of UV exposure on the expression of TRAIL in the skin by immunohistochemical analysis. TRAIL and its receptors TRAIL-R1 and TRAIL-R4 were constitutively expressed in normal epidermis and not altered in a variety of inflammatory dermatoses including those associated with interface dermatitis. TRAIL was not altered in biopsies of acute sunburn, polymorphic light eruption, and photoprovocation testing, indicating that acute UV exposure does not affect TRAIL expression. No differences were observed in UV-protected and chronically UV-exposed skin samples of younger adults. In contrast, TRAIL was significantly reduced in chronically UV-exposed skin of elderly individuals. In addition, TRAIL expression was reduced in actinic keratoses and Bowen disease and almost completely lost in basal cell and squamous cell carcinomas. In contrast, keratoacanthomas did not reveal any alterations in TRAIL expression. Taken together, these data indicate that chronic UV exposure in elderly patients results in the loss of TRAIL expression, which might contribute to the increased risk of skin cancer in this population. Down-regulation of TRAIL might represent another example of a natural protection mechanism that is eliminated by chronic UV exposure.

Stratigos, A. J., N. Kapranos, et al. (2005). "Immunophenotypic analysis of the p53 gene in non-melanoma skin cancer and correlation with apoptosis and cell proliferation." J Eur Acad Dermatol Venereol **19**(2): 180-6.

BACKGROUND: Sunlight precipitates a series of genetic events that lead to the development of skin cancers such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). The p53 tumour suppressor gene, which plays a pivotal role in cell division and apoptosis, is frequently found mutated in sunlight-induced skin tumours. OBJECTIVE: To investigate the immunoreactivity of the p53 gene in non-melanoma skin cancers and to correlate its expression with apoptotic and cell proliferation markers. METHODS: We analysed 35 non-melanoma tumours including 19 BCCs and 16 SCCs from sun-exposed skin areas. p53 protein expression was studied immunohistochemically using the DO7 monoclonal antibody against wild-type and mutant p53 forms. The percentage of p53-immunopositive nuclei was measured by image analysis. Cell proliferation and apoptosis were also assessed by image analysis following Ki-67 immunostaining and application of the TUNEL method on paraffin sections, respectively. RESULTS: The percentage of p53-expressing cells varied from 3.5 to 90 in BCCs (median value 54.4%) and from 3.7 to 94 in SCCs (median value 40.3%). The mean value of Ki-67-positive cells was comparable in both groups of tumours with a mean value of 40.6% in BCCs and 34.6% in SCCs. Conversely, the TUNEL assay showed sporadic staining of apoptotic cells within the tumours with a mean value of 1.12% in BCCs and 1.8% in SCCs. p53 protein expression was correlated positively with cell proliferation ($r = 0.75$, $P = 0.000001$) and negatively with apoptosis ($r = -0.23$, $P = 0.05$). CONCLUSION: p53 immunoreactivity was high in the majority of the skin carcinomas examined and correlated positively with cell proliferation and negatively with apoptosis. The p53 protein overexpression appears to be related to an inactivated protein resulting from mutations of the p53 gene or other unclear molecular mechanisms.

Sturm, R. A. (2002). "Skin colour and skin cancer - MC1R, the genetic link." Melanoma Res **12**(5): 405-16.

Pigmentary traits such as red hair, fair skin, lack of tanning ability and propensity to freckle (the RHC phenotype) have been identified as genetic risk factors for both melanoma and non-melanocytic skin cancers when combined with the environmental risk factor of high ultraviolet light exposure. The human melanocortin-1 receptor (MC1R) is a key determinant of the pigmentation process and can account in large part for the diverse range of variation in human pigmentation phenotypes and skin phototypes. The coding sequence is highly polymorphic in human populations, with several of these variant forms of the receptor now known to be associated with the RHC phenotype. We have examined variant allele frequencies in the general population and in a collection of adolescent dizygotic and monozygotic twins with defined pigmentation characteristics. Variant allele frequencies have also been determined in several case-control studies of sporadic melanoma, basal cell carcinoma and squamous cell carcinoma, and in familial melanoma kindreds collected within Australia. These studies have shown that three RHC alleles - Arg151Cys, Arg160Trp and Asp294His - were associated with increased risk in all forms of skin cancer and with penetrance and age of onset in familial melanoma in mutation carriers. There is a significant RHC allele heterozygote carrier effect on skin phototype and skin cancer risk, which indicates that variant alleles do not behave in a strictly recessive manner. Ultimately, the genetic and chemical assessment of melanin synthesis rather than skin colour will be the best indicator for skin cancer risk, and such genetic association studies combined with functional analysis of variant alleles should provide the link to understanding skin phototypes.

Sturm, R. A., D. L. Duffy, et al. (2003). "The role of melanocortin-1 receptor polymorphism in skin cancer risk phenotypes." Pigment Cell Res **16**(3): 266-72.

We have examined melanocortin-1 receptor (MC1R) variant allele frequencies in the general population and in a collection of adolescent dizygotic and monozygotic twins to determine statistical associations of pigmentation phenotypes with increased skin cancer risk. This included hair and skin color, freckling, mole count and sun exposed skin reflectance. Nine variants were studied and designated as either strong R (OR = 63; 95% CI 32-140) or weak r (OR = 5; 95% CI 3-11) red hair alleles. Penetrance of each MC1R variant allele was consistent with an allelic model where effects were multiplicative for red hair but additive for skin reflectance. To assess the interaction of the brown eye color gene BEY2/OCA2 on the phenotypic effects of variant MC1R alleles we imputed OCA2 genotype in the twin collection. A modifying effect of OCA2 on MC1R variant alleles was seen on constitutive skin color, freckling and mole count. In order to study the individual effects of these variants on pigmentation phenotype we have established a series of human primary melanocyte strains genotyped for the MC1R receptor. These include strains which are MC1R wild-type consensus, variant heterozygotes, and homozygotes for strong R alleles Arg151Cys and Arg160Trp. Ultrastructural analysis demonstrated that only consensus strains contained stage III and IV melanosomes in their terminal dendrites whereas Arg151Cys and Arg160Trp homozygous strains contained only immature stage I and II melanosomes. Such genetic association studies combined with the functional analysis of MC1R variant alleles in melanocytic cells should provide a link in understanding the association between pigmentary phototypes and skin cancer risk.

