c-Myc and stem cell literatures

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Abstract: Myc (c-Myc) is a regulator gene. Myc is a multifunctional, nuclear phosphoprotein that plays a role in cell cycle progression, apoptosis and cellular transformation. Myc protein belongs to Myc family of transcription factors, which includes N-Myc and L-Myc genes. Myc mRNA contains an IRES (internal ribosome entry site) that allows the RNA to be translated into protein when 5' cap-dependent translation is inhibited. Myc protein is a transcription factor that activates expression of many genes through binding on consensus sequences and recruiting histone acetyltransferases. Myc has a direct role in the control of DNA replication. Myc is activated upon various mitogenic signals, such as Wnt, Shh and EGF. Myc plays role in cell proliferation, cell growth regulation, apoptosis, cancer formation, differentiation, and stem cell self-renewal, etc. c-Myc plays a crucial role in iPSC generation through the control of histone acetylation.
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Key words: life; stem cell; c-Myc

1. Introduction

Myc (c-Myc) is a regulator gene. Myc is a multifunctional, nuclear phosphoprotein that plays a role in cell cycle progression, apoptosis and cellular transformation.

Myc is related to the cell proliferation and cancer formation, and can be a candidate of anti-cancer drugs. Myc is located on chromosome 8 of the human genome. Myc gene was first discovered in Burkitt's lymphoma patients. Cloning the break-point of the fusion chromosomes reveals a gene that is similar to myelocytomatosis viral oncogene (v-Myc). Then, the newfound cellular gene was named c-Myc.

Myc protein belongs to Myc family of transcription factors, which includes N-Myc and L-Myc genes. Myc mRNA contains an IRES (internal ribosome entry site) that allows the RNA to be translated into protein when 5' cap-dependent translation is inhibited.

Myc protein is a transcription factor that activates expression of many genes through binding on consensus sequences and recruiting histone acetyltransferases. Myc has a direct role in the control of DNA replication. Myc is activated upon various mitogenic signals, such as Wnt, Shh and EGF. Myc plays role in cell proliferation, cell growth regulation, apoptosis, cancer formation, differentiation, and stem cell self-renewal, etc.

c-Myc plays a crucial role in iPSC generation through the control of histone acetylation.

The induced pluripotent stem cells (iPSC or iPS cells) are the pluripotent stem cells that are induced from differentiated cells. The iPSC was first discovered by Yamanaka et al at Kyoto University of Japan after identifying several genes that are active in embryonic stem cells. Further studies identified 4 transcription factors (Oct4, Sox2, Klf4 and c-Myc) essential for the production of pluripotent stem cells from differentiated cells. By using retroviral vectors to express these genes, animal somatic cells can be re-programmed into iPSCs to form the germ line in the animals after their injection into blastocysts.

iPSCs can be derived by expression of Oct4 alone or a combination of two or three or four of the transcription factors Oct4, Sox2, Klf4, and c-Myc, with or without the help of small molecules such as the histone deacetylase inhibitor valproic acid or the histone methyltransferase inhibitor BIX-1294. Success of each of these approaches is dependent on the starting cell populations. Neural stem cells expressing Sox2, c-Myc, Klf4, and several intermediate reprogramming markers can be induced into iPSCs with Oct4 alone. To date, iPSCs have been successfully generated from skin, stomach, liver, pancreatic, lymphocytes, testis germline and neural cells.

Oct4 is encoded by the gene Pou5f1. As a member of the "Oct" transcription factor family, this 38 kD protein contains a POU domain and a homeobox domain, and binds to the octamer motif (5'-ATTTGCAT-3'). It forms a trimeric complex with Sox2 on DNA and is implicated in regulating the expression of a number of genes such as YES1, FGF4, UTF1, and ZFP206 that are involved in embryonic development. Oct4 is a necesarry factor to produce.

Sox2 is a 34 kD transcription factor containing a HMG box for DNA binding and forms trimeric complexes with Oct4 and the octamer motif in certain gene expression. Sox2 is expressed in pluripotent, multipotent, and unipotent stem cells. The Sox family

of genes is associated with maintaining pluripotency, multipotent and unipotent of stem cells.

Klf4 (Krueppel-like factor 4) is a 55 kD transcription factor containing three zinc finger domains. Klf4 binds the CACCC core sequence at multiple sites in the 5' flanking region of the gene and can activate its transcription. It interacts with the c-terminal domain of MUC1 to enhance the suppression of TP53/p53 tran-scription.

Nanog is a 35 kD transcription factor related to in ES cell proliferation and self-renewal. In ES cells, Nanog, Oct4, and Sox2 co-occupy promoters of several hundred genes. Lin28 is an mRNA binding protein expressed in ES cells.

There are many methods to deliver the transcription factors into target cells to generate iPSCs. The first method is retrovirus or lentivirus transduction. The problem of this technique is the genome integration of virus DNA which could possibly alter differentiation potential or other malignant transformation. The second method is adenoviral vectors to induce iPSC. The advantage of adenovirus vector based expression is that the transgenes will not integrate into the house genome, thus reduces the risk of tumorogenesis. The third one is a plasmid based transfection that can avoid the genome integration also. Recently, the Cre-recombinase excisable systems are used in iPSC induction and subsequent transgene removal making the iPSC technology closer to clinic applications.

Literautres

The following gives some recent reference papers on c-Myc.

Ai, Z. H., J. Wang, et al. "Suppression of RNA interference on expression of c-myc of SKOV3 ovarian carcinoma cell line." Eur Rev Med Pharmacol Sci. 2013 Nov;17(22):3002-6.

To investigate suppression of RNA interference (RNAi) on expression of c-myc of SKOV3 ovarian carcinoma cell line. The c-myc -siRNA was designed and synthesized, then transfected to SKOV3 ovarian carcinoma cell lines. The cell lines were divided into four groups, including the blank control group, the siRNA transfection group, the mock transfection group and the negative control group. The expression level of c-myc mRNA and protein were detected by RT-PCR and Western blotting, respectively. The growth and proliferation of SKOV3 ovarian carcinoma cell lines were observed with CCK-8 assay. After transfected with c-myc -siRNA, the expression level of c-myc mRNA and protein were down-regulated, the growth and proliferation of SKOV3 ovarian carcinoma cell line were inhibited in the siRNA transfection group. There were significant differences between the siRNA transfection group and the blank control group ($p < 0.05$). The silencing efficiency was 77.78%, the protein suppression rate was 67.78%, and the inhibition ratio was 56.35% by CCK-8 assay in siRNA transfection group. The down-regulation of c-myc expression of SKOV3 ovarian carcinoma cell line by c-myc -siRNA can lead to the suppression of cancer cell proliferation. The small interfering RNAs technique can inhibit the proliferation of carcinoma cell by oncogene silencing.

Akinyeke, T., S. Matsumura, et al. "Metformin targets c-MYC oncogene to prevent prostate cancer." Carcinogenesis. 2013 Dec;34(12):2823-32. doi: 10.1093/carcin/bgt307. Epub 2013 Oct 15.

Prostate cancer (PCa) is the second leading cause of cancer-related death in American men and many PCa patients develop skeletal metastasis. Current treatment modalities for metastatic PCa are mostly palliative with poor prognosis. Epidemiological studies indicated that patients receiving the diabetic drug metformin have lower PCa risk and better prognosis, suggesting that metformin may have antineoplastic effects. The mechanism by which metformin acts as chemopreventive agent to impede PCa initiation and progression is unknown. The amplification of c-MYC oncogene plays a key role in early prostate epithelia cell transformation and PCa growth. The purpose of this study is to investigate the effect of metformin on c-myc expression and PCa progression. Our results demonstrated that (i) in Hi-Myc mice that display murine prostate neoplasia and highly resemble the progression of human prostate tumors, metformin attenuated the development of prostate intraepithelial neoplasia (PIN, the precancerous lesion of prostate) and PCa lesions. (ii) Metformin reduced c-myc protein levels in vivo and in vitro. In Myc-CaP mouse PCa cells, metformin decreased c-myc protein levels by at least 50%. (iii) Metformin selectively inhibited the growth of PCa cells by stimulating cell cycle arrest and apoptosis without affecting the growth of normal prostatic epithelial cells (RWPE-1). (iv) Reduced PIN formation by metformin was associated with reduced levels of androgen receptor and proliferation marker Ki-67 in Hi-Myc mouse prostate glands. Our novel findings suggest that by downregulating c-myc, metformin can act as a chemopreventive agent to restrict prostatic neoplasia initiation and transformation. SUMMARY: Metformin, an old antidiabetes drug, may inhibit prostate intraepithelial neoplasia transforming to cancer lesion via reducing c-MYC, an 'old' overexpressed oncogene. This study explores chemopreventive efficacy of metformin in prostate cancer and its link to cMYC in vitro and in vivo.

Allen, A., K. Gill, et al. "C-myc protein expression in B-cell acute lymphoblastic leukemia, prognostic significance?" Leuk Res. 2014 Sep;38(9):1061-6. doi: 10.1016/j.leukres.2014.06.022. Epub 2014 Jul 8.

C-myc protein expression has been studied in mature B-cell lymphomas and overexpression has been associated with poor prognosis. We sought to determine the prognostic significance of c-myc protein expression in B-ALL. We found >/=20% c-myc expression to predict risk of persistent disease in all age groups (odds ratio 7.487, p=0.013). There was no statistically significant association between c-myc expression and risk of relapse or death in our study. Routine c-myc immunostaining may help identify higher risk patients and guide management of B-ALL. Additional studies are needed to further determine the molecular mechanisms and role of c-myc expression in B-ALL.

Ben-David, E., A. C. Bester, et al. "Transcriptional dynamics in colorectal carcinogenesis: new insights into the role of c-Myc and miR-17 in benign to cancer transformation." Cancer Res. 2014 Aug 14. pii: canres.0932.2014.

Colorectal cancer (CRC) develops in a sequential, evolutionary process, leading to a heterogenic tumor. Comprehensive molecular studies of CRC have been previously performed; still the process of carcinogenesis isn't fully understood. We utilized gene expression patterns from 94 samples including normal, adenoma and adenocarcinoma colon biopsies, and performed a co-expression network analysis to determine gene expression trajectories of 8000 genes across carcinogenesis. We found that the majority of gene expression changes occur in the transition from normal tissue to adenoma. The upregulated genes, known to be involved in cellular proliferation, included c-Myc along with its targets. In a cellular model system, we show that physiological upregulation of c-Myc can lead to cellular

proliferation without DNA replication stress. Our analysis also found that carcinogenesis involves a progressive downregulation of genes which are markers of colonic tissue, and propose that this reflects a perturbed differentiation of colon cells during carcinogenesis. The analysis of microRNAs (miRNAs) targets pointed toward the involvement of miR-17 in the regulation of colon cell differentiation. Lastly, we found that copy-number variations (CNVs) enriched in colon adenocarcinoma tend to occur in genes whose expression changes already in adenoma, with deletions occurring in genes downregulated and duplications in genes upregulated in adenomas. We suggest that the CNVs are selected to reinforce changes in gene expression, rather than initiate them. Together, these findings shed new light into the molecular processes that underlie the transformation of colon tissue from normal to cancer, and add a temporal context which has been hitherto lacking.

Chakraborty, A. A., C. Scuoppo, et al. "A common functional consequence of tumor-derived mutations within c-MYC." Oncogene. 2014 Jul 7. doi: 10.1038/onc.2014.186.

The relevance of changes to the coding sequence of the c-MYC oncogene to malignancy is controversial. Overexpression of a pristine form of MYC is observed in many cancers and is sufficient to drive tumorigenesis in most contexts. Yet missense changes to MYC are found in ~50% of Burkitt's lymphomas, aggregate within an amino-terminal degron important for proteasomal destruction of MYC, and where examined profoundly enhance the tumorigenic properties of MYC in vitro and in vivo. Much of the controversy surrounding these mutants stems from the limited number of mutations that have been evaluated and their clustering within a single region of the MYC protein; the highly-conserved Myc box I (MbI) element. Here, by analysis of extant genomic data sets, we identify a previously unrecognized hotspot for tumor-associated MYC mutations, located in a conserved central portion of the protein. We show that, despite their distal location in MYC, mutations in this region precisely phenocopy those in MbI in terms of stability, in vitro transformation, growth-promoting properties, in vivo tumorigenesis and ability to escape p53-dependent tumor surveillance mechanisms. The striking parallels between the behavior of tumor-derived mutations in disparate regions of the MYC protein reveals that a common molecular process is disrupted by these mutations, implying an active role for these mutations in tumorigenesis and suggesting that different therapeutic strategies may be needed for treatment of lymphomas expressing wild type versus mutant forms of MYC protein.Oncogene advance online publication, 7 July 2014; doi:10.1038/onc.2014.186.

Chandra, S., R. Priyadarshini, et al. "Enhancement of c-Myc degradation by BLM helicase leads to delayed tumor initiation." J Cell Sci. 2013 Aug 15;126(Pt 16):3782-95. doi: 10.1242/jcs.124719. Epub 2013 Jun 7.

The spectrum of tumors that arise owing to the overexpression of c-Myc and loss of BLM is very similar. Hence, it was hypothesized that the presence of BLM negatively regulates c-Myc functions. By using multiple isogenic cell lines, we observed that the decrease of endogenous c-Myc levels that occurs in the presence of BLM is reversed when the cells are treated with proteasome inhibitors, indicating that BLM enhances c-Myc turnover. Whereas the N-terminal region of BLM interacts with c-Myc, the rest of the helicase interacts with the c-Myc E3 ligase Fbw7. The two BLM domains act as 'clamp and/or adaptor', enhancing the binding of c-Myc to Fbw7. BLM promotes Fbw7-dependent K48-linked c-Myc ubiquitylation and its subsequent degradation in a helicase-independent manner. A subset of BLM-regulated genes that are also targets of c-Myc were determined and validated at both RNA and protein levels. To obtain an in vivo validation of the effect of BLM on c-Myc-mediated tumor initiation, isogenic cells from colon cancer cells that either do or do not express BLM had been manipulated to block c-Myc expression in a controlled manner. By using these cell lines, the metastatic potential and rate of initiation of tumors in nude mice were determined. The presence of BLM decreases c-Myc-mediated invasiveness and delays tumor initiation in a mouse xenograft model. Consequently, in tumors that express BLM but not c-Myc, we observed a decreased ratio of proliferation to apoptosis together with a suppressed expression of the angiogenesis marker CD31. Hence, partly owing to its regulation of c-Myc stability, BLM acts as a 'caretaker tumor suppressor'.

Chang, M. X. and Y. P. Ma "[Effect of flumatinib mesylate on C-MYC, HIF-1alpha and VEGF in U226 line]." Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2013 Dec;21(6):1496-500. doi: 10.7534/j.issn.1009-2137.2013.06.024.

The objective of this study was to investigate the effect of the new generation of tyrosine kinase inhibitor flumatinib mesylate on C-MYC, HIF-1alpha and VEGF in multiple myeloma (MM) cell line U266. Different concentrations (1, 5, 10 micromol/L) of flumatinib mesylate were used to act on U266 cell line for 8, 16 and 24 h, and the expression of C-MYC, and HIF-1alpha genes was detected by real-time fluorescence-quantitative PCR, the expression of C-MYC, HIF-1alpha and VEGF was measured by Western blot. The results showed that the gene expression of C-MYC and HIF-1 genes decreased gradually with the increasing of flumatinib mesylate concentration ($P < 0.05$). At the same concentration of flumatinib mesylate, the expression of C-MYC and HIF-1alpha gene decreased gradually with prolonging of treatment time with the flumatinib mesylate ($P < 0.05$). When the flumatinib mesylate acted the U266 cell line for 16 h, the expression of C-MYC, HIF-1alpha and VEGF decreased gradually with the increasing of flumatinib mesylate concentration ($P < 0.05$). It is concluded that the flumatinib mesylate can reduce the expression of C-MYC, HIF-1 alpha and VEGF in U266 cell line in a time- and dose-dependent manners, so flumatinib mesylate may become a new drug for MM therapy.

Chauhan, J., H. Wang, et al. "Discovery of Methyl 4'-Methyl-5-(7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)-[1,1'-biphenyl]-3-carboxylate, an Improved Small-Molecule Inhibitor of c-Myc-Max Dimerization." ChemMedChem. 2014 Jun 27. doi: 10.1002/cmdc.201402189.

c-Myc is a basic helix-loop-helix-leucine zipper (bHLH-ZIP) transcription factor that is responsible for the transcription of a wide range of target genes involved in many cancer-related cellular processes. Over-expression of c-Myc has been observed in, and directly contributes to, a variety of human cancers including those of the hematopoietic system, lung, prostate and colon. To become transcriptionally active, c-Myc must first dimerize with Myc-associated factor X (Max) via its own bHLH-ZIP domain. A proven strategy towards the inhibition of c-Myc oncogenic activity is to interfere with the structural integrity of the c-Myc-Max heterodimer. The small molecule 10074-G5 is an inhibitor of c-Myc-Max dimerization (IC50 =146 muM) that operates by binding and stabilizing c-Myc in its monomeric form. We have identified a congener of 10074-G5, termed 3jc48-3 (methyl 4'-methyl-5-(7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)-[1,1'-biphenyl]-3-carboxylate) , that is about five times as potent (IC50 =34 muM) at inhibiting c-Myc-Max dimerization as the parent compound. 3jc48-3 exhibited an approximate twofold selectivity for c-Myc-Max heterodimers over Max-Max homodimers, suggesting that its mode of action is through binding c-Myc. 3jc48-3 inhibited the proliferation of c-Myc-over-expressing HL60 and Daudi cells with single-digit micromolar IC50 values by causing growth arrest at the G0 /G1 phase. Co-immunoprecipitation studies indicated that 3jc48-3 inhibits c-Myc-Max dimerization in cells, which was further substantiated by the specific silencing of a c-Myc-driven luciferase reporter gene. Finally, 3jc48-3's intracellular half-life was >17 h. Collectively, these data demonstrate 3jc48-3 to be one of the most potent, cellularly active and stable c-Myc inhibitors reported to date.

Chen, C. H., D. S. Lin, et al. "Cdc6 cooperates with c-Myc to promote genome instability and epithelial to mesenchymal transition EMT in zebrafish." Oncotarget. 2014 Aug 30;5(15):6300-11.

Aberration in DNA replication is a major cause to genome instability that is a hallmark of cancer cells. Cell division cycle 6 (Cdc6) and c-Myc have a critical role in the initiation of DNA replication. However, whether their interaction induces epithelial-mesenchymal transition (EMT) and promotes tumorigenesis in in vivo animal model remains unclear. Since using zebrafish as a cancer model has been restricted by the late onset of tumorigenesis and extreme difficulty in transformation on skin, we tried to establish a novel non-melanoma skin model in zebrafish to study their role in tumorigenesis. A stable transgenic zebrafish was created by using tol2 transposon, in which cdc6 and c-myc were co-overexpressed in epidermis driven by a skin-specific krt4 promoter. Intriguingly, co-overexpression of cdc6 and c-myc in transgenic zebrafish skin triggered tumor-like transformation, apoptosis attenuation, genomic instability, and EMT, hallmarks of malignant tumorigenesis. Our findings and other characteristics of zebrafish, including optical clarity and small molecule treatment, provide the future utility of this model for easy and non-invasive detection and for identification of new anti-cancer drug.

Chen, S., L. Su, et al. "Mechanistic studies for the role of cellular nucleic-acid-binding protein (CNBP) in regulation of c-myc transcription." Biochim Biophys Acta. 2013 Oct;1830(10):4769-77. doi: 10.1016/j.bbagen.2013.06.007. Epub 2013 Jun 14.

BACKGROUND: Guanine-rich sequence of c-myc nuclease hypersensitive element (NHE) III1 is known to fold in G-quadruplex and subsequently serves as a transcriptional silencer. Cellular nucleic-acid-binding protein (CNBP), a highly conserved zinc-finger protein with multiple biological functions, could bind to c-myc NHE III1 region, specifically to the single strand G-rich sequence. METHODS: In the present study, a variety of methods, including cloning, expression and purification of protein, EMSA, CD, FRET, Ch-IP, RNA interference, luciferase reporter assay, SPR, co-immunoprecipitation, and co-transfection, were applied to investigate the mechanism for the role of CNBP in regulating c-myc transcription. RESULTS: We found that human CNBP specifically bound to the G-rich sequence of c-myc NHE III1 region both in vitro and in cellulo, and subsequently promoted the formation of G-quadruplex. CNBP could induce a transient decrease followed by an increase in c-myc transcription in vivo. The interaction of CNBP with NM23-H2 was responsible for the increase of c-myc transcription. CONCLUSIONS: Based on above experimental results, a new mechanism, involving G-quadruplex related CNBP/NM23-H2 interaction, for the regulation of c-myc transcription was proposed. GENERAL SIGNIFICANCE: These findings indicated that the regulation of c-myc transcription through NHE III1 region might be governed by mechanisms involving complex protein-protein interactions, and suggested a new possibility of CNBP as a potential anti-cancer target based on CNBP's biological function in c-myc transcription.

Chen, W. and W. H. Xu "Wnt/beta-catenin signaling regulates Helicoverpa armigera pupal development by up-regulating c-Myc and AP-4." Insect Biochem Mol Biol. 2014 Jul 16;53C:44-53. doi: 10.1016/j.ibmb.2014.07.004.

Seasonally changing environmental conditions perceived by insect brains can be converted into hormonal signals that prompt insects to make a decision to develop or enter developmental arrest (diapause). Diapause is a complex physiological response, and many signaling pathways may participate in its regulation. However, little is known about these regulatory pathways. In this study, we cloned four genes related to the Wnt/beta-catenin signaling pathway from Helicoverpa armigera, a pupal diapause species. Western blotting shows that expression of Har-Wnt1, Har-beta-catenin, and Har-c-Myc are higher in non-diapause pupal brains than in diapause-destined brains. Har-Wnt1 can promote the accumulation of Har-beta-catenin in the nucleus, and Har-beta-catenin in turn increases the expression of Har-c-Myc. The blockage of Wnt/beta-catenin signaling by the inhibitor XAV939 significantly down-regulates Har-beta-catenin and Har-c-Myc expression and delays pupal development, suggesting that the Wnt/beta-catenin pathway functions in insect development. Furthermore, Har-c-Myc binds to the promoter of Har-AP-4 and regulates its expression. It has been reported that Har-AP-4 activates diapause hormone (DH) expression and that DH up-regulates the growth hormone ecdysteroid for pupal development. Thus, pupal development is regulated by Wnt/beta-catenin signaling through the pathway Wnt-beta-catenin-c-Myc-AP-4-DH-ecdysteroid. In contrast, the down-regulation of Wnt/beta-catenin signaling is likely to induce insects to enter diapause.

Cowling, V. H., S. A. Turner, et al. "Burkitt's lymphoma-associated c-Myc mutations converge on a dramatically altered target gene response and implicate Nol5a/Nop56 in oncogenesis." Oncogene. 2014 Jul 3;33(27):3519-27. doi: 10.1038/onc.2013.338. Epub 2013 Sep 9.

Burkitt's lymphomas (BLs) acquire consistent point mutations in a conserved domain of Myc, Myc Box I. We report that the enhanced transforming activity of BL-associated Myc mutants can be uncoupled from loss of phosphorylation and increased protein stability. Furthermore, two different BL-associated Myc mutations induced similar gene expression profiles independently of T58 phosphorylation, and these profiles are dramatically different from MycWT. Nol5a/Nop56, which is required for ribosomal RNA methylation, was identified as a gene hyperactivated by the BL-associated Myc mutants. We show that Nol5a is necessary for Myc-induced cell transformation, enhances MycWT-induced cell transformation and increases the size of MycWT-induced tumors. Thus, Nol5a expands the link between Myc-induced regulation of nucleolar target genes, which are rate limiting for cell transformation and tumor growth.

Demir, D., B. Yaman, et al. "Prognostic significance of bcl-2, c-myc, survivin and tumor grade in synovial sarcoma." Turk Patoloji Derg. 2014;30(1):55-65. doi: 10.5146/tjpath.2013.01221.

OBJECTIVE: We aimed to determine the prognostic value of bcl-2, c-myc and survivin in synovial sarcoma cases and to evaluate the relationship between the conventional morphological findings with prognosis. MATERIAL AND METHOD: In this study, we evaluated 81 synovial sarcoma cases referred to our tertiary tumor center during a period of 20 years. We applied bcl-2, c-myc and survivin immunohistochemically and investigated the relationship with prognosis for those 65 cases with follow-up. The relationship between the conventional morphological findings (mitosis, necrosis, grade) with prognosis was also investigated. RESULTS: Five-year disease free survival rate was 44% and ten-year progression free survival rate was 38%, reflecting the aggressive behavior of synovial sarcoma. Tumor grade (according to FNCLCC) was the most significant prognostic input in this study. We obtained a significant difference between grade II (40 cases) and grade III (24 cases) group regarding progression-free survival and overall survival ($p < 0.001$ and $p < 0.001$ respectively). Grade II was divided into two groups according to mitotic index and necrosis (grade IIa and IIb) and there was a significant difference between them regarding prognosis ($p=0.013$ for progression free survival, $p=0.003$ for overall survival). There was a significant relationship between bcl-2 negative plus focally weak positive cases (9 cases) and focally strong cases (21 cases) and diffuse strong cases (35 cases) ($p=0.042$ and $p=0.016$ respectively). There was a significant relation between c-myc negative cases (25 cases) and nuclear positive cases (17 cases) regarding overall survival ($p=0.043$) and between c-myc negative cases and cytoplasmic positive cases (23 cases) regarding progression free survival ($p=0.05$). The relation between survivin and prognosis was not significant. CONCLUSION: Tumor grade was the most significant prognostic parameter in this study. The grade IIa group (with less than 10

mitoses in 10 HPF, without necrosis) had a better prognosis than both the grade IIb and III groups. The grade IIb group was closer to grade III regarding the prognosis. Bcl-2 and c-myc (nuclear and/or cytoplasmic) immunohistochemical positivity had prognostic value but this finding has to be confirmed by large series.

Di, J., T. Duiveman-de Boer, et al. "The stem cell markers Oct4A, Nanog and c-Myc are expressed in ascites cells and tumor tissue of ovarian cancer patients." Cell Oncol (Dordr). 2013 Oct;36(5):363-74. doi: 10.1007/s13402-013-0142-8. Epub 2013 Aug 9.

PURPOSE: The aim of this study was to examine the expression of established stem cell markers in ascites and tumor tissue obtained from ovarian cancer patients. METHODS: Mononuclear cells present in ascites were collected by density gradient centrifugation. Intracellular flowcytometry was used to assess the putative presence of stem cell markers. RT-PCR was used to detect full length Oct4A, a splice variant Oct4B, implicated in glioma and breast cancer, Oct4 pseudogenes and c-Myc. Genes were cloned and sequenced to determine putative mutations. Confocal laser scanning microscopy was performed to localize the markers in ascites cells as well as in tumor tissue. Material from carcinomas other than epithelial ovarian carcinoma served as control. RESULTS: A small quantity of cells in ascites and in tumor tissue of ovarian cancer patients was detected that expresses c-Myc, Oct4A and Nanog. Besides Oct4A, present in the nucleus, also the cytoplasmic resident Oct4B splice variant was detected. Remarkably, c-Myc was found partially in the cytoplasm. Since no mutations in c-Myc were found that could explain the cytoplasmic localization, we hypothesize that this is due an IL-6 induced c-Myc shuttle factor. CONCLUSIONS: The expression of stem cell genes was detected in a small proportion of tumor cells present in ascites as well as in tumor tissue. IL-6 plays an important role in the induction of c-Myc.

Ding, Z., X. Liu, et al. "Expression of far upstream element (FUSE) binding protein 1 in human glioma is correlated with c-Myc and cell proliferation." Mol Carcinog. 2013 Dec 17. doi: 10.1002/mc.22114.

Glioma is one of the most common type of primary intracranial tumor. Although great advances have been achieved in treatment of glioma, the underlying molecular mechanisms remain largely unknown. Previous studies demonstrated that FBP1 is a transcriptional regulator of c-Myc and acts as an important prognostic indicator in many cancers. Our study aimed to assess the expression and function of FBP1 in human glioma. Immunohistochemical and Western blot analysis were performed in human glioma and normal brain tissues. High FBP1 expression (located in cell nuclei) was observed in 70 samples and its level was correlated with the grade of malignancy. A strongly positive correlation was observed between FBP1 and c-Myc (P = 0.005) and Ki-67 expression (P = 0.009). In a multivariate analysis, high FBP1 and c-Myc expressions were showed to be associated with poor prognosis in glioma. While in vitro, following serum stimulation of starved U87MG cells, the expression of FBP1 was upregulated, as well as c-Myc and PCNA. Moreover, knockdown of FBP1 by siRNA transfection diminished the expression of c-Myc and arrested cell growth at G1 phase. Collectively, our results shows that the expression of FBP1 is in close correlation with c-Myc level and cell proliferation in glioma and provides a potential strategy to develop FBP1 inhibitors as novel anti-tumor agents. (c) 2013 Wiley Periodicals, Inc.

Dueck, A. C., M. M. Reinholz, et al. "Impact of c-MYC protein expression on outcome of patients with early-stage HER2+ breast cancer treated with adjuvant trastuzumab NCCTG (alliance) N9831." Clin Cancer Res. 2013 Oct 15;19(20):5798-807. doi: 10.1158/1078-0432.CCR-13-0558. Epub 2013 Aug 21.

PURPOSE: This study investigated the association between tumor MYC protein expression and disease-free survival (DFS) of patients randomized to receive chemotherapy alone (Arm A) or chemotherapy with sequential (Arm B) or concurrent trastuzumab (Arm C) in the N9831 (Alliance) adjuvant HER2(+) trastuzumab breast cancer trial. EXPERIMENTAL DESIGN: This analysis included 1,736 patients randomized to Arms A, B, and C on N9831. Nuclear MYC protein expression was determined in tissue microarray sections containing three biopsies per patient or whole tissue sections using standard immunohistochemistry (clone 9E10). A tumor was considered positive for MYC protein overexpression (MYC(+)) if the nuclear 3+ staining percentage was more than 30%. RESULTS: Five hundred and seventy-four (33%) tumors were MYC(+). MYC(+) was associated with hormone receptor positivity (chi(2), P = 0.006), tumors 2 cm or more (chi(2), P = 0.02), and a higher rate of nodal positivity (chi(2), P < 0.001). HRs for DFS (median follow-up: 6.1 years) for Arm C versus A were 0.52 (P = 0.006) and 0.65 (P = 0.006) for patients with MYC(+) and MYC(-) tumors, respectively (P(interaction) = 0.40). For Arm B versus A, HRs for patients with MYC(+) and MYC(-) tumors were 0.79 (P = 0.21) and 0.74 (P = 0.04), respectively (P(interaction) = 0.71). For Arm C versus B, HRs for patients with MYC(+) and MYC(-) tumors were 0.56 (P = 0.02) and 0.89 (P = 0.49), respectively (P(interaction) = 0.17). CONCLUSIONS: Our data do not support an impact of tumor MYC protein expression on differential benefit from adjuvant trastuzumab.

Edmunds, L. R., L. Sharma, et al. "c-Myc Programs Fatty Acid Metabolism and Dictates Acetyl-CoA Abundance and Fate." J Biol Chem. 2014 Sep 5;289(36):25382-92. doi: 10.1074/jbc.M114.580662. Epub 2014 Jul 22.

myc(-/-) rat fibroblasts (KO cells) differ from myc(+/+) (WT) cells and KO cells with enforced Myc re-expression (KO-Myc cells) with respect to mitochondrial structure and function, utilization of glucose and glutamine as energy-generating substrates, and ATP levels. Specifically, KO cells demonstrate low levels of glycolysis and oxidative phosphorylation, dysfunctional mitochondria and electron transport chain complexes, and depleted ATP stores. We examined here how these cells adapt to their energy-deficient state and how they differ in their uptake and utilization of long- and medium-chain fatty acids such as palmitate and octanoate, respectively. Metabolic tracing of these molecules showed that KO cells preferentially utilize them as beta-oxidation substrates and that, rather than directing them into phospholipids, preferentially store them as neutral lipids. KO cell transcriptional profiling and functional assays revealed a generalized up-regulation of pathways involved in fatty acid transport and catabolism as well as evidence that these cells attempt to direct acetyl-CoA into the tricarboxylic acid (TCA) cycle for ATP production rather than utilizing it for anabolic purposes. Additional evidence to support this idea included the finding that AMP-dependent protein kinase was constitutively activated in KO cells. The complex control of pyruvate dehydrogenase, which links glycolysis to the TCA cycle, was also maximized to ensure the conversion of pyruvate to acetyl-CoA. Despite these efforts to maximize acetyl-CoA for energy-generating purposes, its levels remained chronically low in KO cells. This suggests that tumor cells with Myc deregulation might be susceptible to novel therapies that limit acetyl-CoA availability.

Ehninger, A., T. Boch, et al. "Posttranscriptional regulation of c-Myc expression in adult murine HSCs during homeostasis and interferon-alpha-induced stress response." Blood. 2014 Jun 19;123(25):3909-13. doi: 10.1182/blood-2013-10-531038. Epub 2014 May 2.

Previous studies have established pivotal roles for c-Myc and its homolog N-Myc in hematopoietic stem cell (HSC) maintenance and niche-dependent differentiation. However, it remains largely unclear how c-Myc expression is regulated in this context. Here, we show that HSCs and more committed progenitors express similar levels of c-myc transcripts. Using knock-in mice expressing a functional enhanced green fluorescent protein-c-Myc fusion protein under control of the endogenous c-myc locus, c-Myc protein levels were assessed. Although HSCs express low levels of c-Myc protein, its expression increases steadily during progenitor

differentiation. Thus, mRNA and protein expression patterns differ significantly in stem/progenitor cells, suggesting that c-Myc expression is largely controlled posttranscriptionally. Moreover, interferon-alpha exposure, which activates dormant HSCs, strongly induces c-Myc expression at the protein level but not at the transcript level. This posttranscriptional mechanism of c-Myc regulation provides the blood system with a rapid way to adjust c-Myc expression according to demand during hematopoietic stress.

El-Chemaly, S., G. Pacheco-Rodriguez, et al. "Nuclear localization of vascular endothelial growth factor-D and regulation of c-Myc-dependent transcripts in human lung fibroblasts." Am J Respir Cell Mol Biol. 2014 Jul;51(1):34-42. doi: 10.1165/rcmb.2013-0417OC.

Lymphangiogenesis and angiogenesis are processes that are, in part, regulated by vascular endothelial growth factor (VEGF)-D. The formation of lymphatic structures has been implicated in multiple lung diseases, including pulmonary fibrosis. VEGF-D is a secreted protein produced by fibroblasts and macrophages, which induces lymphangiogenesis by signaling via VEGF receptor-3, and angiogenesis through VEGF receptor-2. VEGF-D contains a central VEGF homology domain, which is the biologically active domain, with flanking N- and C-terminal propeptides. Full-length VEGF-D (approximately 50 kD) is proteolytically processed in the extracellular space, to generate VEGF homology domain that contains the VEGF-D receptor-binding sites. Here, we report that, independent of its cell surface receptors, full-length VEGF-D accumulated in nuclei of fibroblasts, and that this process appears to increase with cell density. In nuclei, full-length VEGF-D associated with RNA polymerase II and c-Myc. In cells depleted of VEGF-D, the transcriptionally regulated genes appear to be modulated by c-Myc. These findings have potential clinical implications, as VEGF-D was found in fibroblast nuclei in idiopathic pulmonary fibrosis, a disease characterized by fibroblast proliferation. These findings are consistent with actions of full-length VEGF-D in cellular homeostasis in health and disease, independent of its receptors.

Fan, H., Y. Cai, et al. "Microcystin-LR stabilizes c-myc protein by inhibiting protein phosphatase 2A in HEK293 cells." Toxicology. 2014 May 7;319:69-74. doi: 10.1016/j.tox.2014.02.015. Epub 2014 Mar 7.