Suga, T., A. Ishikawa, et al. (2007). "Haplotype-based analysis of genes associated with risk of adverse skin reactions after radiotherapy in breast cancer patients." Int J Radiat Oncol Biol Phys **69**(3): 685-93.

PURPOSE: To identify haplotypes of single nucleotide polymorphism markers associated with the risk of early adverse skin reactions (EASRs) after radiotherapy in breast cancer patients. METHODS AND MATERIALS: DNA was sampled from 399 Japanese breast cancer patients who qualified for breast-conserving radiotherapy. Using the National Cancer Institute-Common Toxicity Criteria scoring system, version 2, the patients were grouped according to EASRs, defined as those occurring within 3 months of starting radiotherapy (Grade 1 or less, n = 290; Grade 2 or greater, n = 109). A total of 999 single nucleotide polymorphisms from 137 candidate genes for radiation susceptibility were genotyped, and the haplotype associations between groups were assessed. RESULTS: The global haplotype association analysis ($p < 0.05$ and false discovery rate < 0.05) indicated that estimated haplotypes in six loci were associated with EASR risk. A comparison of the risk haplotype with the most frequent haplotype in each locus showed haplotype GGTT in CD44 (odds ratio [OR] = 2.17; 95% confidence interval [CI], 1.07-4.43) resulted in a significantly greater EASR risk. Five haplotypes, CG in MAD2L2 (OR = 0.55; 95% CI, 0.35-0.87), GTTG in PTTG1 (OR = 0.48; 95% CI, 0.24-0.96), TCC (OR = 0.48; 95% CI, 0.26-0.89) and CCG (OR = 0.50; 95% CI, 0.27-0.92) in RAD9A, and GCT in LIG3 (OR = 0.46; 95% CI, 0.22-0.93) were associated with a reduced EASR risk. No significant risk haplotype

was observed in REV3L. CONCLUSION: Individual radiosensitivity can be partly determined by these haplotypes in multiple loci. Our findings may lead to a better understanding of the mechanisms underlying the genetic variation in radiation sensitivity and resistance among breast cancer patients.

Suh, K. S., M. Malik, et al. (2007). "CLIC4, skin homeostasis and cutaneous cancer: surprising connections." Mol Carcinog **46**(8): 599-604.

Chloride intracellular channel 4 (CLIC4) is a putative chloride channel for intracellular organelles. CLIC4 has biological activities in addition to or because of its channel activity. In keratinocytes, CLIC4 resides in the mitochondria and cytoplasm, and CLIC4 gene expression is regulated by p53, TNF-alpha, and c-Myc. Cytoplasmic CLIC4 translocates to the nucleus in response to cellular stress conditions including DNA damage, metabolic inhibition, senescence, and exposure to certain trophic factors such as TNF-alpha and LPS. Nuclear translocation is associated with growth arrest or apoptosis, depending on the level of expression. In the nucleus CLIC4 interacts with several nuclear proteins as demonstrated by yeast two-hybrid screening and co-immunoprecipitation. Nuclear CLIC4 appears to act on the TGF-beta pathway, and TGF-beta also causes CLIC4 nuclear translocation. In human and mouse cancer cell lines, CLIC4 levels are reduced, and CLIC4 is excluded from the nucleus. CLIC4 soluble or membrane-inserted status is dependent on redox state, and redox alterations in cancer cells could underly the defect in nuclear translocation. CLIC4 is reduced and excluded from the nucleus of many human epithelial neoplasms. Paradoxically, CLIC4 is reciprocally upregulated in tumor stroma in conjunction with the expression of alpha-smooth muscle actin in the fibroblast to myofibroblast transition. Overexpression of CLIC4 in cancer cells inhibits tumor growth in vivo. Conversely, overexpression of CLIC4 in tumor stromal cells stimulates tumor growth in vivo. Thus, CLIC4 participates in normal and pathological processes and may serve as a useful target for therapies in disturbances of homeostasis and neoplastic transformation.

Svingen, T. and K. F. Tonissen (2003). "Altered HOX gene expression in human skin and breast cancer cells." Cancer Biol Ther **2**(5): 518-23.

Human HOX genes are expressed in a spatio-temporal fashion during embryogenesis and early development where they act as master transcriptional regulators. HOX genes are also expressed in normal adult cells, potentially in a tissue specific manner involving maintenance of the normal phenotype. In selected oncogenic transformations, mis-expression of many HOX genes have been shown, indicating an involvement of these transcriptional regulators in carcinogenesis and metastasis. Utilising quantitative real-time RT-PCR assays, the expression of 20 HOX genes and two known HOX co-factors, PBX1B and MEIS1, were analysed in human melanoma and breast cancer cell lines, comparing results against non-malignant cells. Alterations in HOX gene expression were observed for all malignant cells examined, with some dysregulated transcript levels seemingly random, and the expression of other HOX genes apparently following the same patterns in both skin and breast cancer establishment. Furthermore, HOX gene expression was correlated with the invasive capacity of the cells. The expression of the HOX co-factors PBX1B and MEIS1 showed no marked changes from the non-malignant to the malignant phenotypes, further indicating that it is dysregulated HOX gene expression, rather than dysregulated gene expression of HOX co-factors, that potentially commit the cell to re-differentiate and undergo oncogenic transformation.

Swale, V. J., A. G. Quinn, et al. (1999). "Microsatellite instability in benign skin lesions in hereditary non-polyposis colorectal cancer syndrome." J Invest Dermatol **113**(6): 901-5.

The coexistence of cutaneous and extra-cutaneous malignancies within one family could be explained by shared genetic mechanisms such as common tumor suppressor gene mutations or oncogene activation, as well as mutations in DNA repair genes. Hereditary non-polyposis colorectal cancer syndrome (HNPCC) and its variant Muir-Torre syndrome (MTS) are caused by germline DNA mismatch repair gene mutations. Colonic and endometrial tumors from HNPCC patients exhibit microsatellite instability (MSI), as do sebaceous lesions in MTS. We recruited individuals from cancer prone families to determine if MSI is found in benign and malignant skin lesions and to assess whether MSI in the skin is predictive of genomic instability with susceptibility to tumors characteristic of HNPCC. One hundred and fifteen benign, dysplastic, and malignant skin lesions from 39 cancer prone families were analyzed. Thirteen benign skin lesions from three individuals belonging to two HNPCC pedigrees showed MSI. No mutations in hMSH2 and hMLH1 were found in two of the three individuals with RER + skin lesions. We found MSI in non-sebaceous non-dysplastic skin lesions in HNPCC pedigrees. MSI was not found in skin lesions within other family cancer syndromes. These results have important clinical implications as the detection of MSI in prevalent readily accessible skin lesions could form the basis of

noninvasive screening for HNPCC families. It may also be a valuable tool in the search for new mismatch repair genes.