Microcystin-LR is the most toxic and the most frequently encountered toxin produced by the cyanobacteria in the contaminated aquatic environment. Previous studies have demonstrated that Microcystin-LR is a potential carcinogen for animals and humans, and the International Agency for Research on Cancer has classified Microcystin-LR as a possible human carcinogen. However, the precise molecular mechanisms of Microcystin-LR-induced carcinogenesis remain a mystery. C-myc is a proto-oncogene, abnormal expression of which contributes to the tumor development. Although several studies have demonstrated that Microcystin-LR could induce c-myc expression at the transcriptional level, the exact connection between Microcystin-LR toxicity and c-myc response remains unclear. In this study, we showed that the c-myc protein increased in HEK293 cells after exposure to Microcystin-LR. Coexpression of protein phosphatase 2A and two stable c-myc protein point mutants (either c-myc(T58A) or c-myc(S62A)) showed that Microcystin-LR increased c-myc protein level mainly through inhibiting protein phosphatase 2A activity which altered the phosphorylation status of serine 62 on c-myc. In addition, we also showed that Microcystin-LR could increase c-myc promoter activity as revealed by luciferase reporter assay. And the TATA box for P1 promoter of c-myc might be involved. Our results suggested that Microcystin-LR can stimulate c-myc transcription and stabilize c-myc protein, which might contribute to hepatic tumorigenesis in animals and humans.

Fang, I. M., C. M. Yang, et al. "Transplantation of induced pluripotent stem cells without C-Myc attenuates retinal ischemia and reperfusion injury in rats." Exp Eye Res. 2013 Aug;113:49-59. doi: 10.1016/j.exer.2013.05.007. Epub 2013 May 28.

Induced pluripotent stem cells (iPSC) are novel stem cell populations, but the role of iPSC in retinal ischemia and reperfusion (I/R) injury remains unknown. Since oncogene c-Myc is substantially contributed to tumor formation, in this study, we investigated the effects, mechanisms and safety of subretinal transplantation of iPSC without c-Myc (non-c-Myc iPSC) in a rat model of retinal I/R injury. Retinal I/R injury was induced by raising the intraocular pressure of Sprague-Dawley rats to 110 mmHg for 60 min. A subretinal injection of non-c-Myc iPSC or murine epidermal fibroblast was given 2 h after I/R injury. Electroretinograms (ERG) were performed to determine the functionality of the retinas. The surviving retinal ganglion cells (RGCs) and retinal apoptosis following I/R injury were determined by counting NeuN-positive cells in whole-mounted retinas and TUNEL staining, respectively. The generation of reactive oxygen species (ROS) and the activities of superoxide dismutase (SOD) and catalase (CAT) in the retinal tissues were determined by lucigenin- and luminol-enhanced chemiluminescence and enzyme-linked immunosorbent assay (ELISA). The degree of retinal oxidative damage was assessed by nitrotyrosine, acrolein, and 8-hydroxy-2'-deoxyguanosine (8-OHdG) staining. The expression of brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF) and basic fibroblast growth factor (bFGF) in retinas was measured by immunohistochemistry and ELISA. We found that subretinal transplantation of non-c-Myc iPSC significantly suppressed the I/R-induced reduction in the ERG a- and b-wave ratio, attenuated I/R-induced loss of RGCs and remarkably ameliorated retinal morphological changes. Non-c-Myc iPSC potentially increased the activities of SOD and CAT, decreased the levels of ROS, which may account for preventing retinal cells from apoptotic cell death. In addition, the levels of BDNF and CNTF in retina were significantly elevated in non-c-Myc iPSC-treated eyes. Track the non-c-Myc iPSC after transplantation, most transplanted cells are remained in the subretinal space, with spare cells express neurofilament M markers at day 28. Six months after transplantation in I/R injured rats, no tumor formation was seen in non-c-Myc iPSC graft. In conclusion, non-c-Myc iPSC effectively rescued I/R-induced retinal damages and diminished tumorigenicity. Non-c-Myc iPSC transplantation attenuated retinal I/R injury, possibly via a mechanism involving the regulation of oxidative parameters and paracrinal secretion of trophic factors.

Farrell, A. S., C. Pelz, et al. "Pin1 regulates the dynamics of c-Myc DNA binding to facilitate target gene regulation and oncogenesis." Mol Cell Biol. 2013 Aug;33(15):2930-49. doi: 10.1128/MCB.01455-12. Epub 2013 May 28.

The Myc oncoprotein is considered a master regulator of gene transcription by virtue of its ability to modulate the expression of a large percentage of all genes. However, mechanisms that direct Myc's recruitment to DNA and target gene selection to elicit specific cellular functions have not been well elucidated. Here, we report that the Pin1 prolyl isomerase enhances recruitment of serine 62-phosphorylated Myc and its coactivators to select promoters during gene activation, followed by promoting Myc's release associated with its degradation. This facilitates Myc's activation of genes involved in cell growth and metabolism, resulting in enhanced proproliferative activity, even while controlling Myc levels. In cancer cells with impaired Myc degradation, Pin1 still enhances Myc DNA binding, although it no longer facilitates Myc degradation. Thus, we find that Pin1 and Myc are cooverexpressed in cancer, and this drives a gene expression pattern that we show is enriched in poor-outcome breast cancer subtypes. This study provides new insight into mechanisms regulating Myc DNA binding and oncogenic activity, it reveals a novel role for Pin1 in the regulation of transcription factors, and it elucidates a mechanism that can contribute to oncogenic cooperation between Pin1 and Myc.

Feng, Z., J. Zhou, et al. "An unusual case of mycosis fungoides with

high proliferation index and C-MYC/8q24 translocation." J La State Med Soc. 2013 Nov-Dec;165(6):324-8.

Mycosis fungoides is the most common entity among all cutaneous T cell lymphomas. Herein, we report for the first time a case of mycosis fungoides in a 51-year-old man with aggressive clinical course and confirmed C-MYC/8q24 translocation. Review of the literature reveals that dermal Ki-67 proliferation index not only correlates with the type and extent of skin involvement and clinical stage, but is also an independent adverse prognostic factor. Mycosis fungoides is associated with multiple genomic abnormalities, particularly in patients with tumor stage and advanced clinical stage, and gain of C-MYC/8q24 is associated with a shorter survival. Our patient showed a high dermal Ki-67 level and concomitant C-MYC/8q24 translocation, which may account for the aggressive clinical course and refractoriness to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy.

Fiorito, F., A. Cantiello, et al. "Modulation of telomerase activity, bTERT and c-Myc induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin during Bovine Herpesvirus 1 infection in MDBK cells." Toxicol In Vitro. 2014 Feb;28(1):24-30. doi: 10.1016/j.tiv.2013.06.020. Epub 2013 Jul 9.

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) influences infection of kidney cells (MDBK) with Bovine Herpesvirus 1 (BHV-1) through an increase in virus replication and an acceleration of BHV-1-induced apoptosis. Previously our group demonstrated that BHV-1, in the early stages of infection, significantly up-regulates telomerase activity in MDBK cells, while, in the late phases of infection, when BHV-1-induced apoptosis occurred, a down-regulation of telomerase activity was detected. Hence, herein, for the first time, we described the influences of TCDD on telomerase activity during virus infection. In kidney cells (MDBK) infected with BHV-1 and exposed to different doses of TCDD we explored telomerase activity by TRAP assay. Concomitantly, we examined protein levels of both bTERT and c-Myc by Western blot analysis. In all groups, TCDD induced an acceleration in down-regulation of telomerase activity. Particularly, TCDD drastically and significantly decreased telomerase activity when virus-induced apoptosis took place. This result was accompanied from an accelerated down-regulation of bTERT and c-Myc. Finally, in the presence of TCDD, we evidenced a dose-dependent overexpression of aryl hydrocarbon receptor. Hence, our data suggest that TCDD, through a significant acceleration in down-regulation of telomerase activity, bTERT and c-Myc, may contribute to accelerated BHV-1-induced apoptosis.

Fonseca-Alves, C. E., M. M. Rodrigues, et al. "Alterations of C-MYC, NKX3.1, and E-cadherin expression in canine prostate carcinogenesis." Microsc Res Tech. 2013 Dec;76(12):1250-6. doi: 10.1002/jemt.22292. Epub 2013 Sep 12.

The dog (canis lupus familiaris) is the only other species besides humans that develop spontaneous prostatic carcinomas (PCa) at a high frequency. The canine model is primarily utilized for the study of the PCa molecular mechanisms and provides a natural animal model for the study of potential therapies. In humans, the PCa frequently exhibits mutations in the C-MYC and a reduced expression of the E-cadherin and NKX3.1 proteins. This study's objective was to evaluate the NKX3.1, C-MYC, and E-cadherin expression in the canine normal prostate, benign prostatic hyperplasia (BPH), proliferative inflammatory atrophy (PIA) and PCa and to verify differences in expression and subcellular localization of these proteins in the prostatic carcinogenesis. A tissue microarray (TMA) slide was constructed, and immunohistochemistry with antibodies raised against C-MYC, NKX3.1, E-cadherin and p63 was performed using the peroxidase and DAB methods. The C-MYC protein expression was elevated in the cytoplasm and nuclei of the canine PCa and PIA compared with the normal prostate (P = 0.004. The NKX3.1 protein expression was reduced in 94.75% of the PCa and 100% of the PIA compared with the normal prostate (P = 0.0022). In fact, the expression of E-cadherin trended towards a decrease in carcinomas when compared to normal prostate and PIA. By immunohistochemistry, more p63-positive basal cells were observed in the PCa and PIA when compared with the normal prostate (P = 0.0002). This study has demonstrated that the carcinogenesis of canine prostatic tissue may be related to basal cell proliferation, the gain of C-MYC function and the loss of NKX3.1 protein expression.

Franco, M., A. J. Shastri, et al. "Infection by Toxoplasma gondii specifically induces host c-Myc and the genes this pivotal transcription factor regulates." Eukaryot Cell. 2014 Apr;13(4):483-93. doi: 10.1128/EC.00316-13. Epub 2014 Feb 14.

Toxoplasma gondii infection has previously been described to cause dramatic changes in the host transcriptome by manipulating key regulators, including STATs, NF-kappaB, and microRNAs. Here, we report that Toxoplasma tachyzoites also mediate rapid and sustained induction of another pivotal regulator of host cell transcription, c-Myc. This induction is seen in cells infected with all three canonical types of Toxoplasma but not the closely related apicomplexan parasite Neospora caninum. Coinfection of cells with both Toxoplasma and Neospora still results in an increase in the level of host c-Myc, showing that c-Myc is actively upregulated by Toxoplasma infection (rather than repressed by Neospora). We further demonstrate that this upregulation may be mediated through c-Jun N-terminal protein kinase (JNK) and is unlikely to be a nonspecific host response, as heat-killed Toxoplasma parasites do not induce this increase and neither do nonviable parasites inside the host cell. Finally, we show that the induced c-Myc is active and that transcripts dependent on its function are upregulated, as predicted. Hence, c-Myc represents an additional way in which Toxoplasma tachyzoites have evolved to specifically alter host cell functions during intracellular growth.

Fusello, A., J. Horowitz, et al. "Histone H2AX suppresses translocations in lymphomas of Emu-c-Myc transgenic mice that contain a germline amplicon of tumor-promoting genes." Cell Cycle. 2013 Sep 1;12(17):2867-75. doi: 10.4161/cc.25922. Epub 2013 Aug 8.

The DNA damage response (DDR) can restrain the ability of oncogenes to cause genomic instability and drive malignant transformation. The gene encoding the histone H2AX DDR factor maps to 11q23, a region frequently altered in human cancers. Since H2ax functions as a haploinsufficient suppressor of B lineage lymphomas with c-Myc amplification and/or translocation, we determined the impact of H2ax expression on the ability of deregulated c-Myc expression to cause genomic instability and drive transformation of B cells. Neither H2ax deficiency nor haploinsufficiency affected the rate of mortality of Emu-c-Myc mice from B lineage lymphomas with genomic deletions and amplifications. Yet H2ax functioned in a dosage-dependent manner to prevent unbalanced translocations in Emu-c-Myc tumors, demonstrating that H2ax functions in a haploinsufficient manner to suppress allelic imbalances and limit molecular heterogeneity within and among Emu-c-Myc lymphomas. Regardless of H2ax copy number, all Emu-c-Myc tumors contained identical amplification of chromosome 19 sequences spanning 20 genes. Many of these genes encode proteins with tumor-promoting activities, including Cd274, which encodes the PD-L1 programmed death ligand that induces T cell apoptosis and enables cancer cells to escape immune surveillance. This amplicon was in non-malignant B and T cells and non-lymphoid cells, linked to the Emu-c-Myc transgene, and associated with overexpression of PD-L1 on non-malignant B cells. Our data demonstrate that, in addition to deregulated c-Myc expression, non-malignant B lineage lymphocytes of Emu-c-Myc transgenic mice may have constitutive amplification and increased expression of other tumor-promoting genes.

Ghosh, S., S. K. Pradhan, et al. "Molecular basis of recognition of

quadruplexes human telomere and c-myc promoter by the putative anticancer agent sanguinarine." Biochim Biophys Acta. 2013 Aug;1830(8):4189-201. doi: 10.1016/j.bbagen.2013.03.027. Epub 2013 Apr 4.

BACKGROUND: Interaction of putative anticancer agent sanguinarine with two quadruplex forming sequences, human telomeric DNA (H24) and NHE III1 upstream of the P1 promoter of c-myc (Pu27), has been studied to understand the structural basis of the recognition. METHODS: Absorption, fluorescence and circular dichroism spectroscopy have been employed to characterize the association. Energetics of the interaction was studied by isothermal titration and differential scanning calorimetry. TRAP assay was done to assess the inhibitory potential of sanguinarine. RESULTS: Absorption and fluorescence studies show that sanguinarine has high binding affinity of ~10(5)M(-1) for both sequences. Binding stoichiometry is 2:1 for H24 and 3:1 for Pu27. Results suggest stacking interaction between planar sanguinarine moiety and G-quartets. Circular dichroism spectra show that sanguinarine does not cause structural perturbation in the all-parallel Pu27 but causes a structural transition from mixed hybrid to basket form at higher sanguinarine concentration in case of H24. The interaction is characterized by total enthalpy-entropy compensation and high heat capacity values. Differential scanning calorimetry studies suggest that sanguinarine binding increases the melting temperature and also the total enthalpy of transition of both quadruplexes. TRAP results show that sanguinarine effectively blocks telomerase activity in a concentration dependent manner in cell extracts from MDAMB-231 breast cancer cell lines. CONCLUSION: These results suggest that there is a difference in the structural modes of association of sanguinarine to the quadruplexes. GENERAL SIGNIFICANCE: It helps to understand the role of quadruplex structures as a target of small molecule inhibitors of telomerase.

Glitza, I. C., G. Lu, et al. "Chromosome 8q24.1/c-MYC abnormality: a marker for high-risk myeloma." Leuk Lymphoma. 2014 Aug 18:1-6.

The proto-oncogene c-MYC is rearranged in about 15% of patients with multiple myeloma (MM). We identified 23 patients with MM and c-MYC. Primary objectives were to describe the clinical characteristics, response to therapy, progression-free survival and overall survival (OS). Twelve out of twenty-three patients presented with or progressed to either plasma cell leukemia (PCL) and/or extramedullary disease (EMD). Induction therapy consisted of an immunomodulatory, proteasome inhibitor-based or conventional chemotherapy regimen. Fifteen patients achieved a partial response and three achieved a very good partial response. Sixteen patients received an autologous and one patient an allogeneic hematopoietic stem cell transplant. Median OS from diagnosis was 20.2 months. Patients with PCL or EMD had significantly shorter OS (15.5 vs. 40.4 months, p = 0.0005). This is the first report describing the clinical characteristics of patients with MM and c-MYC. These abnormalities are associated with an aggressive form of MM, high incidence of PCL/EMD and short OS.

Gokulan, R. and D. Halagowder "Expression pattern of Notch intracellular domain (NICD) and Hes-1 in preneoplastic and neoplastic human oral squamous epithelium: their correlation with c-Myc, clinicopathological factors and prognosis in Oral cancer." Med Oncol. 2014 Aug;31(8):126. doi: 10.1007/s12032-014-0126-1. Epub 2014 Jul 19.

Notch pathway molecules crosstalk with Wnt/beta-catenin signaling cascade in stem cells and tumors. However, the correlation between the expression pattern of Notch intracellular domain NICD, Hes-1 and c-Myc has not been studied in oral squamous cell carcinoma. The aim of this study is to investigate the correlation and prognostic significance of NICD, Hes-1 and c-Myc in oral cancer. Immunohistochemistry was used to study the expression pattern of NICD, Hes-1 and c-Myc in oral preneoplastic and neoplastic tissues. In addition, double immunofluorescence was used to examine the co-localization of NICD, Hes-1 and c-Myc in H314 cells. The expression pattern of NICD and Hes-1 was gradually increased from normal to dysplasia to carcinoma. Interestingly, statistically significant correlation was not observed between NICD, Hes-1 and c-Myc in oral squamous cell carcinoma. Furthermore, NICD+/c-Myc+ and Hes-1+/c-Myc+ double positive cases showed worst survival when compared with other cases in oral cancer. Notch signaling molecules, NICD and Hes-1, are found to be involved in the progression of oral squamous cell carcinoma. Interestingly, NICD, Hes-1 and c-Myc may have independent roles in oral cancer. On the other hand, we have demonstrated that NICD+/c-Myc+ and Hes-1+/c-Myc+ double positivity might be used as independent prognostic indicator of oral carcinoma.

Grandjenette, C., M. Schnekenburger, et al. "5-aza-2'-deoxycytidine-mediated c-myc Down-regulation Triggers Telomere-dependent Senescence by Regulating Human Telomerase Reverse Transcriptase in Chronic Myeloid Leukemia." Neoplasia. 2014 Jun;16(6):511-28. doi: 10.1016/j.neo.2014.05.009. Epub 2014 Jun 24.

Increased proliferation rates as well as resistance to apoptosis are considered major obstacles for the treatment of patients with chronic myelogenous leukemia (CML), thus highlighting the need for novel therapeutic approaches. Since senescence has been recognized as a physiological barrier against tumorigenesis, senescence-based therapy could represent a new strategy against CML. DNA demethylating agent 5-aza-2'-deoxycytidine (DAC) was reported to induce cellular senescence but underlying mechanisms remain to be elucidated. Here, we report that exposure to DAC triggers senescence in chronic leukemia cell lines as evidenced by increased senescence-associated beta-galactosidase activity and lysosomal mass, accompanied by an up-regulation of cell cycle-related genes. We provide evidence that DAC is able to decrease telomere length, to reduce telomerase activity and to decrease human telomerase reverse transcriptase (hTERT) expression through decreased binding of c-myc to the hTERT promoter. Altogether, our results reveal the role of c-myc in telomere-dependent DAC-induced senescence and therefore provide new clues for improving chronic human leukemia treatments.

Guo, P., Q. Nie, et al. "C-Myc negatively controls the tumor suppressor PTEN by upregulating miR-26a in glioblastoma multiforme cells." Biochem Biophys Res Commun. 2013 Nov 8;441(1):186-90. doi: 10.1016/j.bbrc.2013.10.034. Epub 2013 Oct 15.

The c-Myc oncogene is amplified in many tumor types. It is an important regulator of cell proliferation and has been linked to altered miRNA expression, suggesting that c-Myc-regulated miRNAs might contribute to tumor progression. Although miR-26a has been reported to be upregulated in glioblastoma multiforme (GBM), the mechanism has not been established. We have shown that ectopic expression of miR-26a influenced cell proliferation by targeting PTEN, a tumor suppressor gene that is inactivated in many common malignancies, including GBM. Our findings suggest that c-Myc modulates genes associated with oncogenesis in GBM through deregulation of miRNAs via the c-Myc-miR-26a-PTEN signaling pathway. This may be of clinical relevance.

Habib, O., G. Habib, et al. "An improved method for the derivation of high quality iPSCs in the absence of c-Myc." Exp Cell Res. 2013 Dec 10;319(20):3190-200. doi: 10.1016/j.yexcr.2013.09.014. Epub 2013 Oct 2.

Induced pluripotent stem cells (iPSCs) hold tremendous potential for the development of new regenerative medicine therapies and the study of molecular mechanisms of pluripotency and development. However, reactivation of c-Myc, which results in tumor formation in chimeric mice, is a major roadblock in the translation of iPSCs into therapies. Although ectopic expression of c-Myc is not absolutely required for somatic reprogramming, in the absence of c-Myc, the overall efficiency of reprogramming is drastically reduced and the reprogramming time is increased.

Subtle, abnormal epigenetic modifications in iPSCs derived in the absence of c-Myc have also been documented. Therefore, we developed a reprogramming method without c-Myc to generate high-quality iPSCs, a prerequisite to harnessing the full potential of iPSCs. In this study, we determined that serum replacement (SR)-based culture conditions dramatically increased the transcription factor-mediated reprogramming of mouse embryonic fibroblast cells (MEFs). The process was shortened to approximately 8 days when Oct4/Sox2/Klf4 (3F)-transduced MEFs were first cultured for 3 days under low serum conditions (LS protocol). The 3F-derived iPSCs that were generated by this method resembled mouse ES cells (mESCs) in morphology, gene expression, and in vitro differentiation. Finally, we observed that 3F-derived iPSC colonies were able to reach definite pluripotency in terms of molecular signatures when the catalytic function of c-Myc was tolerated. The 3F induction of pluripotency described here should facilitate the use of iPSCs and may also facilitate the mechanistic dissection of somatic reprogramming.

Hartwell, H. J., K. Y. Petrosky, et al. "Prolactin prevents hepatocellular carcinoma by restricting innate immune activation of c-Myc in mice." Proc Natl Acad Sci U S A. 2014 Aug 5;111(31):11455-60. doi: 10.1073/pnas.1404267111. Epub 2014 Jul 21.

Women are more resistant to hepatocellular carcinoma (HCC) than men despite equal exposure to major risk factors, such as hepatitis B or C virus infection. Female resistance is hormone-dependent, as evidenced by the sharp increase in HCC incidence in postmenopausal women who do not take hormone replacement therapy. In rodent models sex-dimorphic HCC phenotypes are pituitary-dependent, suggesting that sex hormones act via the gonadal-hypophyseal axis. We found that the estrogen-responsive pituitary hormone prolactin (PRL), signaling through hepatocyte-predominant short-form prolactin receptors (PRLR-S), constrained TNF receptor-associated factor (TRAF)-dependent innate immune responses invoked by IL-1beta, TNF-alpha, and LPS/Toll-like receptor 4 (TLR4), but not TRIF-dependent poly(I:C)/TLR3. PRL ubiquitinated and accelerated poststimulatory decay of a "trafasome" comprised of IRAK1, TRAF6, and MAP3K proteins, abrogating downstream activation of c-Myc-interacting pathways, including PI3K/AKT, mTORC1, p38 MAPK, and NF-kappaB. Consistent with this finding, we documented exaggerated male liver responses to immune stimuli in mice and humans. Tumor promotion through, but regulation above, the level of c-Myc was demonstrated by sex-independent HCC eruption in Alb-Myc transgenic mice. PRL deficiency accelerated liver carcinogenesis in Prl(-/-) mice of both sexes. Conversely, pharmacologic PRL mobilization using the dopamine D2 receptor antagonist domperidone prevented HCC in tumor-prone C3H/HeN males. Viewed together, our results demonstrate that PRL constrains tumor-promoting liver inflammation by inhibiting MAP3K-dependent activation of c-Myc at the level of the trafasome. PRL-targeted therapy may hold promise for reducing the burden of liver cancer in high-risk men and women.

Hassani, L., Z. Fazeli, et al. "A spectroscopic investigation of the interaction between c-MYC DNA and tetrapyridinoporphyrazinatozinc(II)." J Biol Phys. 2014 Jun;40(3):275-83. doi: 10.1007/s10867-014-9348-x. Epub 2014 May 15.

The c-MYC gene plays an important role in the regulation of cell proliferation and growth and it is overexpressed in a wide variety of human cancers. Around 90% of c-MYC transcription is controlled by the nuclease-hypersensitive element III1 (NHE III1), whose 27-nt purine-rich strand has the ability to form a G-quadruplex structure under physiological conditions. Therefore, c-MYC DNA is an attractive target for drug design, especially for cancer chemotherapy. Here, the interaction of water-soluble tetrapyridinoporphyrazinatozinc(II) with 27-nt G-rich strand (G/c-MYC), its equimolar mixture with the complementary sequence (GC/c-MYC) and related C-rich oligonucleotide (C/c-MYC) is investigated. Circular dichroism (CD) measurements of the G-rich 27-mer oligonucleotide in 150 mM KCl, pH 7 demonstrate a spectral signature consistent with parallel G-quadruplex DNA. Furthermore, the CD spectrum of the GC rich oligonucleotide shows characteristics of both duplex and quadruplex structures. Absorption spectroscopy implies that the complex binding of G/c-MYC and GC/c-MYC is a two-step process; in the first step, a very small red shift and hypochromicity and in the second step, a large red shift and hyperchromicity are observed in the Q band. Emission spectra of zinc porphyrazine are quenched upon addition of three types of DNA. According to the results of spectroscopy, it can be concluded the dominant binding mode is probably, outside binding and end stacking.

Hatano, K., S. Yamaguchi, et al. "Residual prostate cancer cells after docetaxel therapy increase the tumorigenic potential via constitutive signaling of CXCR4, ERK1/2 and c-Myc." Mol Cancer Res. 2013 Sep;11(9):1088-100. doi: 10.1158/1541-7786.MCR-13-0029-T. Epub 2013 Jun 20.

Despite an increasing prevalence of patients with docetaxel-refractory prostate cancer, little is known about the tumor biology of the docetaxel-resistant residual tumor cells compared with primary tumor cells. In this study, tumorigenic potential was increased in the docetaxel-resistant residual prostate cancer cell lines (DRD, 1G7 and PC3DR) compared with parental cells (DU145 or PC3). Enhanced tumorigenic potential was conferred by oncogenic c-Myc, which was stabilized by constitutively activated ERK1/2 in DRD, 1G7, and PC3DR cells. Constitutively activated ERK1/2 was maintained by CXCR4, which was upregulated in DRD, 1G7, and PC3DR cells. In docetaxel-treated DU145 cells, transiently activated ERK1/2 induced CXCR4 expression by stabilizing c-Myc. Furthermore, constitutive activation of CXCR4, ERK1/2, and c-Myc signaling was evident in clinical tissue samples from human patients with docetaxel-resistant prostate cancer. In DTX-resistant residual prostate cancer cells, the enhanced tumorigenic potential was reduced by ERK1/2 inhibition, or by AMD3100, a CXCR4 antagonist. Thus, docetaxel treatment constitutively activated the CXCR4, ERK1/2, and c-Myc signaling loop in docetaxel-resistant residual prostate cancer cells. IMPLICATIONS: Constitutive signaling pathways are viable therapeutic targets for residual prostate tumor cells following acquisition of docetaxel resistance.

He, W., Y. Li, et al. "miR-494 acts as an anti-oncogene in gastric carcinoma by targeting c-myc." J Gastroenterol Hepatol. 2014 Jul;29(7):1427-34. doi: 10.1111/jgh.12558.

BACKGROUND: We recently showed that miR-494 was downregulated in gastric carcinoma (GC). The objectives of this study were to determine the role of miR-494 in GC malignancy and to identify its target genes. METHODS: Real-time polymerase chain reaction was employed to quantify the expression level of miR-494 and c-myc in gastric cancer tissues. Bioinformatics was used to predict the downstream target genes of miR-494, which were confirmed by luciferase and RNA immunoprecipitation assays. Cell functional analyses and a xenograft mouse model were used to evaluate the role of miR-494 in malignancy. RESULTS: miR-494 was downregulated in human GC tissues and in GC cells and was negatively correlated with c-myc expression. High level of c-myc or low level of miR-494 correlated with poor prognosis. The miR-494-binding site in the c-myc 3' untranslated region was predicted using TargetScan and was confirmed by the luciferase assay. Additionally, c-myc and miR-494 were enriched in coimmunoprecipitates with tagged Argonaute2 proteins in cells overexpressing miR-494. Furthermore, a miR-494 mimic significantly downregulated endogenous c-myc expression, which may contribute to the delayed G1/S transition, decreased synthesis phase bromodeoxyuridine incorporation, and impaired cell growth and colony formation; on the other hand, treatment with a miR-494 inhibitor displayed the opposite effects. Reduced tumor burden and decreased cell

proliferation were observed following the delivery of miR-494 into xenograft mice. CONCLUSION: miR-494 is downregulated in human GC and acts as an anti-oncogene by targeting c-myc. miR-494 plays a role in the pathogenesis of gastric cancer in a recessive fashion.

He, X., X. Tan, et al. "C-Myc-activated long noncoding RNA CCAT1 promotes colon cancer cell proliferation and invasion." Tumour Biol. 2014 Sep 4.

Recently, more and more evidence are rapidly accumulating that long noncoding RNAs (lncRNAs) are involved in human tumorigenesis and misregulated in many cancers, including colon cancer. LncRNA could regulate essential pathways that contribute to tumor initiation and progression with their tissue specificity, which indicates that lncRNA would be valuable biomarkers and therapeutic targets. Colon cancer-associated transcript 1 (CCAT1) is a 2628 nucleotide-lncRNA and located in the vicinity of a well-known transcription factor c-Myc. CCAT1 has been found to be upregulated in many cancers, including gastric carcinoma and colonic adenoma-carcinoma. However, its roles in colon cancer are still not well documented and need to be investigated. In this study, we aim to investigate the prognostic value and biological function of CCAT1 and discover which factors may contribute to the deregulation of CCAT1 in colon cancer. Our results revealed that CCAT1 was significantly overexpressed in colon cancer tissues when compared with normal tissues, and its increased expression was correlated with patients' clinical stage, lymph nodes metastasis, and survival time after surgery. Moreover, c-Myc could promote CCAT1 transcription by directly binding to its promoter region, and upregulation of CCAT1 expression in colon cancer cells promoted cell proliferation and invasion. These data suggest that c-Myc-activated lncRNA CCAT1 expression contribute to colon cancer tumorigenesis and the metastatic process and could predict the clinical outcome of colon cancer and be a potential target for lncRNA direct therapy.

Hendrix, J., B. van Heertum, et al. "Dynamics of the ternary complex formed by c-Myc interactor JPO2, transcriptional co-activator LEDGF/p75, and chromatin." J Biol Chem. 2014 May 2;289(18):12494-506. doi: 10.1074/jbc.M113.525964. Epub 2014 Mar 14.

Lens epithelium-derived growth factor (LEDGF/p75) is a transcriptional co-activator involved in targeting human immunodeficiency virus (HIV) integration and the development of MLL fusion-mediated acute leukemia. A previous study revealed that LEDGF/p75 dynamically scans the chromatin, and upon interaction with HIV-1 integrase, their complex is locked on chromatin. At present, it is not known whether LEDGF/p75-mediated chromatin locking is typical for interacting proteins. Here, we employed continuous photobleaching and fluorescence correlation and cross-correlation spectroscopy to investigate in vivo chromatin binding of JPO2, a LEDGF/p75- and c-Myc-interacting protein involved in transcriptional regulation. In the absence of LEDGF/p75, JPO2 performs chromatin scanning inherent to transcription factors. However, whereas the dynamics of JPO2 chromatin binding are decelerated upon interaction with LEDGF/p75, very strong locking of their complex onto chromatin is absent. Similar results were obtained with the domesticated transposase PogZ, another cellular interaction partner of LEDGF/p75. We furthermore show that diffusive JPO2 can oligomerize; that JPO2 and LEDGF/p75 interact directly and specifically in vivo through the specific interaction domain of JPO2 and the C-terminal domain of LEDGF/p75, comprising the integrase-binding domain; and that modulation of JPO2 dynamics requires a functional PWWP domain in LEDGF/p75. Our results suggest that the dynamics of the LEDGF/p75-chromatin interaction depend on the specific partner and that strong chromatin locking is not a property of all LEDGF/p75-binding proteins.

Higgs, M. R., H. Lerat, et al. "Hepatitis C virus-induced activation of beta-catenin promotes c-Myc expression and a cascade of pro-carcinogenetic events." Oncogene. 2013 Sep 26;32(39):4683-93. doi: 10.1038/onc.2012.484. Epub 2012 Oct 29.

Chronic infection by hepatitis C virus (HCV) is a major risk factor for the onset and development of hepatocellular carcinoma (HCC), although the underlying mechanisms are unclear. The c-Myc oncogene contributes to the genesis of many types of cancers, including HCC, partly via the induction of genetic damage and the inhibition of the cellular response to genotoxic stress. Here, we show a previously undiscovered mechanistic link between HCV infection and enhanced c-Myc expression. c-Myc expression was augmented in non-tumoral liver tissues from HCV-infected individuals with or without HCC and in hepatocyte cell lines harboring an HCV replicon and the infectious HCV strain JFH1. Increased c-Myc expression was confirmed in vivo in a transgenic murine model expressing the entire HCV open reading frame, demonstrating a direct role for HCV protein expression in c-Myc induction. Mechanistically, activation of Akt by the HCV non-structural protein NS5A, and the subsequent stabilization of the transcription factor beta-catenin, was demonstrated to be responsible for activation of the c-Myc promoter, and for increased c-Myc transcription. beta-Catenin-dependent c-Myc expression in this context led to increased production of reactive oxygen species, mitochondrial perturbation, enhanced DNA damage and aberrant cell-cycle arrest. Together, these data provide a novel insight into the mechanisms involved in HCV-associated HCCs, strongly suggesting that c-Myc has a crucial contributory role in this process.

Huang, H., L. Ma, et al. "NF-kappaB1 inhibits c-Myc protein degradation through suppression of FBW7 expression." Oncotarget. 2014 Jan 30;5(2):493-505.

NF-kappaB is a well-known transcription factor in regulation of multiple gene transcription and biological processes, and most of them are relied on its transcriptional activity of the p65/RelA subunit, while biological function of another ubiquitously expressed subunit NF-kappaB1 (p50) remains largely unknown due to lack transcriptional activation domain. Here we discovered a novel biological function of p50 as a regulator of oncogenic c-Myc protein degradation upon arsenite treatment in a NF-kappaB transcriptional-independent mechanism. Our results found that p50 was crucial for c-Myc protein induction following arsenite treatment by using specific knockdown and deletion of p50 in its normal expressed cells as well as reconstituting expression of p50 in its deficient cells. Subsequently we showed that p50 upregulated c-Myc protein expression mainly through inhibiting its degradation. We also identified that p50 exhibited this novel property by suppression of FBW7 expression. FBW7 was profoundly upregulated in p50-deficient cells in comparison to that in p50 intact cells, whereas knockdown of FBW7 in p50-/- cells restored arsenite-induced c-Myc protein accumulation, assuring that FBW7 up-regulation was responsible for defect of c-Myc protein expression in p50-/- cells. In addition, we discovered that p50 suppressed fbw7 gene transcription via inhibiting transcription factor E2F1 transactivation. Collectively, our studies demonstrated a novel function of p50 as a regulator of c-Myc protein degradation, contributing to our notion that p50-regulated protein expression through multiple levels at protein translation and degradation, further providing a significant insight into the understanding of biomedical significance of p50 protein.

Islam, M. A., S. D. Thomas, et al. "c-Myc quadruplex-forming sequence Pu-27 induces extensive damage in both telomeric and nontelomeric regions of DNA." J Biol Chem. 2014 Mar 21;289(12):8521-31. doi: 10.1074/jbc.M113.505073. Epub 2014 Jan 24.

Quadruplex-forming DNA sequences are present throughout the eukaryotic genome, including in telomeric DNA. We have shown that the c-Myc promoter quadruplex-forming sequence Pu-27 selectively kills transformed cells (Sedoris, K. C., Thomas, S. D., Clarkson, C. R., Muench, D., Islam, A., Singh, R., and Miller, D.