Tahtis, K., F. T. Lee, et al. (2003). "Expression and targeting of human fibroblast activation protein in a human skin/severe combined immunodeficient mouse breast cancer xenograft model." Mol Cancer Ther **2**(8): 729-37.

Antigens and receptors that are highly expressed on tumor stromal cells, such as fibroblast activation protein (FAP), are attractive targets for antibody-based therapies because the supporting stroma and vessel network is essential for a solid neoplasm to grow beyond a size of 1-2 mm. The in vivo characterization of antibodies targeting human stromal or vessel antigens is hindered by the lack of an appropriate mouse model system because xenografts in standard mouse models express stromal and vessels elements of murine origin. This limitation may be overcome by the development of a human skin/mouse chimeric model, which is established by transplanting human foreskin on to the lateral flank of severe combined immunodeficient mice. The subsequent inoculation of breast carcinoma MCF-7 cells within the dermis of the transplanted human skin resulted in the production of xenografts expressing stromal and vessel elements of human origin. Widespread expression of human FAP-positive reactive stromal fibroblasts within xenografts was seen up to 2 months posttransplantation and postinjection of cells. Human blood vessel antigen expression also persisted at 2 months posttransplantation and postinjection of cells with murine vessels coexisting with the human vascular supply. The model was subsequently used to evaluate the biodistribution properties of an iodine-131-labeled humanized anti-FAP monoclonal antibody (BIBH-7). The results showed high specific targeting of the stromal compartment of the xenograft, indicating that the model provides a useful and novel approach for the in vivo assessment of the immunotherapeutic potential of molecules targeting human stroma and angiogenic systems.

Takahashi, S., A. D. Pearse, et al. (1994). "Expression of c-fos proto-oncogene mRNA in non-melanoma skin cancer." J Dermatol Sci **7**(1): 54-62.

c-fos is a member of the proto-oncogene family and is implicated in the modulation of cell proliferation and differentiation. Previous studies have shown that the c-fos gene expression is regulated in a tissue specific manner. In order to clarify the role of the c-fos gene in human epidermis, we have investigated c-fos mRNA expression in both normal skin and non-melanoma skin cancer. In normal skin the intensity of the c-fos mRNA expression in spinous cells was found to be stronger than that observed in basal cells. In lesions of solar keratosis and Bowen's disease the spinous cells also showed stronger c-fos mRNA expression than in basal cells. In two of four cases of Bowen's disease some upper spinous cells showed very strong mRNA expression of the c-fos gene. In squamous cell carcinomas studied there was considerable variation in the intensity of c-fos mRNA expression. Our findings indicate that the degree of c-fos mRNA expression is related to the degree of dysplasia present. In all cases of basal cell carcinoma examined the c-fos mRNA expression was markedly decreased. These results suggest that c-fos expression may be involved in the differentiation of human keratinocytes in vivo rather than in the neoplastic process itself.

Takata, M., F. Shirasaki, et al. (2000). "Hereditary non-polyposis colorectal cancer associated with disseminated superficial porokeratosis. Microsatellite instability in skin tumours." Br J Dermatol **143**(4): 851-5.

A 73-year-old man presented with typical lesions of disseminated superficial porokeratosis (DSP) and multiple seborrhoeic keratoses on his face, trunk and extremities, and later developed a keratoacanthoma on his lip. He belonged to a cancer-prone pedigree susceptible to colonic, uterine and other internal cancers, and had a personal history of early gastric cancer and advanced adenocarcinoma of the descending colon without adenomatous polyps at age 59 years. Polymerase chain reaction amplification of skin samples for seven separate microsatellite polymorphisms revealed microsatellite instability (MSI) at multiple loci in five of six seborrhoeic keratoses and the keratoacanthoma, strongly suggesting underlying defects in DNA mismatch repair. Although no germline mutations in two mismatch repair genes hMSH2 and hMLH1 were found, our patient was recognized as having hereditary non-polyposis colorectal cancer (HNPCC) based on the family history and the findings of the microsatellite analysis of skin tumours. This confirmed the usefulness of detection of MSI in prevalent and readily accessible skin lesions, including non-sebaceous non-dysplastic tumours such as seborrhoeic keratosis in the screening of HNPCC families. Although DSP may also be inherited as an autosomal dominant condition, this particular skin disease appeared to be sporadic in our patient and, to our knowledge, no association of DSP or other forms of porokeratosis with HNPCC has previously been reported. In contrast to the seborrhoeic keratoses and keratoacanthoma, no MSI was observed in two samples from DSP lesional epidermis examined.

Toll, A. and F. X. Real (2008). "Somatic oncogenic mutations, benign skin lesions and cancer progression: where to look next?" Cell Cycle **7**(17): 2674-81.

Somatic oncogenic activating mutations in FGFR3 and/or PIK3CA have recently been described in benign epithelial cutaneous lesions that never progress to malignancy (seborrheic keratoses and epidermal nevi). The same mutations have been observed in malignant neoplasms from other tissues (bladder carcinoma, cervix cancer, colorectal cancer, myeloma). However, many of the abovementioned epithelial benign cutaneous tumors do not harbour mutations in FGFR3 or PIK3CA. In this review, we focus on new candidate genes for discovery and we outline the potential of the skin as a model to achieve a better understanding of cancer biology.

Tomlinson, I. P., N. A. Alam, et al. (2002). "Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer." Nat Genet **30**(4): 406-10.