M. (2012) Genomic c-Myc quadruplex DNA selectively kills leukemia. Mol. Cancer Ther. 11, 66-76). In this study, we show that Pu-27 induces profound DNA damage, resulting in striking chromosomal abnormalities in the form of chromatid or chromosomal breaks, radial formation, and telomeric DNA loss, which induces gamma-H2AX in U937 cells. Pu-27 down-regulates telomeric shelterin proteins, DNA damage response mediators (RAD17 and RAD50), double-stranded break repair molecule 53BP1, G2 checkpoint regulators (CHK1 and CHK2), and anti-apoptosis gene survivin. Interestingly, there are no changes of DNA repair molecules H2AX, BRCA1, and the telomere maintenance gene, hTERT. DeltaB-U937, where U937 cells stably transfected with deleted basic domain of TRF2 is partially sensitive to Pu-27 but exhibits no changes in expression of shelterin proteins. However, there is an up-regulation of CHK1, CHK2, H2AX, BRCA1, and survivin. Telomere dysfunction-induced foci assay revealed co-association of TRF1with gamma-H2AX in ATM deficient cells, which are differentially sensitive to Pu-27 than ATM proficient cells. Alt (alternating lengthening of telomere) cells are relatively resistant to Pu-27, but there are no significant changes of telomerase activity in both Alt and non-Alt cells. Lastly, we show that this Pu-27-mediated sensitivity is p53-independent. The data therefore support two conclusions. First, Pu-27 induces DNA damage within both telomeric and nontelomeric regions of the genome. Second, Pu-27-mediated telomeric damage is due, at least in part, to compromise of the telomeric shelterin protein complex.

Itkonen, H. M., S. Minner, et al. "O-GlcNAc transferase integrates metabolic pathways to regulate the stability of c-MYC in human prostate cancer cells." Cancer Res. 2013 Aug 15;73(16):5277-87. doi: 10.1158/0008-5472.CAN-13-0549. Epub 2013 May 29.

Metabolic disruptions that occur widely in cancers offer an attractive focus for generalized treatment strategies. The hexosamine biosynthetic pathway (HBP) senses metabolic status and produces an essential substrate for O-linked beta-N-acetylglucosamine transferase (OGT), which glycosylates and thereby modulates the function of its target proteins. Here, we report that the HBP is activated in prostate cancer cells and that OGT is a central regulator of c-Myc stability in this setting. HBP genes were overexpressed in human prostate cancers and androgen regulated in cultured human cancer cell lines. Immunohistochemical analysis of human specimens (n = 1987) established that OGT is upregulated at the protein level and that its expression correlates with high Gleason score, pT and pN stages, and biochemical recurrence. RNA interference-mediated siliencing or pharmacologic inhibition of OGT was sufficient to decrease prostate cancer cell growth. Microarray profiling showed that the principal effects of OGT inhibition in prostate cancer cells were related to cell-cycle progression and DNA replication. In particular, c-MYC was identified as a candidate upstream regulator of OGT target genes and OGT inhibition elicited a dose-dependent decrease in the levels of c-MYC protein but not c-MYC mRNA in cell lines. Supporting this relationship, expression of c-MYC and OGT was tightly correlated in human prostate cancer samples (n = 1306). Our findings identify HBP as a modulator of prostate cancer growth and c-MYC as a key target of OGT function in prostate cancer cells.

Jackstadt, R. and H. Hermeking MicroRNAs as regulators and mediators of c-MYC function, Biochim Biophys Acta. 2014 Apr 13. pii: S1874-9399(14)00080-7. doi: 10.1016/j.bbagrm.2014.04.003.

In the past ten years microRNAs (miRNAs) have been widely implicated as components of tumor suppressive and oncogenic pathways. Also the proto-typic oncogene c-MYC has been connected to miRNAs. The c-MYC gene is activated in approximately half of all tumors, and its product, the c-MYC transcription factor, regulates numerous processes e.g. cell cycle progression, metabolism, epithelial-mesenchymal transition (EMT), metastasis, stemness, and angiogenesis, thereby facilitating tumor initiation and progression. c-MYC target-genes, which mediate these functions of c-MYC, represent a complex network of protein- and non-coding RNAs, including numerous miRNAs. For example, c-MYC directly regulates expression of the miR-17-92 cluster, miR-34a, miR-15a/16-1 and miR-9. Moreover, the expression and activity of c-MYC itself are under the control of miRNAs. Here, we survey how these networks mediate and regulate c-MYC functions. In the future, miRNAs connected to c-MYC may be used for diagnostic and therapeutic approaches. This article is part of a Special Issue entitled: Myc proteins in cell biology and pathology.

Jacobs, P. T., L. Cao, et al. "Runx transcription factors repress human and murine c-Myc expression in a DNA-binding and C-terminally dependent manner." PLoS One. 2013 Jul 18;8(7):e69083. doi: 10.1371/journal.pone.0069083. Print 2013.

The transcription factors Runx1 and c-Myc have individually been shown to regulate important gene targets as well as to collaborate in oncogenesis. However, it is unknown whether there is a regulatory relationship between the two genes. In this study, we investigated the transcriptional regulation of endogenous c-Myc by Runx1 in the human T cell line Jurkat and murine primary hematopoietic cells. Endogenous Runx1 binds to multiple sites in the c-Myc locus upstream of the c-Myc transcriptional start site. Cells transduced with a C-terminally truncated Runx1 (Runx1.d190), which lacks important cofactor interaction sites and can block C-terminal-dependent functions of all Runx transcription factors, showed increased transcription of c-Myc. In order to monitor c-Myc expression in response to early and transiently-acting Runx1.d190, we generated a cell membrane-permeable TAT-Runx1.d190 fusion protein. Murine splenocytes treated with TAT-Runx1.d190 showed an increase in the transcription of c-Myc within 2 hours, peaking at 4 hours post-treatment and declining thereafter. This effect is dependent on the ability of Runx1.d190 to bind to DNA. The increase in c-Myc transcripts is correlated with increased c-Myc protein levels. Collectively, these data show that Runx1 directly regulates c-Myc transcription in a C-terminal- and DNA-binding-dependent manner.

Janghorban, M., A. S. Farrell, et al. "Targeting c-MYC by antagonizing PP2A inhibitors in breast cancer." Proc Natl Acad Sci U S A. 2014 Jun 24;111(25):9157-62. doi: 10.1073/pnas.1317630111. Epub 2014 Jun 9.

The transcription factor c-MYC is stabilized and activated by phosphorylation at serine 62 (S62) in breast cancer. Protein phosphatase 2A (PP2A) is a critical negative regulator of c-MYC through its ability to dephosphorylate S62. By inactivating c-MYC and other key signaling pathways, PP2A plays an important tumor suppressor function. Two endogenous inhibitors of PP2A, I2PP2A, Inhibitor-2 of PP2A (SET oncoprotein) and cancerous inhibitor of PP2A (CIP2A), inactivate PP2A and are overexpressed in several tumor types. Here we show that SET is overexpressed in about 50-60% and CIP2A in about 90% of breast cancers. Knockdown of SET or CIP2A reduces the tumorigenic potential of breast cancer cell lines both in vitro and in vivo. Treatment of breast cancer cells in vitro or in vivo with OP449, a novel SET antagonist, also decreases the tumorigenic potential of breast cancer cells and induces apoptosis. We show that this is, at least in part, due to decreased S62 phosphorylation of c-MYC and reduced c-MYC activity and target gene expression. Because of the ubiquitous expression and tumor suppressor activity of PP2A in cells, as well as the critical role of c-MYC in human cancer, we propose that activation of PP2A (here accomplished through antagonizing endogenous inhibitors) could be a novel antitumor strategy to posttranslationally target c-MYC in breast cancer.

Jeong, K. C., K. T. Kim, et al. "Intravesical instillation of c-MYC inhibitor KSI-3716 suppresses orthotopic bladder tumor growth." J Urol. 2014 Feb;191(2):510-8. doi: 10.1016/j.juro.2013.07.019. Epub 2013 Jul 17.

PURPOSE: c-MYC is a promising target for cancer therapy but its use is restricted by unwanted, devastating side effects. We explored whether intravesical instillation of the c-MYC

inhibitor KSI-3716 could suppress tumor growth in murine orthotopic bladder xenografts. MATERIALS AND METHODS: The small molecule KSI-3716, which blocks c-MYC/MAX binding to target gene promoters, was used as an intravesical chemotherapy agent. KSI-3716 action was assessed by electrophoretic mobility shift assay, chromatin immunoprecipitation, transcription reporter assay and quantitative reverse transcriptase-polymerase chain reaction. Inhibition of cell proliferation and its mechanism was monitored by cell cytotoxicity assay, EdU incorporation assay and flow cytometry. The in vivo efficacy of KSI-3716 was examined by noninvasive luminescence imaging and histological analysis after intravesical instillation of KSI-3716 in murine orthotopic bladder xenografts. RESULTS: KSI-3716 blocked c-MYC/MAX from forming a complex with target gene promoters. c-MYC mediated transcriptional activity was inhibited by KSI-3716 at concentrations as low as 1 muM. The expression of c-MYC target genes, such as cyclin D2, CDK4 and hTERT, was markedly decreased. KSI-3716 exerted cytotoxic effects on bladder cancer cells by inducing cell cycle arrest and apoptosis. Intravesical instillation of KSI-3716 at a dose of 5 mg/kg significantly suppressed tumor growth with minimal systemic toxicity. CONCLUSIONS: The c-MYC inhibitor KSI-3716 could be developed as an effective intravesical chemotherapy agent for bladder cancer.

Kim, J., H. Ahn, et al. "Generation of liver-specific TGF-alpha and c-Myc-overexpressing fibroblasts for future creation of a liver cancer porcine model." Mol Med Rep. 2014 Jul;10(1):329-35. doi: 10.3892/mmr.2014.2217. Epub 2014 May 7.

Liver cancer is one of the most serious life-threatening diseases in the world. Although the rodent model of hepatocellar carcinoma (HCC) is commonly used, it is limited when considering preclinical applications, including transarterial chemoembolization. The pig is a more appropriate model for applying preclinical procedures as it has similar anatomical and physiological characteristics to humans. In the current study, transgenic fibroblasts were generated that overexpressed two proto-oncogenes specifically in hepatocytes. Porcine TGF-alpha and c-myc genes were isolated and these were linked with the porcine albumin promoter, which has exhibited selective activity in liver cells. Targeting vectors were introduced into the porcine fibroblasts using a liposome-mediated delivery system and the transgenic cell line was screened with 3 weeks of G-418 treatment. Selected vectorpositive colonies were further confirmed with polymerase chain reaction-based genotyping. Thus, the transgenic cell lines created in the current study should induce liver cancer in pig models following somatic cell nuclear transfer.

Koehler, A., J. Schlupf, et al. "Loss of Xenopus cadherin-11 leads to increased Wnt/beta-catenin signaling and up-regulation of target genes c-myc and cyclin D1 in neural crest." Dev Biol. 2013 Nov 1;383(1):132-45. doi: 10.1016/j.ydbio.2013.08.007. Epub 2013 Aug 17.

Xenopus cadherin-11 (Xcadherin-11) is an exceptional cadherin family member, which is predominantly expressed in cranial neural crest cells (NCCs). Apart from mediating cell-cell adhesion it promotes cranial NCC migration by initiating filopodia and lamellipodia formation. Here, we demonstrate an unexpected function of Xcadherin-11 in NCC specification by interfering with canonical Wnt/beta-catenin signaling. Loss-of-function experiments, using a specific antisense morpholino oligonucleotide against Xcadherin-11, display a nuclear beta-catenin localization in cranial NCCs and a broader expression domain of the proto-oncogene cyclin D1 which proceeds c-myc up-regulation. Additionally, we observe an enhanced NCC proliferation and an expansion of specific NCC genes like AP2 and Sox10. Thereby, we could allocate NCC proliferation and specification to different gene functions. To clarify which domain in Xcadherin-11 is required for early NCC development we tested different deletion mutants for their rescue ability in Xcadherin-11 morphants. We identified the cytoplasmic tail, specifically the beta-catenin binding domain, to be necessary for proper NCC development. We propose that Xcadherin-11 is necessary for controlled NCC proliferation and early NCC specification in tuning the expression of the canonical Wnt/beta-catenin target genes cyclin D1 and c-myc by regulating the concentration of the nuclear pool of beta-catenin.

Kong, L. M., C. G. Liao, et al. "A regulatory loop involving miR-22, Sp1, and c-Myc modulates CD147 expression in breast cancer invasion and metastasis." Cancer Res. 2014 Jul 15;74(14):3764-78. doi: 10.1158/0008-5472.CAN-13-3555. Epub 2014 Jun 6.

Breast cancer is the most common cancer in women for which the metastatic process is still poorly understood. CD147 is upregulated in breast cancer and has been associated with tumor progression, but little is known about its regulatory mechanisms. In this study, we demonstrated that CD147 was overexpressed in breast cancer tissues and cell lines, and the high expression correlated with tumor invasion and metastasis. We also found that the transcription factors Sp1 and c-Myc could bind to the CD147 promoter and enhance its expression. The CD147 mRNA has a 748-bp 3'-untranslated region (UTR) with many miRNA target sites, suggesting possible regulation by miRNAs. We discovered that miR-22 repressed CD147 expression by directly targeting the CD147 3'UTR. We also determined that miR-22 could indirectly participate in CD147 modulation by downregulating Sp1 expression. miR-22 could form an autoregulatory loop with Sp1, which repressed miR-22 transcription by binding to the miR-22 promoter. Together with the c-Myc-mediated inhibition of miR-22 expression, our investigation identified a miR-22/Sp1/c-Myc network that regulates CD147 gene transcription. In addition, miR-22 overexpression suppressed breast cancer cell invasion, metastasis, and proliferation by targeting CD147 in vitro and in vivo. Furthermore, we found that miR-22 was significantly downregulated in breast cancer tissues and that its expression was inversely correlated with the tumor-node-metastasis stage and lymphatic metastasis in patients. Our study provides the first evidence that an miR-22/Sp1/c-Myc network regulates CD147 upregulation in breast cancer and that miR-22 represses breast cancer invasive and metastatic capacities.

Krysan, K., R. Kusko, et al. "PGE2-driven expression of c-Myc and oncomiR-17-92 contributes to apoptosis resistance in NSCLC." Mol Cancer Res. 2014 May;12(5):765-74. doi: 10.1158/1541-7786.MCR-13-0377. Epub 2014 Jan 27.

Aberrant expression of microRNAs (miRNA) with oncogenic capacities (oncomiRs) has been described for several different malignancies. The first identified oncomiR, miR-17-92, is frequently overexpressed in a variety of cancers and its targets include the tumor suppressor PTEN. The transcription factor c-Myc (MYC) plays a central role in proliferative control and is rapidly upregulated upon mitogenic stimulation. Expression of c-Myc is frequently deregulated in tumors, facilitating proliferation and inhibiting terminal differentiation. The c-Myc-regulated network comprises a large number of transcripts, including those encoding miRNAs. Here, prostaglandin E2 (PGE2) exposure rapidly upregulates the expression of the MYC gene followed by the elevation of miR-17-92 levels, which in turn suppresses PTEN expression, thus enhancing apoptosis resistance in non-small cell lung cancer (NSCLC) cells. Knockdown of MYC expression or the miR-17-92 cluster effectively reverses this outcome. Similarly, miR-17-92 levels are significantly elevated in NSCLC cells ectopically expressing COX-2. Importantly, circulating miR-17-92 was elevated in the blood of patients with lung cancer as compared with subjects at risk for developing lung cancer. Furthermore, in patients treated with celecoxib, miR-17-92 levels were significantly reduced. These data demonstrate that PGE2, abundantly produced by NSCLC and inflammatory cells in the tumor microenvironment, is able to stimulate cell proliferation and promote resistance to pharmacologically induced apoptosis in a c-Myc and miR-17-92-dependent manner. IMPLICATIONS: This study describes a novel mechanism, involving c-Myc and miR-17-92, which integrates cell

proliferation and apoptosis resistance.

Kuzyk, A. and S. Mai "c-MYC-induced genomic instability." Cold Spring Harb Perspect Med. 2014 Apr 1;4(4):a014373. doi: 10.1101/cshperspect.a014373.

MYC dysregulation initiates a dynamic process of genomic instability that is linked to tumor initiation. Early studies using MYC-carrying retroviruses showed that these viruses were potent transforming agents. Cell culture models followed that addressed the role of MYC in transformation. With the advent of MYC transgenic mice, it became obvious that MYC deregulation alone was sufficient to initiate B-cell neoplasia in mice. More than 70% of all tumors have some form of c-MYC gene dysregulation, which affects gene regulation, microRNA expression profiles, large genomic amplifications, and the overall organization of the nucleus. These changes set the stage for the dynamic genomic rearrangements that are associated with cellular transformation.

Lee, K. B., S. Ye, et al. "p63-Mediated activation of the beta-catenin/c-Myc signaling pathway stimulates esophageal squamous carcinoma cell invasion and metastasis." Cancer Lett. 2014 Oct 10;353(1):124-32. doi: 10.1016/j.canlet.2014.07.016. Epub 2014 Jul 18.

The development of esophageal squamous carcinomas (ESC) results from numerous genetic alterations. Our previous study demonstrated that p63 is highly expressed in human ESC cells and stimulates their growth; however, the mechanism by which p63 regulates ESC cell adhesion and invasion remains unclear. In the present study, we further elucidated the underlying molecular mechanisms by which p63 regulates metastasis in ESC cells. Knockdown of p63 significantly diminished the invasion of ESC cell lines TE-8 and TE-12, whereas overexpression of p63 significantly increased the migration rates of BE3 and OE33 cells. The mRNA and protein levels of vimentin, twist, SUSD2, and uPA were significantly decreased in p63-knockdown ESC cells, while overexpression of p63 induced an increase in vimentin, SUSD2, and uPA. In addition, knockdown of p63 in ESC cells significantly reduced levels of beta-catenin and c-Myc, while overexpression of p63 increased beta-catenin, but reduced p-beta-catenin level. Therefore, p63 regulates the migration and invasion of ESC cells through activation of the beta-catenin/c-Myc pathway. Our results suggest that targeting p63 may constitute a potential therapeutic strategy for ESC.

Leu, W. J., H. S. Chang, et al. "Reevesioside A, a cardenolide glycoside, induces anticancer activity against human hormone-refractory prostate cancers through suppression of c-myc expression and induction of G1 arrest of the cell cycle." PLoS One. 2014 Jan 27;9(1):e87323. doi: 10.1371/journal.pone.0087323. eCollection 2014.