Uterine leiomyomata (fibroids) are common and clinically important tumors, but little is known about their etiology and pathogenesis. We previously mapped a gene that predisposes to multiple fibroids, cutaneous leiomyomata and renal cell carcinoma to chromosome 1q42.3-q43 (refs 4-6). Here we show, through a combination of mapping critical recombinants, identifying individuals with germline mutations and screening known and predicted transcripts, that this gene encodes fumarate hydratase, an enzyme of the tricarboxylic acid cycle. Leiomyomatosis-associated mutations are predicted to result in absent or truncated protein, or substitutions or deletions of highly conserved amino acids. Activity of fumarate hydratase is reduced in lymphoblastoid cells from individuals with leiomyomatosis. This enzyme acts as a tumor suppressor in familial leiomyomata, and its measured activity is very low or absent in tumors from individuals with leiomyomatosis. Mutations in FH also occur in the recessive condition fumarate hydratase deficiency, and some parents of people with this condition are susceptible to leiomyomata. Thus, heterozygous and homozygous or compound heterozygous mutants have very different clinical phenotypes. Our results provide clues to the pathogenesis of fibroids and emphasize the importance of mutations of housekeeping and mitochondrial proteins in the pathogenesis of common types of tumor.

Tormanen, V. T. and G. P. Pfeifer (1992). "Mapping of UV photoproducts within ras proto-oncogenes in UV-irradiated cells: correlation with mutations in human skin cancer." Oncogene **7**(9): 1729-36.

Mutations in ras proto-oncogenes have been found in human skin cancers. Since ultraviolet light is implicated in the development of skin cancers, we have investigated the formation of UV-induced photoproducts along exons 1 and 2 of the three ras proto-oncogenes, H-ras, K-ras, and N-ras, in UV-irradiated human cells. The two major types of DNA photoproducts, cyclobutane pyrimidine dimers and pyrimidine (6-4) pyrimidone photoproducts [(6-4) photoproducts], were mapped at the DNA sequence level by ligation-mediated polymerase chain reaction (LMPCR). No significant differences were seen between irradiated purified DNA and irradiated cells, implying that local chromatin structure does not influence the distribution of photoproducts along exons 1 and 2 of the three ras genes. We find that the transcribed strand near codon 61 in H-ras, K-ras and N-ras shows a high frequency of potentially mutagenic cyclobutane dimers and (6-4) photoproducts. Codon 12 of H-ras, K-ras and N-ras displays only barely detectable photoproducts at a CpC dinucleotide. In human skin cancers, mutations were most frequently detected at codon 12 of H-ras and K-ras. These results imply that the initial frequency distribution of a mutagenic DNA adduct may not correlate with mutation spectra in human tumors.

Tornaletti, S. and G. P. Pfeifer (1994). "Slow repair of pyrimidine dimers at p53 mutation hotspots in skin cancer." Science **263**(5152): 1436-8.

Ultraviolet light has been linked with the development of human skin cancers. Such cancers often exhibit mutations in the p53 tumor suppressor gene. Ligation-mediated polymerase chain reaction was used to analyze at nucleotide resolution the repair of cyclobutane pyrimidine dimers along the p53 gene in ultraviolet-irradiated human fibroblasts. Repair rates at individual nucleotides were highly variable and sequence-dependent. Slow repair was seen at seven of eight positions frequently mutated in skin cancer, suggesting that repair efficiency may strongly contribute to the mutation spectrum in a cancer-associated gene.

Tornaletti, S., D. Rozek, et al. (1993). "The distribution of UV photoproducts along the human p53 gene and its relation to mutations in skin cancer." Oncogene **8**(8): 2051-7.

Mutations in the p53 gene have been found in a large proportion of human skin cancers. These mutations show the same characteristics as mutations induced by UV light in experimental systems. To establish correlations between formation of DNA adducts by a known carcinogen and incidence of mutations within a specific human gene, we have

investigated the formation of UV-induced photoproducts along exons 5-9 of the p53 gene after UV irradiation of human cells. The two major types of DNA photoproducts, cyclobutane pyrimidine dimers and pyrimidine (6-4) pyrimidone photoproducts [(6-4) photoproducts], were mapped at the DNA sequence level by strand cleavage at the sites of photoproducts. This was followed by ligation-mediated polymerase chain reaction (LMPCR) to amplify gene-specific fragments. In human skin cancers, mutations were most frequently found at codons 151/152, 245, 248, 278 and 286 of the p53 gene. The frequency of UV photoproducts is particularly high at codon 286, which is within a run of 12 adjacent pyrimidines. High levels of both photoproducts were also seen at codons 151 and 278. However, UV-induced DNA adducts are barely detectable at codons 245 and 248, which are mutation hotspots also for internal malignancies. At these positions, the frequency of photoproducts is much lower than at surrounding dipyrimidine sequences. These findings have some implications on molecular mechanisms of mutagenesis in the human genome.

Trumpp, A. (2006). "c-Myc and activated Ras during skin tumorigenesis: cooperation at the cancer stem cell level?" Ernst Schering Found Symp Proc(5): 13-26.

Mutations leading to overexpression and activation of the oncogenes Myc and Ras are among the most frequent lesions known to occur in human and murine cancers. These genes are also the pioneering example for oncogene cooperation during tumorigenesis, whereby the anticancer effects of Myc deregulation (apoptosis) and oncogenic Ras (senescence) are antagonized and therefore canceled out by each other. Here I review the role of endogenous and overexpressed c-Myc in murine skin, focusing primarily on epidermal stem cells. In addition, recent data suggesting an essential role for the endogenous c-Myc-p21(CIP1) pathway in Ras-driven skin tumorigenesis are discussed.

Tsao, H. (2000). "Update on familial cancer syndromes and the skin." J Am Acad Dermatol **42**(6): 939-69; quiz 970-2.

Familial cancer syndromes reflect an inherited predisposition to develop benign and malignant tumors. Clinically, the cancers occur at an earlier age and involve multiple foci of tumor formation at multiple sites. In the past 10 years, the molecular basis of many of these cancer syndromes have been unraveled with the advent of powerful genetic technologies. Entities which were hypothesized to be related on the basis of clinical features have now been shown to be linked or disparate through genetic analysis. This article reviews some of the recent advances in the clinical and molecular aspects of familial cancer syndromes that involve the skin. (J Am Acad Dermatol 2000;42:939-69.) Learning Objective: After completing this article, the reader should become (1) fluent with some basic genetic principles underlying the mechanisms of cancer predisposition and positional cloning and (2) aware of the recent breakthroughs in the identification of familial cancer syndrome disease genes.

Tsao, H. (2001). "Genetics of nonmelanoma skin cancer." Arch Dermatol **137**(11): 1486-92.

Cancer is in essence a genetic disease characterized by genomic instability. Unlike classic genetic syndromes in which a single inherited mutation is often sufficient to determine the perturbed phenotype, most cancers, especially solid tumors, develop after an accumulation of multiple genetic lesions. Inherited mutations that predispose individuals to cancer formation are termed germline, while acquired mutations that contribute to tumor development are designated somatic. Bona fide hereditary cancers account for only a small proportion of all documented cancers. Most tumors result from mutations caused by inherent infidelities in DNA replication, carcinogens, or defects in the DNA reparative apparatus. When mutations occur in critical growth regulatory genes, variations in cellular proliferation and survival contribute to the selection of dominant tumor population(s). Furthermore, these mutations may alter the antigenic properties of the cancerous cell and encourage escape from the host response. Thus, cancer is evolution at the microscopic level.

Utikal, J., M. Udart, et al. (2005). "Numerical abnormalities of the Cyclin D1 gene locus on chromosome 11q13 in non-melanoma skin cancer." Cancer Lett **219**(2): 197-204.

Deregulation of the cell-cycle G1-restriction point control via abnormalities of Rb-pathway components is a frequent event in the formation of cancer. The aim of this study was to evaluate numerical aberrations of the Cyclin D1 (CCND1, PRAD1, bcl-1) gene locus at chromosome 11q13 in basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs) of the skin and to compare it with the Cyclin D1 protein expression. Fluorescence in situ hybridization with DNA-probes specific for the Cyclin D1 gene locus and the centromere of chromosome 11 as well as immunostaining for Cyclin D1 protein was applied on 5 microm serial paraffin sections. Six of the 30 (20%) SCCs showed additional Cyclin D1 gene copies and 2/30 (6.6%) cases had a

loss of the Cyclin D1 gene locus in relation to the centromere 11 number. In contrast, only one of the 14 BCCs (7%) showed one additional Cyclin D1 gene copy in relation to the centromere 11 number. None of the BCCs demonstrated aneusomy for chromosome 11 in contrast to SCCs, where it was found in 21/30 (70%) cases. Twenty-six of the 30 (86.6%) cutaneous SCCs and 13/14 (93%) BCCs expressed Cyclin D1 protein. All SCCs and the BCC with additional Cyclin D1 gene copies showed positivity for Cyclin D1 protein. Both SCCs with less Cyclin D1 gene copies than centromere 11 signals showed a weak protein expression. Our findings suggest that numerical abnormalities of the Cyclin D1 gene locus could result in an altered gene-dose effect, possibly leading to an aberrant expression in affected tumor cells. This might result in deregulation of cell cycle control, eventually leading to uncontrolled cell cycle progression.

van der Horst, G. T., H. van Steeg, et al. (1997). "Defective transcription-coupled repair in Cockayne syndrome B mice is associated with skin cancer predisposition." Cell **89**(3): 425-35.

A mouse model for the nucleotide excision repair disorder Cockayne syndrome (CS) was generated by mimicking a truncation in the CSB(ERCC6) gene of a CS-B patient. CSB-deficient mice exhibit all of the CS repair characteristics: ultraviolet (UV) sensitivity, inactivation of transcription-coupled repair, unaffected global genome repair, and inability to resume RNA synthesis after UV exposure. Other CS features thought to involve the functioning of basal transcription/repair factor TFIIH, such as growth failure and neurologic dysfunction, are present in mild form. In contrast to the human syndrome, CSB-deficient mice show increased susceptibility to skin cancer. Our results demonstrate that transcription-coupled repair of UV-induced cyclobutane pyrimidine dimers contributes to the prevention of carcinogenesis in mice. Further, they suggest that the lack of cancer predisposition in CS patients is attributable to a global genome repair process that in humans is more effective than in rodents.

van Kranen, H. J. and F. R. de Gruijl (1999). "Mutations in cancer genes of UV-induced skin tumors of hairless mice." J Epidemiol **9**(6 Suppl): S58-65.

Ultraviolet (UV) radiation is a very common carcinogen in our environment. Epidemiological data on the relationship between skin cancers and ambient solar UV radiation are very limited. Hairless mice provide the possibility to study the process of UV carcinogenesis in more detail. Experiments with this animal model have yielded quantitative data on how tumor development depends on dose, time and wavelength of the UV radiation. In addition, at the molecular level the interactions between UV, specific cancer genes-like the Ras oncogene family and the p53 tumor suppressor gene, together with the role of DNA repair in this process have been addressed recently. In wildtype hairless mice mutations in the p53 gene are clearly linked to UVB but not to UVA radiation. Furthermore, the p53 alterations seem to be essential early in tumor development. However, in Xpa-deficient mice this dependency on p53 alterations appeared to be different as is the tumor type induced by UVB. Research using genetically modified hairless mice should enable us to further unravel the mechanisms of UV-induced skin cancer.

van Steeg, H. and K. H. Kraemer (1999). "Xeroderma pigmentosum and the role of UV-induced DNA damage in skin cancer." Mol Med Today **5**(2): 86-94.

Xeroderma pigmentosum (XP) is a rare, autosomal recessive disease that is characterized by the extreme sensitivity of the skin to sunlight. Compared to normal individuals, XP patients have a more than 1000-fold increased risk of developing cancer on sun-exposed areas of the skin. Genetic and molecular analyses have revealed that the repair of ultraviolet (UV)-induced DNA damage is impaired in XP patients owing to mutations in genes that form part of a DNA-repair pathway known as nucleotide excision repair (NER). Two other diseases, Cockayne syndrome (CS) and the photosensitive form of trichothiodystrophy (TTD), are linked to a defect in the NER pathway. Strikingly, although CS and TTD patients are UV-sensitive, they do not develop skin cancer. The recently developed animal models that mimic the human phenotypes of XP, CS and TTD will contribute to a better understanding of the etiology of these diseases and the role of UV-induced DNA damage in the development of skin cancer.

Verma, A. K., D. L. Wheeler, et al. (2006). "Protein kinase Cepsilon and development of squamous cell carcinoma, the nonmelanoma human skin cancer." Mol Carcinog **45**(6): 381-8.