In the past decade, there has been a profound increase in the number of studies revealing that cardenolide glycosides display inhibitory activity on the growth of human cancer cells. The use of potential cardenolide glycosides may be a worthwhile approach in anticancer research. Reevesioside A, a cardenolide glycoside isolated from the root of Reevesia formosana, displayed potent anti-proliferative activity against human hormone-refractory prostate cancers. A good correlation (r(2) = 0.98) between the expression of Na(+)/K(+)-ATPase alpha(3) subunit and anti-proliferative activity suggested the critical role of the alpha(3) subunit. Reevesioside A induced G1 arrest of the cell cycle and subsequent apoptosis in a thymidine block-mediated synchronization model. The data were supported by the down-regulation of several related cell cycle regulators, including cyclin D1, cyclin E and CDC25A. Reevesioside A also caused a profound decrease of RB phosphorylation, leading to an increased association between RB and E2F1 and the subsequent suppression of E2F1 activity. The protein and mRNA levels of c-myc, which can activate expression of many downstream cell cycle regulators, were dramatically inhibited by reevesioside A. Transient transfection of c-myc inhibited the down-regulation of both cyclin D1 and cyclin E protein expression to reevesioside A action, suggesting that c-myc functioned as an upstream regulator. Flow cytometric analysis of JC-1 staining demonstrated that reevesioside A also induced the significant loss of mitochondrial membrane potential. In summary, the data suggest that reevesioside A inhibits c-myc expression and down-regulates the expression of CDC25A, cyclin D1 and cyclin E, leading to a profound decrease of RB phosphorylation. G1 arrest is, therefore, induced through E2F1 suppression. Consequently, reevesioside A causes mitochondrial damage and an ultimate apoptosis in human hormone-refractory prostate cancer cells.

Li, Z., L. Dong, et al. "Acidosis decreases c-Myc oncogene expression in human lymphoma cells: a role for the proton-sensing G protein-coupled receptor TDAG8." Int J Mol Sci. 2013 Oct 11;14(10):20236-55. doi: 10.3390/ijms141020236.

Acidosis is a biochemical hallmark of the tumor microenvironment. Here, we report that acute acidosis decreases c-Myc oncogene expression in U937 human lymphoma cells. The level of c-Myc transcripts, but not mRNA or protein stability, contributes to c-Myc protein reduction under acidosis. The pH-sensing receptor TDAG8 (GPR65) is involved in acidosis-induced c-Myc downregulation. TDAG8 is expressed in U937 lymphoma cells, and the overexpression or knockdown of TDAG8 further decreases or partially rescues c-Myc expression, respectively. Acidic pH alone is insufficient to reduce c-Myc expression, as it does not decrease c-Myc in H1299 lung cancer cells expressing very low levels of pH-sensing G protein-coupled receptors (GPCRs). Instead, c-Myc is slightly increased by acidosis in H1299 cells, but this increase is completely inhibited by ectopic overexpression of TDAG8. Interestingly, TDAG8 expression is decreased by more than 50% in human lymphoma samples in comparison to non-tumorous lymph nodes and spleens, suggesting a potential tumor suppressor function of TDAG8 in lymphoma. Collectively, our results identify a novel mechanism of c-Myc regulation by acidosis in the tumor microenvironment and indicate that modulation of TDAG8 and related pH-sensing receptor pathways may be exploited as a new approach to inhibit Myc expression.

Liao, P., W. Wang, et al. "A positive feedback loop between EBP2 and c-Myc regulates rDNA transcription, cell proliferation, and tumorigenesis." Cell Death Dis. 2014 Jan 30;5:e1032. doi: 10.1038/cddis.2013.536.

The oncoprotein c-Myc is a key transcription factor with essential functions in the nucleolus (NO) to regulate ribosomal RNA (rRNA) synthesis, ribosome biogenesis, and cell proliferation. Yet, the mechanism that regulates the distribution and function of nucleolar c-Myc is still not completely understood. In this study, we identified nucleolar protein ENBA1 binding protein 2 (EBP2) as a novel functional binding partner of c-Myc. We found that coexpression of EBP2 markedly relocalized c-Myc from the nucleus to the NO, whereas depletion of EBP2 reduced the nucleolar distribution of c-Myc. Further study indicated that EBP2 is a direct binding partner of c-Myc and can block the degradation of c-Myc in a FBW7 (F-box and WD repeat domain containing 7)-independent manner. Moreover, EBP2 is a transcriptional target of c-Myc. c-Myc can bind to the promoter of EBP2 and positively regulate the EBP2 expression. Both protein and mRNA levels of EBP2 are upregulated in lung cancer samples and positively correlated with c-Myc expression. Functionally, EBP2 promotes c-Myc-mediated rRNA synthesis and cell proliferation. Collectively, our study indicates that EBP2 is a novel binding partner of c-Myc that regulates the function of nucleolar c-Myc, cell proliferation, and tumorigenesis via a positive feedback loop.

Liu, Z., G. Zhang, et al. "The tumor-suppressive microRNA-135b targets c-myc in osteoscarcoma." PLoS One. 2014 Jul 15;9(7):e102621. doi: 10.1371/journal.pone.0102621. eCollection 2014.

Osteosarcoma is the most common primary tumor of the

bone. It leads to many deaths because of its rapid proliferation and metastasis. Recent studies have shown that microRNAs are important gene regulators that are involved in various cancer-related processes. In this study, we found that miR-135b was down-regulated in both osteoscarcoma patient tumor tissues and osteoscarcoma cell lines in comparison to paired adjacent non-tumor bone tissue. We observed that a lower level of miR-135b was associated with metastasis. The ectopic expression of miR-135b markedly suppressed osteoscarcoma cell proliferation, migration, and invasion. Conversely, the inhibition of miR-135b expression dramatically accelerated cell proliferation, migration, and invasion. The forced expression of miR-135b in osteosarcoma cells resulted in a significant reduction in the protein level of c-Myc and repressed the activity of a luciferase reporter that contained the 3'-untranslated region of the c-Myc mRNA. These effects were abolished by the mutation of the predicted miR-135b-binding site, which indicates that c-Myc may be a miR-135b target gene. Moreover, the ectopic expression of c-Myc partially reversed the inhibition of cell proliferation and invasion that was caused by miR-135b. These data therefore suggest that miR-135b may function as a tumor suppressor to regulate osteosarcoma cell proliferation and invasion through a mechanism that targets the c-Myc oncogene. These findings indicate that miR-135b may play a role in the pathogenesis of osteosarcoma.

Llorente-Izquierdo, C., R. Mayoral, et al. "Progression of liver oncogenesis in the double transgenic mice c-myc/TGF alpha is not enhanced by cyclooxygenase-2 expression." Prostaglandins Other Lipid Mediat. 2013 Oct;106:106-15. doi: 10.1016/j.prostaglandins.2013.03.006. Epub 2013 Apr 8.

Cyclooxygenase-2 (COX-2) has been associated with cell growth regulation, tissue remodeling and carcinogenesis. Overexpression of COX-2 in hepatocytes constitutes an ideal condition to evaluate the role of prostaglandins (PGs) in liver pathogenesis. The effect of COX-2-dependent PGs in genetic hepatocarcinogenesis has been investigated in triple c-myc/transforming growth factor alpha (TGF-alpha) transgenic mice that express human COX-2 in hepatocytes on a B6CBAxCD1xB6DBA2 background. Analysis of the contribution of COX-2-dependent PGs to the development of hepatocarcinogenesis, evaluated in this model, suggested a minor role of COX-2-dependent prostaglandins to liver oncogenesis as indicated by liver histopathology, morphometric analysis and specific markers of tumor progression. This allows concluding that COX-2 is insufficient for modifying the hepatocarcinogenesis course mediated by c-myc/TGF-alpha.

Loosveld, M., R. Castellano, et al. "Therapeutic targeting of c-Myc in T-cell acute lymphoblastic leukemia, T-ALL." Oncotarget. 2014 May 30;5(10):3168-72.

T-ALL patients treated with intensive chemotherapy achieve high rates of remission. However, frequent long-term toxicities and relapses into chemotherapy-refractory tumors constitute major clinical challenges which could be met by targeted therapies. c-MYC is a central oncogene in T-ALL, prompting the exploration of the efficacy of MYC inhibitors such as JQ1 (BET-bromodomain inhibitor), and SAHA (HDAC inhibitor). Using a standardized ex vivo drug screening assay, we show here that JQ1 and SAHA show competitive efficiency compared to inhibitors of proteasome, PI3K/AKT/mTOR and NOTCH pathways, and synergize in combination with Vincristine. We also compared for the first time the in vivo relevance of such associations in mice xenografted with human primary T-ALLs. Our data indicate that although treatments combining JQ1 or SAHA with chemotherapeutic regimens might represent promising developments in T-ALL, combinations will need to be tailored to specific subgroups of responsive patients, the profiles of which still remain to be precisely defined.

Lwin, T., X. Zhao, et al. "A microenvironment-mediated c-Myc/miR-548m/HDAC6 amplification loop in non-Hodgkin B cell lymphomas." J Clin Invest. 2013 Nov 1;123(11):4612-26.

A dynamic interaction occurs between the lymphoma cell and its microenvironment, with each profoundly influencing the behavior of the other. Here, using a clonogenic coculture growth system and a xenograft mouse model, we demonstrated that adhesion of mantle cell lymphoma (MCL) and other non-Hodgkin lymphoma cells to lymphoma stromal cells confers drug resistance, clonogenicity, and induction of histone deacetylase 6 (HDAC6). Furthermore, stroma triggered a c-Myc/miR-548m feed-forward loop, linking sustained c-Myc activation, miR-548m downregulation, and subsequent HDAC6 upregulation and stroma-mediated cell survival and lymphoma progression in lymphoma cell lines, primary MCL and other B cell lymphoma cell lines. Treatment with an HDAC6-selective inhibitor alone or in synergy with a c-Myc inhibitor enhanced cell death, abolished cell adhesion-mediated drug resistance, and suppressed clonogenicity and lymphoma growth ex vivo and in vivo. Together, these data suggest that the lymphoma-stroma interaction in the lymphoma microenvironment directly impacts the biology of lymphoma through genetic and epigenetic regulation, with HDAC6 and c-Myc as potential therapeutic targets.

Ma, M. Z., C. X. Li, et al. "Long non-coding RNA HOTAIR, a c-Myc activated driver of malignancy, negatively regulates miRNA-130a in gallbladder cancer." Mol Cancer. 2014 Jun 23;13:156. doi: 10.1186/1476-4598-13-156.

BACKGROUND: Protein coding genes account for only about 2% of the human genome, whereas the vast majority of transcripts are non-coding RNAs including long non-coding RNAs. A growing volume of literature has proposed that lncRNAs are important players in cancer. HOTAIR was previously shown to be an oncogene and negative prognostic factor in a variety of cancers. However, the factors that contribute to its upregulation and the interaction between HOTAIR and miRNAs are largely unknown. METHODS: A computational screen of HOTAIR promoter was conducted to search for transcription-factor-binding sites. HOTAIR promoter activities were examined by luciferase reporter assay. The function of the c-Myc binding site in the HOTAIR promoter region was tested by a promoter assay with nucleotide substitutions in the putative E-box. The association of c-Myc with the HOTAIR promoter in vivo was confirmed by chromatin immunoprecipitation assay and Electrophoretic mobility shift assay. A search for miRNAs with complementary base paring with HOTAIR was performed utilizing online software program. Gain and loss of function approaches were employed to investigate the expression changes of HOTAIR or miRNA-130a. The expression levels of HOTAIR, c-Myc and miRNA-130a were examined in 65 matched pairs of gallbladder cancer tissues. The effects of HOTAIR and miRNA-130a on gallbladder cancer cell invasion and proliferation was tested using in vitro cell invasion and flow cytometric assays. RESULTS: We demonstrate that HOTAIR is a direct target of c-Myc through interaction with putative c-Myc target response element (RE) in the upstream region of HOTAIR in gallbladder cancer cells. A positive correlation between c-Myc and HOTAIR mRNA levels was observed in gallbladder cancer tissues. We predicted that HOTAIR harbors a miRNA-130a binding site. Our data showed that this binding site is vital for the regulation of miRNA-130a by HOTAIR. Moreover, a negative correlation between HOTAIR and miRNA-130a was observed in gallbladder cancer tissues. Finally, we demonstrate that the oncogenic activity of HOTAIR is in part through its negative regulation of miRNA-130a. CONCLUSION: Together, these results suggest that HOTAIR is a c-Myc-activated driver of malignancy, which acts in part through repression of miRNA-130a.

Ma, T., J. L. Jiang, et al. "Preparation and evaluation of nanoparticles loading plasmid DNAs inserted with siRNA fragments targeting c-Myc gene." Pharm Biol. 2014 Sep;52(9):1179-88. doi: 10.3109/13880209.2014.880489. Epub 2014 Mar 19.

Abstract Context: c-Myc plays a key role in glioma cancer stem cell maintenance. A drug delivery system, nanoparticles loading plasmid DNAs inserted with siRNA fragments targeting c-Myc gene (NPs-c-Myc-siRNA-pDNAs), for the treatment of glioma, has not previously been reported. OBJECTIVE: NPs-c-Myc-siRNA-pDNAs were prepared and evaluated in vitro. MATERIALS AND METHODS: Three kinds of c-Myc-siRNA fragments were separately synthesized and linked with empty siRNA expression vectors in the mole ratio of 3:1 by T4 DNA ligase. The linked products were then separately transfected into Escherichia coli. DH5alpha followed by extraction with Endofree plasmid Mega kit (Qiagen, Hilden, Germany) obtained c-Myc-siRNA-pDNAs. Finally, the recombinant c-Myc-siRNA3-pDNAs, generating the highest transfection efficiency and the greatest apoptotic ability, were chosen for encapsulation into NPs by the double-emulsion solvent-evaporation procedure, followed by stability, transfection efficiency, as well as qualitative and quantitative apoptosis evaluation. RESULTS: NPs-c-Myc-siRNA3-pDNAs were obtained with spherical shape in uniform size below 150 nm, with the zeta potential about -18 mV, the encapsulation efficiency and loading capacity as 76.3 +/- 5.4% and 1.91 +/- 0.06%, respectively. The stability results showed that c-Myc-siRNA3-pDNAs remained structurally and functionally stable after encapsulated into NPs, and NPs could prevent the loaded c-Myc-siRNA3-pDNAs from DNase degradation. The transfection efficiency of NPs-c-Myc-siRNA3-pDNAs was proven to be positive. Furthermore, NPs-c-Myc-siRNA3-pDNAs produced significant apoptosis with the apoptotic rate at 24.77 +/- 5.39% and early apoptosis cells observed. DISCUSSION AND CONCLUSION: Methoxy-poly-(ethylene-glycol)-poly-(lactide-co-glycolide) nanoparticles (MPEG-PLGA-NPs) are potential delivery carriers for c-Myc-siRNA3-pDNAs.

Magri, L., M. Gacias, et al. "c-Myc-dependent transcriptional regulation of cell cycle and nucleosomal histones during oligodendrocyte differentiation." Neuroscience. 2014 Sep 12;276:72-86. doi: 10.1016/j.neuroscience.2014.01.051. Epub 2014 Feb 4.

Oligodendrocyte progenitor cells (OPCs) have the ability to divide or to growth arrest and differentiate into myelinating oligodendrocytes in the developing brain. Due to their high number and the persistence of their proliferative capacity in the adult brain, OPCs are being studied as potential targets for myelin repair and also as a potential source of brain tumors. This study addresses the molecular mechanisms regulating the transcriptional changes occurring at the critical transition between proliferation and cell cycle exit in cultured OPCs. Using bioinformatic analysis of existing datasets, we identified c-Myc as a key transcriptional regulator of this transition and confirmed direct binding of this transcription factor to identified target genes using chromatin immunoprecipitation. The expression of c-Myc was elevated in proliferating OPCs, where it also bound to the promoter of genes involved in cell cycle regulation (i.e. Cdc2) or chromosome organization (i.e. H2afz). Silencing of c-Myc was associated with decreased histone acetylation at target gene promoters and consequent decrease of gene transcripts. c-Myc silencing also induced a global increase of repressive histone methylation and premature peripheral nuclear chromatin compaction while promoting the progression towards differentiation. We conclude that c-Myc is an important modulator of the transition between proliferation and differentiation of OPCs, although its decrease is not sufficient to induce progression into a myelinating phenotype.

Maj, J., A. Jankowska-Konsur, et al. "Altered expression of Bcl-2, c-Myc, H-Ras, K-Ras, and N-Ras does not influence the course of mycosis fungoides." Arch Med Sci. 2013 Oct 31;9(5):895-8. doi: 10.5114/aoms.2013.38684. Epub 2013 Nov 5.

INTRODUCTION: Data about genetic alterations in mycosis fungoides (MF) are limited and their significance not fully elucidated. The aim of the study was to explore the expression of various oncogenes in MF and to assess their influence on the disease course. MATERIAL AND METHODS: Skin biopsies from 27 MF patients (14 with early MF and 13 with advanced disease) and 8 healthy volunteers were analyzed by real-time polymerase chain reaction (PCR) to detect Bcl-2, c-Myc, H-Ras, K-Ras and N-Ras expression. All PCR reactions were performed using an Applied Biosystems 7900HT Fast Real-Time PCR System and interpreted using Sequence Detection Systems software which utilizes the comparative delta Ct method. The level of mRNA was normalized to GAPDH expression. All data were analyzed statistically. RESULTS: All evaluated oncogenes were found to be expressed in the skin from healthy controls and MF patients. Bcl-2 (-4.2 +/-2.2 vs. -2.2 +/-1.1; $p = 0.01$), H-Ras (-3.0 +/-3.3 vs. 0.6 +/-2.6; $p = 0.01$) and N-Ras (-3.6 +/-2.0 vs. -1.1 +/-2.4; $p = 0.03$) were expressed at significantly lower levels in MF. No relationships between oncogene expression and disease stage, presence of distant metastases and survival were observed ($p > 0.05$ for all comparisons). CONCLUSIONS: The pathogenic role and prognostic significance of analyzed oncogenes in MF seem to be limited and further studies are needed to establish better prognostic factors for patients suffering from MF.