Protein kinase C (PKC) represents a large family of phosphatidylserine (PS)-dependent serine/threonine protein kinases. At least five PKC isoforms (alpha, delta, epsilon, eta, and zeta) are expressed in epidermal keratinocytes. PKC isoforms are differentially expressed in proliferative (basal layer) and nonproliferative compartments (spinous, granular, cornified layers), which exhibit divergence in their roles in the regulation of epidermal cell proliferation, differentiation, and apoptosis. Immunocytochemical localization of PKC isoforms indicate that PKCalpha is found in the membranes of

suprabasal cells in the spinous and granular layers. PKCepsilon is mostly localized in the proliferative basal layers. PKCeta is localized exclusively in the granular layer. PKCdelta is detected throughout the epidermis. PKC isozymes exhibit specificities in their signals to the development of skin cancer. PKCepsilon, a calcium-insensitive PKC isoform mediates the induction of squamous cell carcinoma (SCC) elicited either by the DMBA-TPA protocol or by repeated exposures to ultraviolet radiation (UVR). PKCepsilon overexpression, which sensitizes skin to UVR-induced carcinogenesis, suppresses UVR-induced sunburn (apoptotic) cell formation, and enhances both UVR-induced levels of TNFalpha and hyperplasia. UVR-induced sunburn cell formation is mediated by Fas/Fas-L and TNFalpha NFR1 extrinsic apoptotic pathways. The death adaptor protein termed Fas-associated death domain (FADD) is a common adaptor protein for both of these apoptotic pathways. PKCepsilon inhibits UVR-induced expression of FADD leading to the inhibition of both apoptotic pathways. It appears that PKCepsilon sensitizes skin to the development of SCC by UVR by transducting signals, which inhibit apoptosis on one hand, and enhances proliferation of preneoplastic cells on the other hand.

Vogt, T., M. Kroiss, et al. (1999). "Deficiency of a novel retinoblastoma binding protein 2-homolog is a consistent feature of sporadic human melanoma skin cancer." Lab Invest **79**(12): 1615-27.

Using RNA arbitrarily primed PCR, the authors selected for transcripts with cell cycle-related differential expression in cultured human melanocytes. Among the partial cDNAs cloned, a novel cDNA was identified, which showed 54% identity to the recently cloned cDNA of the retinoblastoma binding protein-2 (RBP2). The 6.5-kB full-length cDNA of this RBP2-related gene, termed RBP2 homolog 1 (RBP2-H1), was obtained from a human teratocarcinoma cDNA library. Two independent libraries from human malignant melanomas were negative. A computerized sequence analysis revealed highly conserved motifs with possible functional meaning: two domains that, in the RBP2 homolog, mediate the binding and interaction with the proteins encoded by the retinoblastoma susceptibility gene, the TATA-binding protein, and the oncoprotein rhombotin 2; in addition, two DNA-binding zinc finger/leukemia-associated protein motifs were detected. Because a functional role in cell-cycle control and transcriptional activation can be envisioned, we investigated the expression of this novel transcript in normal fetal and adult tissues, as well as tissues of benign and malignant melanocytic tumors. By conducting multiple Northern blot, RT-PCR, and in situ hybridization analyses, the authors showed that the corresponding mRNA is expressed in virtually all normal tissues. Accordingly, they found RBP2-H1 expression in microdissected tissue samples from benign melanocytic nevi (n = 10). In contrast, the transcript is significantly down-regulated or even lost in tissue samples from human malignant melanomas (n = 13), melanoma metastases (n = 10), and melanoma cell lines (n = 7). The authors concluded that the loss or down-regulation of RBP2-H1 expression could be a useful molecular marker for a transformed phenotype in the human melanocytic system.

Waalkes, M. P., J. Liu, et al. (2008). "Arsenic exposure in utero exacerbates skin cancer response in adulthood with contemporaneous distortion of tumor stem cell dynamics." Cancer Res **68**(20): 8278-85.

Arsenic is a carcinogen with transplacental activity that can affect human skin stem cell population dynamics in vitro by blocking exit into differentiation pathways. Keratinocyte stem cells (KSC) are probably a key target in skin carcinogenesis. Thus, we tested the effects of fetal arsenic exposure in Tg.AC mice, a strain sensitive to skin carcinogenesis via activation of the v-Ha-ras transgene likely in KSCs. After fetal arsenic treatment, offspring received topical 12-O-tetradecanoyl phorbol-13-acetate (TPA) through adulthood. Arsenic alone had no effect, whereas TPA alone induced papillomas and squamous cell carcinomas (SCC). However, fetal arsenic treatment before TPA increased SCC multiplicity 3-fold more than TPA alone, and these SCCs were much more aggressive (invasive, etc.). Tumor v-Ha-ras levels were 3-fold higher with arsenic plus TPA than TPA alone, and v-Ha-ras was overexpressed early on in arsenic-treated fetal skin. CD34, considered a marker for both KSCs and skin cancer stem cells, and Rac1, a key gene stimulating KSC self-renewal, were greatly increased in tumors produced by arsenic plus TPA exposure versus TPA alone, and both were elevated in arsenic-treated fetal skin. Greatly increased numbers of CD34-positive probable cancer stem cells and marked overexpression of RAC1 protein occurred in tumors induced by arsenic plus TPA compared with TPA alone. Thus, fetal arsenic exposure, although by itself oncogenically inactive in skin, facilitated cancer response in association with distorted skin tumor stem cell signaling and population dynamics, implicating stem cells as a target of arsenic in the fetal basis of skin cancer in adulthood.

Welsh, M. M., M. R. Karagas, et al. (2008). "A role for ultraviolet radiation immunosuppression in non-melanoma skin cancer as evidenced by gene-

environment interactions." Carcinogenesis **29**(10): 1950-4.

The genotoxic effects of ultraviolet (UV) radiation are well-known causes of skin cancers; however, UV radiation also suppresses the immune system, decreasing the body's surveillance for tumor cells. In experimental systems, UV radiation immunosuppression is at least partially mediated through urocanic acid (UCA), an UV radiation-absorbing molecule in the stratum corneum. We tested the hypothesis that genetic variation in the histidase gene (HAL), which catalyzes the formation of UCA in the skin, modifies risk of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) in a population-based study (914 BCC, 702 SCC and 848 controls). We observed no evidence of a main gene effect for the HAL I439V polymorphism (rs7297245) and BCC or SCC. However, we found a HAL genotype-sunburn interaction in association with BCC (P for interaction = 0.040) and SCC (P for interaction = 0.018). A HAL genotype-SCC association was observed primarily among women (odds ratio = 1.5, 95% confidence interval 1.1-2.2), and among women, we found an interaction between HAL genotype and oral contraceptive use on SCC risk (P = 0.040). The variant HAL allele likewise appeared to modify the SCC risk associated with glucocorticoid steroid usage (P for interaction = 0.0004). In conclusion, our findings are a first step in determining the genetic underpinnings of UV immune suppression and have identified important new genetic interactions contributing to the etiology of skin cancer.

Winsey, S. L., N. A. Haldar, et al. (2000). "A variant within the DNA repair gene XRCC3 is associated with the development of melanoma skin cancer." Cancer Res **60**(20): 5612-6.

Exposure to UV radiation is a major risk factor for the development of malignant melanoma. DNA damage caused by UV radiation is thought to play a major role in carcinogenesis induction. Multiprotein pathways involved in repairing UV-DNA damage are the base excision, the nucleotide excision, and the homologous double-stranded DNA repair pathways. This study used a sequence-specific primer PCR (PCR-SSP) genotyping method to investigate the association between polymorphisms in DNA repair genes from these pathways with the development of malignant melanoma. The patient cohort was comprised of 125 individuals with malignant melanoma with lesions or staging suggesting a high risk of relapse or metastatic disease. The control population consisted of 211 individuals. We found the presence of a T allele in exon 7 (position 18067) of the XRCC3 gene was significantly associated with melanoma development (P = 0.004; odds ratio, 2.36; relative risk, 1.74). This gene codes for a protein involved in the homologous pathway of double-stranded DNA repair, thought to repair chromosomal fragmentation, translocations, and deletions. These results may provide further insights into the pathogenesis and the mechanism of UV-radiation induced carcinogenesis as well as having a role in prevention.

Winship, I. M. and T. E. Dudding (2008). "Lessons from the skin--cutaneous features of familial cancer." Lancet Oncol **9**(5): 462-72.

As the molecular basis of disease continues to be elucidated, familial cancer syndromes, which consist of a range of neoplastic and non-neoplastic features, are emerging. The usual pathway of referral to a genetics clinic or familial cancer centre is via an oncologist, when high-risk features that suggest a possible hereditary basis for the presenting cancer are recognised. Traditionally, these high-risk features include more than two family members with similar cancers over two or more generations, a young age of onset, and more than one synchronous or metachronous tumour. These features are effective in ascertaining a substantial proportion of families with hereditary breast and ovarian cancer due to a BRCA mutation, or the more common bowel-cancer predisposition syndromes, such as hereditary non-polyposis colon cancer and familial adenomatous polyposis. However, there are a range of familial cancer syndromes that are not easily detected and that can remain undiagnosed when history and examination are not extended to include non-malignant features. The identification of cutaneous signs associated with rare familial-cancer syndromes provides individuals and their families with the opportunity to undertake early surveillance for malignant and non-malignant complications that might in time be shown to improve outcomes.

You, Y. H. and G. P. Pfeifer (2001). "Similarities in sunlight-induced mutational spectra of CpG-methylated transgenes and the p53 gene in skin cancer point to an important role of 5-methylcytosine residues in solar UV mutagenesis." J Mol Biol **305**(3): 389-99.

In the p53 gene of human sunlight-associated skin cancers, 35 % of the mutations involve trinucleotide sequences with the rare base 5-methylcytosine (5'PymCG). In order to determine the involvement of 5-methylcytosine in sunlight-induced mutations, we have analyzed the cII transgene in mouse cells, a mutational target gene that we found is methylated at most CpG sequences. We report that the mutational spectra produced by irradiation with 254 nm UVC radiation and simulated sunlight,

respectively, differ most dramatically by the much higher involvement of dipyrimidine structures containing 5-methylcytosine in the solar UV mutation spectrum (32 % versus 9 % of all mutations). A distinct mutational hotspot induced by simulated sunlight occurs at a sequence 5'TmCG and is associated with high levels of cis-syn cyclobutane pyrimidine dimer formation. A comparison of sunlight-induced mutational spectra of the cII and lacI transgenes, as well as the p53 gene in skin tumors, shows that 5-methylcytosine is involved in 25 to 40 % of all mutations in all three systems. The combined data make a strong case that cyclobutane pyrimidine dimers forming preferentially at dipyrimidine sequences with 5-methylcytosine are responsible for a considerable fraction of the mutations induced by sunlight in mammalian cells.

Yuspa, S. H. (1998). "The pathogenesis of squamous cell cancer: lessons learned from studies of skin carcinogenesis." J Dermatol Sci **17**(1): 1-7.

This study used the induction of squamous cell carcinomas on mouse skin as an experimental model to evaluate molecular and biochemical changes that contribute to the neoplastic phenotype. The study was facilitated by the development of keratinocyte cell culture assays that reproduce each stage of the carcinogenesis process, by discoveries of stage-specific genetic and epigenetic changes and by application of pharmacological and molecular tools that modify each step. An early event in the transformation of keratinocytes involves mutation and activation of the rasHa gene, producing a benign tumor. The phenotypic consequences of ras mutations are mediated by activation of the epidermal growth factor receptor (EGFR), upregulation of protein kinase C (PKC) alpha and AP-1 mediated transcriptional activity and inactivation of PKC delta through tyrosine phosphorylation. These changes in benign tumors are manifested by hyperproliferation (EGFR), aberrant expression of keratinocyte genes (PKC alpha and AP-1) and delayed terminal differentiation (PKC delta). Accumulated chromosomal abnormalities, multifocal phenotypic changes and alterations in gene expression are associated with premalignant progression. Upregulation of the fos gene and AP-1 transcriptional activity causes malignant conversion of benign keratinocytes. In the absence of c-fos, benign tumor cells fail to upregulate secreted angiogenic and proteolytic factors and this may prevent malignant conversion. These pathways provide targets for preventive strategies to interrupt the process of carcinogenesis prior to the evolution of the fully malignant tumor.

Zak-Nejmark, T., R. Jankowska, et al. (2004). "Skin reactivity to histamine and expression of histamine receptors mRNA in lymphocytes of healthy subjects and non-small-cell lung cancer patients before and after surgery." Lung Cancer **45**(1): 31-8.