Martino, T., F. C. Magalhaes, et al. "The pterocarpanquinone LQB-118 inhibits tumor cell proliferation by downregulation of c-Myc and cyclins D1 and B1 mRNA and upregulation of p21 cell cycle inhibitor expression." Bioorg Med Chem. 2014 Jun 15;22(12):3115-22. doi: 10.1016/j.bmc.2014.04.025. Epub 2014 Apr 20.

The incidence of cancer grows annually worldwide and in Brazil it is the second cause of death. The search for anti-cancer drugs has then become urgent. It depends on the studies of natural and chemical synthesis products. The antitumor action of LQB-118, a pterocarpanquinone structurally related to lapachol, has been demonstrated to induce mechanisms linked to leukemia cell apoptosis. This work investigated some mechanisms of the in vitro antitumor action of LQB-118 on prostate cancer cells. LQB-118 reduced the expression of the c-Myc transcription factor, downregulated the cyclin D1 and cyclin B1 mRNA levels and upregulated the p21 cell cycle inhibitor. These effects resulted in cell cycle arrest in the S and G2/M phases and inhibition of tumor cell proliferation. LQB-118 also induced programmed cell death of the prostate cancer cells, as evidenced by internucleosomal DNA fragmentation and annexin-V positive cells. Except the cell cycle arrest in the S phase and enhanced c-Myc expression, all the mechanisms observed here for the in vitro antitumor action of LQB-118 were also found for Paclitaxel, a traditional antineoplastic drug. These findings suggest new molecular mechanisms for the LQB-118 in vitro antitumor action.

Masui, K., K. Tanaka, et al. "mTOR complex 2 controls glycolytic metabolism in glioblastoma through FoxO acetylation and upregulation of c-Myc." Cell Metab. 2013 Nov 5;18(5):726-39. doi: 10.1016/j.cmet.2013.09.013. Epub 2013 Oct 17.

Aerobic glycolysis (the Warburg effect) is a core hallmark of cancer, but the molecular mechanisms underlying it remain unclear. Here, we identify an unexpected central role for mTORC2 in cancer metabolic reprogramming where it controls glycolytic metabolism by ultimately regulating the cellular level of c-Myc. We show that mTORC2 promotes inactivating phosphorylation of class IIa histone deacetylases, which leads to the acetylation of FoxO1 and FoxO3, and this in turn releases c-Myc from a suppressive miR-34c-dependent network. These central features of activated mTORC2 signaling, acetylated FoxO, and c-Myc levels are highly intercorrelated in clinical samples and with shorter survival of GBM patients. These results identify a specific, Akt-independent role for mTORC2 in regulating glycolytic metabolism in cancer.

Matsushita, K., H. Shimada, et al. "Non-transmissible Sendai virus vector encoding c-myc suppressor FBP-interacting repressor for cancer therapy." World J Gastroenterol. 2014 Apr 21;20(15):4316-

28. doi: 10.3748/wjg.v20.i15.4316.

AIM: To investigate a novel therapeutic strategy to target and suppress c-myc in human cancers using far up stream element (FUSE)-binding protein-interacting repressor (FIR). METHODS: Endogenous c-Myc suppression and apoptosis induction by a transient FIR-expressing vector was examined in vivo via a HA-tagged FIR (HA-FIR) expression vector. A fusion gene-deficient, non-transmissible, Sendai virus (SeV) vector encoding FIR cDNA, SeV/dF/FIR, was prepared. SeV/dF/FIR was examined for its gene transduction efficiency, viral dose dependency of antitumor effect and apoptosis induction in HeLa (cervical squamous cell carcinoma) cells and SW480 (colon adenocarcinoma) cells. Antitumor efficacy in a mouse xenograft model was also examined. The molecular mechanism of the anti-tumor effect and c-Myc suppression by SeV/dF/FIR was examined using Spliceostatin A (SSA), a SAP155 inhibitor, or SAP155 siRNA which induce c-Myc by increasing FIRexon2 in HeLa cells. RESULTS: FIR was found to repress c-myc transcription and in turn the overexpression of FIR drove apoptosis through c-myc suppression. Thus, FIR expressing vectors are potentially applicable for cancer therapy. FIR is alternatively spliced by SAP155 in cancer cells lacking the transcriptional repression domain within exon 2 (FIRexon2), counteracting FIR for c-Myc protein expression. Furthermore, FIR forms a complex with SAP155 and inhibits mutual well-established functions. Thus, both the valuable effects and side effects of exogenous FIR stimuli should be tested for future clinical application. SeV/dF/FIR, a cytoplasmic RNA virus, was successfully prepared and showed highly efficient gene transduction in in vivo experiments. Furthermore, in nude mouse tumor xenograft models, SeV/dF/FIR displayed high antitumor efficiency against human cancer cells. SeV/dF/FIR suppressed SSA-activated c-Myc. SAP155 siRNA, potentially produces FIRexon2, and led to c-Myc overexpression with phosphorylation at Ser62. HA-FIR suppressed endogenous c-Myc expression and induced apoptosis in HeLa and SW480 cells. A c-myc transcriptional suppressor FIR expressing SeV/dF/FIR showed high gene transduction efficiency with significant antitumor effects and apoptosis induction in HeLa and SW480 cells. CONCLUSION: SeV/dF/FIR showed strong tumor growth suppression with no significant side effects in an animal xenograft model, thus SeV/dF/FIR is potentially applicable for future clinical cancer treatment.

Menssen, A. "[c-MYC-mediated regulations in colorectal cancer]." Pathologe. 2013 Nov;34 Suppl 2:274-6. doi: 10.1007/s00292-013-1819-5.

In the majority of human tumors the oncogenic transcription factor c-MYC is deregulated and contributes to the formation of many biologically important tumor properties. These include the induction of cell cycle progression, transformation, genomic instability and immortalization. So far it was unclear which target genes of c-MYC mediate the effects. Using genome-wide approaches we identified a large number of c-MYC target genes. Subsequently, we characterized some target genes for their role in c-MYC-induced genomic instability and immortalization. The protein deacetylase SIRT1 was found to be an important mediator of c-MYC-induced immortalization. Using in situ analyses of colorectal cancer specimens we demonstrated that c-MYC is a regulator of the identified target genes in human tumors thus implicating their relevance for tumorigenesis in humans.

Mostocotto, C., M. Carbone, et al. "Poly(ADP-ribosyl)ation is required to modulate chromatin changes at c-MYC promoter during emergence from quiescence." PLoS One. 2014 Jul 21;9(7):e102575. doi: 10.1371/journal.pone.0102575. eCollection 2014.

Poly(ADP-ribosyl)ation is a post-translational modification of various proteins and participates in the regulation of chromatin structure and transcription through complex mechanisms not completely understood. We have previously shown that PARP-1, the major family member of poly(ADP-ribose)polymerases, plays an important role in the cell cycle reactivation of resting cells by regulating the expression of Immediate Early Response Genes, such as c-MYC, c-FOS, JUNB and EGR-1. In the present work we have investigated the molecular mechanisms by which the enzyme induces c-MYC transcription upon serum stimulation of quiescent cells. We show that PARP-1 is constitutively associated in vivo to a c-MYC promoter region recognized as biologically relevant for the transcriptional regulation of the gene. Moreover, we report that serum stimulation causes the prompt accumulation of ADP-ribose polymers on the same region and that this modification is required for chromatin decondensation and for the exchange of negative for positive transcriptional regulators. Finally we provide evidence that the inhibition of PARP activity along with serum stimulation impairs c-MYC induction by preventing the proper accumulation of histone H3 phosphoacetylation, a specific chromatin mark for the activation of Immediate Early Response Genes. These findings not only suggest a novel strategy by which PARP-1 regulates the transcriptional activity of promoters but also provide new information about the complex regulation of c-MYC expression, a critical determinant of the transition from quiescence to proliferation.

Mu, Q., Q. Ma, et al. "10058-F4, a c-Myc inhibitor, markedly increases valproic acid-induced cell death in Jurkat and CCRF-CEM T-lymphoblastic leukemia cells." Oncol Lett. 2014 Sep;8(3):1355-1359. Epub 2014 Jun 24.

Adult T-cell acute lymphoblastic leukemia (T-ALL) has a poor prognosis. Although it has been found that activation of Notch1 signaling occurs in >50% T-ALL patients, gamma-secretase inhibitors that target Notch1 signaling are of limited efficacy. However, c-Myc is an important direct target of Notch1 and, thus, c-Myc is another potential therapeutic target for T-ALL. Valproic acid (VPA), a histone deacetylase inhibitor, has been reported to treat various hematological malignancies. In the present study, we showed that c-Myc expression, at a transcriptional level, was dose-dependently downregulated in VPA-induced growth inhibition in T-ALL cell lines, Jurkat and CCRF-CEM cells. 10058-F4, a small molecule c-Myc inhibitor, could increase the downregulation of c-Myc and markedly increase the growth inhibition and cell death induced by VPA in Jurkat and CCRF-CEM cells, which was accompanied by obvious cleavage of capase-3. Z-VAD-FMK, a caspase inhibitor, partially prevented the anti-leukemic effect. The results of the present study suggest that c-Myc inhibitors increase cell death induced by VPA in a caspase-dependent and -independent manner, and their combination could be a potent therapeutic strategy for adult T-ALL patients.

Muller, I., K. Larsson, et al. "Targeting of the MYCN protein with small molecule c-MYC inhibitors." PLoS One. 2014 May 23;9(5):e97285. doi: 10.1371/journal.pone.0097285. eCollection 2014.

Members of the MYC family are the most frequently deregulated oncogenes in human cancer and are often correlated with aggressive disease and/or poorly differentiated tumors. Since patients with MYCN-amplified neuroblastoma have a poor prognosis, targeting MYCN using small molecule inhibitors could represent a promising therapeutic approach. We have previously demonstrated that the small molecule 10058-F4, known to bind to the c-MYC bHLHZip dimerization domain and inhibiting the c-MYC/MAX interaction, also interferes with the MYCN/MAX dimerization in vitro and imparts anti-tumorigenic effects in neuroblastoma tumor models with MYCN overexpression. Our previous work also revealed that MYCN-inhibition leads to mitochondrial dysfunction resulting in accumulation of lipid droplets in neuroblastoma cells. To expand our understanding of how small molecules interfere with MYCN, we have now analyzed the direct binding of 10058-F4, as well as three of its analogs; #474, #764 and 10058-F4(7RH), one metabolite C-m/z 232, and a structurally unrelated c-MYC inhibitor 10074-G5, to the bHLHZip domain of MYCN. We also assessed their ability to induce apoptosis, neurite outgrowth and lipid accumulation in

neuroblastoma cells. Interestingly, all c-MYC binding molecules tested also bind MYCN as assayed by surface plasmon resonance. Using a proximity ligation assay, we found reduced interaction between MYCN and MAX after treatment with all molecules except for the 10058-F4 metabolite C-m/z 232 and the non-binder 10058-F4(7RH). Importantly, 10074-G5 and 10058-F4 were the most efficient in inducing neuronal differentiation and lipid accumulation in MYCN-amplified neuroblastoma cells. Together our data demonstrate MYCN-binding properties for a selection of small molecules, and provide functional information that could be of importance for future development of targeted therapies against MYCN-amplified neuroblastoma.

Nair, R., D. L. Roden, et al. "c-Myc and Her2 cooperate to drive a stem-like phenotype with poor prognosis in breast cancer." Oncogene. 2014 Jul 24;33(30):3992-4002. doi: 10.1038/onc.2013.368. Epub 2013 Sep 23.

The HER2 (ERBB2) and MYC genes are commonly amplified in breast cancer, yet little is known about their molecular and clinical interaction. Using a novel chimeric mammary transgenic approach and in vitro models, we demonstrate markedly increased self-renewal and tumour-propagating capability of cells transformed with Her2 and c-Myc. Coexpression of both oncoproteins in cultured cells led to the activation of a c-Myc transcriptional signature and acquisition of a self-renewing phenotype independent of an epithelial-mesenchymal transition programme or regulation of conventional cancer stem cell markers. Instead, Her2 and c-Myc cooperated to induce the expression of lipoprotein lipase, which was required for proliferation and self-renewal in vitro. HER2 and MYC were frequently coamplified in breast cancer, associated with aggressive clinical behaviour and poor outcome. Lastly, we show that in HER2(+) breast cancer patients receiving adjuvant chemotherapy (but not targeted anti-Her2 therapy), MYC amplification is associated with a poor outcome. These findings demonstrate the importance of molecular and cellular context in oncogenic transformation and acquisition of a malignant stem-like phenotype and have diagnostic and therapeutic consequences for the clinical management of HER2(+) breast cancer.

Nanbakhsh, A., C. Pochon, et al. "c-Myc regulates expression of NKG2D ligands ULBP1/2/3 in AML and modulates their susceptibility to NK-mediated lysis." Blood. 2014 Jun 5;123(23):3585-95. doi: 10.1182/blood-2013-11-536219. Epub 2014 Mar 27.

Cytarabine (cytosine arabinoside) is one of the most effective drugs for the treatment of patients diagnosed with acute myeloid leukemia (AML). Despite its efficiency against AML cells, the emergence of drug resistance due to prolonged chemotherapy in most patients is still a major obstacle. Several studies have shown that drug resistance mechanisms alter the sensitivity of leukemia cells to immune system effector cells. To investigate this phenomenon, parental acute myeloid cell lines, HL-60 and KG-1, were continuously exposed to increasing doses of cytarabine in order to establish equivalent resistant cell lines, HL-60(R) and KG-1(R). Our data indicate that cytarabine-resistant cells are more susceptible to natural killer (NK)-mediated cell lysis as compared with parental cytarabine-sensitive cells. The increased susceptibility correlates with the induction of UL-16 binding proteins (ULBP) 1/2/3 and NK group 2, member D (NKG2D) ligands on target cells by a mechanism involving c-Myc induction. More importantly, chromatin immunoprecipitation assay revealed that ULBP1/3 are direct targets of c-Myc. Using drug-resistant primary AML blasts as target cells, inhibition of c-Myc resulted in decreased expression of NKG2D ligands and the subsequent impairment of NK cell lysis. This study provides for the first time, the c-Myc dependent regulation of NKG2D ligands in AML.

Nuvoli, B., R. Santoro, et al. "CELLFOOD induces apoptosis in human mesothelioma and colorectal cancer cells by modulating p53, c-myc and pAkt signaling pathways." J Exp Clin Cancer Res. 2014 Mar 5;33:24. doi: 10.1186/1756-9966-33-24.

BACKGROUND: CELLFOOD (CF) is a nutraceutical non-addictive, non-invasive, and completely non-toxic unique proprietary colloidal-ionic formula. Little is known about its effect on cancer cells in solid tumors. The aim of this study was to evaluate the effect that CF has on different cancer cell lines and the mechanism by which the nutraceutical works. METHODS: The effect of CF on HFF (normal fibroblasts), Met5A (mesothelium), MSTO-211H, NCI-2452, Ist-Mes1, MPP89, Ist-Mes2 (mesothelioma), M14 (melanoma), H1650, H1975 (lung cancer), SKRB3 (breast cancer), and HCT-116 (colorectal cancer) cell growth was tested by cell proliferation and clonogenic assay. Among all of them, MSTO-211 and HCT-116 were analyzed for cell cycle by flow cytometry and western blot. RESULTS: All human cancer lines were suppressed on cell growth upon 1:200 CF treatment for 24 and 48 hours. Death was not observed in HFF and Met5A cell lines. Cell cycle analysis showed an increased sub-G1 with reduction of G1 in MSTO-211 and a cell cycle arrest of in G1 in HCT116. Activation of caspase-3 and cleavage of PARP confirmed an apoptotic death for both cell lines. Increased expression levels of p53, p21, and p27, downregulation of c-myc and Bcl-2, and inhibition of Akt activation were also found in CF-treated MSTO-211 and HCT-116 cells. CONCLUSIONS: These findings ascertained an interaction between p53, c-myc, p21, p27, Bcl-2, PI3K/Akt pathway, and CF-induced apoptosis in MSTO-211H and HCT-116 cells, suggesting that CF acts as an important regulator of cell growth in human cancer cell lines. CF could be a useful nutraceutical intervention for prevention in colon cancer and mesothelioma.

Ogami, K., N. Hosoda, et al. "Antiproliferative protein Tob directly regulates c-myc proto-oncogene expression through cytoplasmic polyadenylation element-binding protein CPEB." Oncogene. 2014 Jan 2;33(1):55-64. doi: 10.1038/onc.2012.548. Epub 2012 Nov 26.

The regulation of mRNA deadenylation constitutes a pivotal mechanism of the post-transcriptional control of gene expression. Here we show that the antiproliferative protein Tob, a component of the Caf1-Ccr4 deadenylase complex, is involved in regulating the expression of the proto-oncogene c-myc. The c-myc mRNA contains cis elements (CPEs) in its 3'-untranslated region (3'-UTR), which are recognized by the cytoplasmic polyadenylation element-binding protein (CPEB). CPEB recruits Caf1 deadenylase through interaction with Tob to form a ternary complex, CPEB-Tob-Caf1, and negatively regulates the expression of c-myc by accelerating the deadenylation and decay of its mRNA. In quiescent cells, c-myc mRNA is destabilized by the trans-acting complex (CPEB-Tob-Caf1), while in cells stimulated by the serum, both Tob and Caf1 are released from CPEB, and c-Myc expression is induced early after stimulation by the stabilization of its mRNA as an 'immediate-early gene'. Collectively, these results indicate that Tob is a key factor in the regulation of c-myc gene expression, which is essential for cell growth. Thus, Tob appears to function in the control of cell growth at least, in part, by regulating the expression of c-myc.

Oh, E. J., W. I. Yang, et al. "Diffuse large B-cell lymphoma with histone H3 trimethylation at lysine 27: another poor prognostic phenotype independent of c-Myc/Bcl2 coexpression." Hum Pathol. 2014 Jul 23. pii: S0046-8177(14)00284-6. doi: 10.1016/j.humpath.2014.07.002.