Histamine modulates an immunological response through stimulation of appropriate receptor--H1R proinflammatory or H2R suppressive. The participation of histamine in regulation of an immunological response in the course of neoplastic disease is determined by the expression of particular receptor. The aim of our work was the investigation of the expression of mRNA of two types of histamine receptors in peripheral blood lymphocytes and the evaluation of skin-prick test with histamine in lung cancer patients before and after surgery. The investigation was performed on 15 patients qualified to surgery before and 7-10 days after treatment and on 12 healthy subjects. Reverse transcriptase polymerase chain reaction (RT-PCR) with primers labeled with fluorescent dyes was performed. Intensity of fluorescence was expressed as relative fluorescence units (RFU). The data were analysed using ABI Prism 310 GeneScan collection software Version 3.1. Skin-prick test with histamine was evaluated after 10 min by measuring the diameter of the weal. The expression of H1R and H2R mRNA in healthy subjects was not significantly different in contrast to the lung cancer patients in which a significant prevalence of H2R mRNA expression was observed before surgery and only slightly decreased after ($P < 0.001$). Skin-prick test--negative in one patient before surgery, after treatment was positive in all patients and the diameter of histamine weal was significantly increased ($P < 0.001$). One may assume that the prevalence of the expression of H2R mRNA in patients reflects the status of immunosuppression caused by cancer. Since histamine exerts its suppressive activity trough H2R it seems reasonably to include the antagonists of this receptor to the cancer therapy which may restore a relative balance between accessibility of both types of histamine receptors.

Zanesi, N. and C. M. Croce (2001). "Fragile histidine triad gene and skin cancer." Eur J Dermatol **11**(5): 401-4.

Five years ago the fragile histidine triad (FHIT) gene including the most common fragile site locus of the human genome, FRA3B, was identified. The gene is altered in many types of cancer and several data support the idea that FHIT has to be considered a tumor suppressor. FHIT abnormalities were investigated in some skin tumors. Fifty-seven per cent of Merkel cell carcinomas displayed abnormal FHIT products but the involvement of FHIT in human non-melanoma skin cancer is still unclear.

Because the murine Fhit locus is similar to its human homologue and is altered in cancer cell lines, we have established a strain of Fhit-deficient mice. After N-nitrosomethylbenzylamine treatment, the spectrum of tumors developed by the Fhit-deficient mice was similar to those observed in a familial skin cancer condition, the Muir-Torre syndrome, although there is no clear evidence yet for a relationship of FHIT and the human syndrome. Because cancer cells lacking in FHIT are defective in apoptosis, we propose the Fhit-deficient mouse as a model to understand a possible proapoptotic mechanism deficiency in the human syndrome.

Zhao, Y., T. D. Oberley, et al. (2002). "Manganese superoxide dismutase deficiency enhances cell turnover via tumor promoter-induced alterations in AP-1 and p53-mediated pathways in a skin cancer model." Oncogene **21**(24): 3836-46.

Previous studies in our laboratories demonstrated that overexpression of manganese superoxide dismutase (MnSOD) suppressed both the incidence and multiplicity of papillomas in a DMBA/TPA multi-stage skin carcinogenesis model. The activity of activator protein-1 (AP-1), which is associated with tumor promotion, was reduced in MnSOD transgenic mice overexpressing MnSOD in the skin, suggesting that MnSOD may reduce tumor incidence by suppressing AP-1 activation. In the present study, we report that reduction of MnSOD by heterozygous knockout of the MnSOD gene (Sod2 -/+, MnSOD KO) increased the levels of oxidative damage proteins and the activity of AP-1 following TPA treatment. RNA levels of ornithine decarboxylase (ODC) were also increased, suggesting an increase in cell proliferation in the KO mice. Histological examination confirmed that the number of proliferating cells in DMBA/TPA-treated mouse skin were higher in the KO mice. Interestingly, histological examination also demonstrated greater numbers of apoptotic cells in the KO mice after DMBA/TPA treatment. Evidence of apoptosis, including DNA fragmentation, cytochrome c release from mitochondria, and caspase 3 activation were also observed by biochemical assays of the skin tissues. Apoptosis was associated with an increase in nuclear levels of p53 as determined by Western analysis. Quantitative immunogold ultrastructural analysis confirmed that p53 immunoreactive protein levels were increased to a greater level in the nuclei of epidermal cells from MnSOD KO mice compared to epidermal nuclei from wild type mice similarly treated. Moreover, p53 levels further increased in the mitochondria of DMBA/TPA treated mice, and this increase was much greater in the MnSOD KO than in the wild type mice, suggesting a link between MnSOD deficiency and mitochondrial-mediated apoptosis. Pathological examination reveals no difference in the incidence and frequency of papillomas comparing the KO mice and their wild type littermates. Taken together, these results suggest that: (1) MnSOD deficiency enhanced TPA-induced oxidative stress and AP-1 and p53 levels, consistent with the increase in both proliferation and apoptosis events in the MnSOD KO mice, and (2) increased apoptosis may negate increased proliferation in the MnSOD deficient mice during an early stage of tumor development.

Ziegler, A., A. S. Jonason, et al. (1994). "Sunburn and p53 in the onset of skin cancer." Nature **372**(6508): 773-6.

Squamous cell carcinoma of the skin (SCC) can progress by stages: sun-damaged epidermis, with individual disordered keratinocytes; actinic keratosis (AK), spontaneously regressing keratinized patches having aberrant cell differentiation and proliferation; carcinoma in situ; SCC and metastasis. To understand how sunlight acts as a carcinogen, we determined the stage at which sunlight mutates the p53 tumour-suppressor gene and identified a function for p53 in skin. The p53 mutations induced by ultraviolet radiation and found in > 90% of human SCCs were present in AKs. Inactivating p53 in mouse skin reduced the appearance of sunburn cells, apoptotic keratinocytes generated by overexposure to ultraviolet. Skin thus appears to possess a p53-dependent 'guardian-of-the-tissue' response to DNA damage which aborts precancerous cells. If this response is reduced in a single cell by a prior p53 mutation, sunburn can select for clonal expansion of the p53-mutated cell into the AK. Sunlight can act twice: as tumour initiator and tumour promoter.

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