Deregulation of histone H3 trimethylation at lysine 27 (H3K27me3) via aberration of the histone methyltransferase, enhancer of zeste homologue 2 (EZH2), is suggested to play a critical role in cancers including hematologic malignancies. In the present study, implications of H3K27me3 were investigated in diffuse large B-cell lymphoma (DLBCL) with respect to clinicopathological factors, especially in association with c-Myc/Bcl2 coexpression and germinal center B-like (GCB) or non-GCB subtype. By immunohistochemistry, a high level of

H3K27me3 was observed in approximately one-third (35.3%, 79/224) of DLBCL cases, and this subset of cases was related to poor performance status (Eastern Cooperative Oncology Group scores >/= 2) (P = .013), elevated lactate dehydrogenase level (P = .001), and a higher international prognostic index risk group (scores >/=3) (P = .005). H3K27me3 level was significantly correlated with EZH2 expression (P = .004) and c-Myc protein expression (P = .003) but not correlated with c-Myc/Bcl2 coexpression or with GCB or non-GCB subtype. A high level of H3K27me3 was related to an inferior overall survival (P = .006) and was shown to be an independent prognostic factor for overall survival along with the higher international prognostic index risk group and c-Myc/Bcl2 coexpression. In conclusion, H3K27me3 was related to EZH2 and c-Myc expression, suggesting formation of a MYC-EZH2-H3K27me3 loop in a subgroup of DLBCL cases. H3K27me3 was associated with poor patient outcome and revealed as an independent predictor for overall survival of DLBCL patients. H3K27me3 in DLBCL may be another high-risk phenotype independent of the phenotype of c-Myc/Bcl2 coexpression or other known poor prognostic subgroups.

Ooi, K. L., T. S. Muhammad, et al. "Physalin F from Physalis minima L. triggers apoptosis-based cytotoxic mechanism in T-47D cells through the activation caspase-3- and c-myc-dependent pathways." J Ethnopharmacol. 2013 Oct 28;150(1):382-8. doi: 10.1016/j.jep.2013.09.014. Epub 2013 Sep 17.

ETHNOPHARMACOLOGICAL RELEVANCE: Physalin F (a secosteroid derivative), is well recognized as a potent anticancer compound from Physalis minima L., a plant that is traditionally used to treat cancer. However, the exact molecular anticancer mechanism remains to be elucidated. AIM OF THE STUDY: We have recently reported the apoptosis-based cytotoxic effect of the chloroform extract of this plant. Here, we investigated the cytotoxicity and possible cell death mechanism elicited by the active constituent, physalin F on human breast T-47D carcinoma. MATERIALS AND METHODS: Cytotoxic-guided fractionation of the chloroform extract of Physalis minima has led to the isolation of physalin F. The cytotoxicity activity was assayed using MTS assay. The effect of the compound to induce apoptosis was determined by biochemical and morphological observations through DeadEnd Colorimetric and annexin V assays, respectively, and RT-PCR analysis of mRNA expression of the apoptotic-associated genes. RESULTS: Cytotoxicity screening of physalin F displayed a remarkable dose-dependent inhibitory effect on T-47D cells with lower EC50 value (3.60 mug/ml) than the crude extract. mRNA expression analysis revealed the co-regulation of c-myc- and caspase-3-apoptotic genes in the treated cells with the peak expression at 9 and 12h of treatment, respectively. This apoptotic mechanism is reconfirmed by DNA fragmentation and phosphatidylserine externalization. CONCLUSION: These findings indicate that physalin F may potentially act as a chemopreventive and/or chemotherapeutic agent by triggering apoptosis mechanism via the activation of caspase-3 and c-myc pathways in T-47D cells.

Palko, E., S. Poliska, et al. "The c-MYC protooncogene expression in cholesteatoma." Biomed Res Int. 2014;2014:639896. doi: 10.1155/2014/639896. Epub 2014 Feb 10.

Cholesteatoma is an epidermoid cyst, which is most frequently found in the middle ear. The matrix of cholesteatoma is histologically similar to the matrix of the epidermoid cyst of the skin (atheroma); their epithelium is characterized by hyperproliferation. The c-MYC protooncogene located on chromosome 8q24 encodes a transcription factor involved in the regulation of cell proliferation and differentiation. Previous studies have found aneuploidy of chromosome 8, copy number variation of c-MYC gene, and the presence of elevated level c-MYC protein in cholesteatoma. In this study we have compared the expression of c-MYC gene in samples taken from the matrix of 26 acquired cholesteatomas (15 children and 11 adults), 15 epidermoid cysts of the skin (atheromas; head and neck region) and 5 normal skin samples (retroauricular region) using RT-qPCR, providing the first precise measurement of the expression of c-MYC gene in cholesteatoma. We have found significantly elevated c-MYC gene expression in cholesteatoma compared to atheroma and to normal skin samples. There was no significant difference, however, in c-MYC gene expression between cholesteatoma samples of children and adults. The significant difference in c-MYC gene expression level in cholesteatoma compared to that of atheroma implies a more prominent hyperproliferative phenotype which may explain the clinical behavior typical of cholesteatoma.

Pan, X. N., J. J. Chen, et al. "Inhibition of c-Myc Overcomes Cytotoxic Drug Resistance in Acute Myeloid Leukemia Cells by Promoting Differentiation." PLoS One. 2014 Aug 15;9(8):e105381. doi: 10.1371/journal.pone.0105381. eCollection 2014.

Nowadays, drug resistance still represents a major obstacle to successful acute myeloid leukemia (AML) treatment and the underlying mechanism is not fully elucidated. Here, we found that high expression of c-Myc was one of the cytogenetic characteristics in the drug-resistant leukemic cells. c-Myc over-expression in leukemic cells induced resistance to chemotherapeutic drugs, enhanced colony formation capacity and inhibited cell differentiation induced by all-trans retinoic acid (ATRA). Meanwhile, inhibition of c-Myc by shRNA or specific c-Myc inhibitor 10058-F4 rescued the sensitivity to cytotoxic drugs, restrained the colony formation ability and promoted differentiation. RT-PCR and western blotting analysis showed that down-regulation of C/EBPbeta contributed to the poor differentiation state of leukemic cells induced by c-Myc over-expression. Importantly, over-expression of C/EBPbeta could reverse c-Myc induced drug resistance. In primary AML cells, the c-Myc expression was negatively correlated with C/EBPbeta. 10058-F4, displayed anti-proliferative activity and increased cellular differentiation with up-regulation of C/EBPbeta in primary AML cells. Thus, our study indicated that c-Myc could be a novel target to overcome drug resistance, providing a new approach in AML therapy.

Pannem, R. R., C. Dorn, et al. "CYLD controls c-MYC expression through the JNK-dependent signaling pathway in hepatocellular carcinoma." Carcinogenesis. 2014 Feb;35(2):461-8. doi: 10.1093/carcin/bgt335. Epub 2013 Oct 8.

Posttranslational modification of different proteins via direct ubiquitin attachment is vital for mediating various cellular processes. Cylindromatosis (CYLD), a deubiquitination enzyme, is able to cleave the polyubiquitin chains from the substrate and to regulate different signaling pathways. Loss, or reduced expression, of CYLD is observed in different types of human cancer, such as hepatocellular carcinoma (HCC). However, the molecular mechanism by which CYLD affects cancerogenesis has to date not been unveiled. The aim of the present study was to examine how CYLD regulates cellular functions and signaling pathways during hepatocancerogenesis. We found that mice lacking CYLD were highly susceptible to chemically induced liver cancer. The mechanism behind proved to be an elevated proliferation rate of hepatocytes, owing to sustained c-Jun N-terminal kinase 1 (JNK1)-mediated signaling via ubiquitination of TNF receptor-associated factor 2 and expression of c-MYC. Overexpression of wild-type CYLD in HCC cell lines prevented cell proliferation, without affecting apoptosis, adhesion and migration. A combined immunohistochemical and tissue microarray analysis of 81 human HCC tissues revealed that CYLD expression is negatively correlated with expression of proliferation markers Ki-67 and c-MYC. To conclude, we found that downregulation of CYLD induces tumor cell proliferation, consequently contributing to the aggressive growth of HCC. Our findings suggest that CYLD holds potential to serve as a marker for HCC progression, and its link to c-MYC via JNK1 may provide the foundation for new therapeutic strategies for HCC patients.

Perez-Sayans, M., J. M. Suarez-Penaranda, et al. "Quantitative

determination of c-myc facilitates the assessment of prognosis of OSCC patients." Oncol Rep. 2014 Apr;31(4):1677-82. doi: 10.3892/or.2014.3040. Epub 2014 Feb 20.

Myc genes are a family of proto-oncogenes whose proteins are implicated in the regulation of cell proliferation, differentiation and apoptosis, and in regulating the activity of genes involved in cell division. The aim of the present study was to establish a quantitative description of the expression of c-myc and evaluate its relationship with other clinical and prognostic factors, as well as to establish a multivariate survival prediction model. This is a retrospective study of 68 patients diagnosed with oral squamous cell carcinoma (OSCC). We constructed a tissue microarray for investigating the expression of c-myc by immunohistochemistry. Statistical analyses were carried out, and a multivariate model that predicts survival was established. The average expression of c-myc was 50.32 (SD, 26.05) with a range from 6.60 to 99.48; similar for initial and advanced tumor stages. Non-smoking patients had higher levels of c-myc, showing statistically significant differences (Kruskal-Wallis chi2=5.975; p=0.05). We found no statistically significant relationship between the quantitative expression of c-myc and any other clinical or pathological parameters. For each unit of increase of c-myc, the risk increased by 1.15 ($p<0.001$; HR, 1.150; 95% CI, 1062-1245). Further study of this protein, which may have a significant diagnostic, prognostic and therapeutic value is warranted. Its determination can be valuable when used together with other markers to assess the prognosis of OSCC patients.

Phesse, T. J., K. B. Myant, et al. "Endogenous c-Myc is essential for p53-induced apoptosis in response to DNA damage in vivo." Cell Death Differ. 2014 Jun;21(6):956-66. doi: 10.1038/cdd.2014.15. Epub 2014 Feb 28.

Recent studies have suggested that C-MYC may be an excellent therapeutic cancer target and a number of new agents targeting C-MYC are in preclinical development. Given most therapeutic regimes would combine C-MYC inhibition with genotoxic damage, it is important to assess the importance of C-MYC function for DNA damage signalling in vivo. In this study, we have conditionally deleted the c-Myc gene in the adult murine intestine and investigated the apoptotic response of intestinal enterocytes to DNA damage. Remarkably, c-Myc deletion completely abrogated the immediate wave of apoptosis following both ionizing irradiation and cisplatin treatment, recapitulating the phenotype of p53 deficiency in the intestine. Consistent with this, c-Myc-deficient intestinal enterocytes did not upregulate p53. Mechanistically, this was linked to an upregulation of the E3 Ubiquitin ligase Mdm2, which targets p53 for degradation in c-Myc-deficient intestinal enterocytes. Further, low level overexpression of c-Myc, which does not impact on basal levels of apoptosis, elicited sustained apoptosis in response to DNA damage, suggesting c-Myc activity acts as a crucial cell survival rheostat following DNA damage. We also identify the importance of MYC during DNA damage-induced apoptosis in several other tissues, including the thymus and spleen, using systemic deletion of c-Myc throughout the adult mouse. Together, we have elucidated for the first time in vivo an essential role for endogenous c-Myc in signalling DNA damage-induced apoptosis through the control of the p53 tumour suppressor protein.

Pyko, I. V., M. Nakada, et al. "Glycogen synthase kinase 3beta inhibition sensitizes human glioblastoma cells to temozolomide by affecting O6-methylguanine DNA methyltransferase promoter methylation via c-Myc signaling." Carcinogenesis. 2013 Oct;34(10):2206-17. doi: 10.1093/carcin/bgt182. Epub 2013 May 28.

Glycogen synthase kinase 3beta (GSK3beta) is a serine/threonine protein kinase involved in human cancers including glioblastoma. We have previously demonstrated that GSK3beta inhibition enhances temozolomide effect in glioma cells. In this report, we investigated the molecular mechanisms of sensitization of glioblastoma cells to temozolomide by GSK3beta inhibition, focusing on O(6)-methylguanine DNA methyltransferase (MGMT) gene silencing. Glioblastoma tissues from patients treated with the GSK3beta-inhibiting drugs were subjected to immunohistochemistry and methylation-specific PCR assay. Human glioblastoma cell lines T98G, U138, U251 and U87 were treated with a small-molecule GSK3beta inhibitor, AR-A014418 or GSK3beta-specific small interfering RNA. The combined effect of temozolomide and AR-A014418 on cell proliferation was determined by AlamarBlue assay and an isobologram method. MGMT promoter methylation was estimated by methylation-specific PCR and MethyLight assay. MGMT gene expression was evaluated by real-time quantitative reverse transcriptase-PCR. c-Myc and DNA (cytosine-5)-methyltransferase 3A binding to the MGMT promoter was estimated by chromatin immunoprecipitation assay. GSK3beta inhibition decreased phosphorylation of glycogen synthase and reduced MGMT expression and increased MGMT promoter methylation in clinical tumors. In glioblastoma cell lines, GSK3beta inhibition decreased cell viability, enhanced temozolomide effect and downregulated MGMT expression with relevant changes in the methylation levels of the MGMT promoter. Here, we showed for the first time that c-Myc binds to the MGMT promoter with consequent recruitment of DNA (cytosine-5)-methyltransferase 3A, regulating the levels of MGMT promoter methylation. The results of this study suggest that GSK3beta inhibition enhances temozolomide effect by silencing MGMT expression via c-Myc-mediated promoter methylation.

Qu, X., L. Shen, et al. "A signal transduction pathway from TGF-beta1 to SKP2 via Akt1 and c-Myc and its correlation with progression in human melanoma." J Invest Dermatol. 2014 Jan;134(1):159-67. doi: 10.1038/jid.2013.281. Epub 2013 Jun 21.

Both SKP2 (S-phase kinase-associated protein 2) and transforming growth factor-beta1 (TGF-beta1) play important roles in cancer metastasis through different mechanisms: TGF-beta1 via induction of epithelial-mesenchymal transition (EMT) and SKP2 via downregulating p27(kip1). Recent studies indicated that c-Myc and Akt1 were active players in metastasis. In this study we demonstrated a crosstalk between these pathways. Specifically, we found that TGF-beta1 treatment increased SKP2 expression accompanied with increased phosphorylation of Akt1 and c-Myc protein accumulation during EMT. We demonstrated that Akt1 was required for TGF-beta1-mediated SKP2 upregulation and that c-Myc transcription factor specifically bound to the promoter of SKP2 for its enhanced transcription. Analysis of 25 samples of normal human skin, nevi, and melanomas revealed a positive correlation between c-Myc and SKP2 accumulation. Furthermore, accumulation of SKP2 and c-Myc proteins was significantly higher in metastatic melanoma samples as compared with that in primary melanomas, which again was higher than that in normal skin or nevi. In summary, our results integrated TGF-beta1 signals to SKP2 via Akt1 and c-Myc during EMT, and provided, to our knowledge, a previously unreported mechanistic molecular event for TGF-beta1-induced metastasis in human melanoma.

Qu, Y., L. Zhang, et al. "c-MYC overexpression overrides TAK1 dependency in efficient tumorigenicity of AKT-transformed cells." Cancer Lett. 2013 Aug 19;336(2):290-8. doi: 10.1016/j.canlet.2013.03.014. Epub 2013 Mar 21.

Transforming growth factor activated kinase 1 (TAK1) provides prosurvival signals in various types of cells, and emerging evidence indicates that targeting TAK1 is a promising means to eliminate certain types of cancer cells. Here, we show that TAK1 is required for efficient tumorigenicity of AKT-transformed cells. TAK1 inhibition accelerates cell apoptosis of AKT-transformed cells in anchorage-independent cell growth accompanying by the downregulation of Mcl-1 and Bcl-2 expression. On the contrary, the tumorigenicity of c-Myc-transformed cells is not significantly affected by TAK1 inhibition. Moreover, AKT-transformed cells with c-Myc overexpression tolerate TAK1 inhibition in anchorage-independent growth and tumorigenicity in vivo. Together, our

results provide evidence that TAK1-dependency in the tumorigenicity of AKT-transformed cells can be alleviated by c-Myc overexpression. These findings suggest that dual-targeting TAK1 and c-Myc might be a rational therapeutic strategy for treatment of certain types of cancer.

Rahat, B., A. Hamid, et al. "Epigenetic mechanisms regulate placental c-myc and hTERT in normal and pathological pregnancies; c-myc as a novel fetal DNA epigenetic marker for pre-eclampsia." Mol Hum Reprod. 2014 Jul 14. pii: gau053.

Placental development is known for its resemblance with tumor development, such as in the expression of oncogenes (c-myc) and telomerase (hTERT). The expression of c-myc and hTERT is up-regulated during early pregnancy and gestational trophoblastic diseases (GTDs). To determine the role of DNA methylation [via methylation-sensitive high resolution melting (MS-HRM)] and histone modifications [via chromatin immunoprecipitation (ChIP assay)] in regulating the differential expression of c-myc and hTERT during normal gestation and their dysregulation during placental disorders, we obtained placental samples from 135 pregnant women, in five groups: normal first, second and third trimester (n = 30 each), pre-eclamptic pregnancy (n = 30) and molar pregnancy (n = 15). Two placental cell lines (JEG-3 and HTR-8/SVneo) and isolated first-trimester cytotrophoblasts were also studied. Quantitative RT-PCR revealed decreased mRNA expression levels of c-myc and hTERT, which were associated with a higher level of H3K9me3 (1.5-fold, $P < 0.05$) and H3K27me3 (1.9-fold, $P < 0.05$), respectively, in third-trimester placental villi versus first-trimester villi. A significantly lower level of H3K27me3 in molar placenta was associated with a higher mRNA expression of c-myc and hTERT. The development of pre-eclampsia (PE) was associated with increased methylation ($P < 0.001$) and H3K27me3 ($P < 0.01$) at the c-myc promoter and reduced H3K9me3 ($P < 0.01$) and H3K27me3 ($P < 0.05$) at the hTERT promoter. Further, mRNA expression of c-myc and hTERT was strongly correlated in molar villi ($r = 0.88$, $P < 0.01$) and JEG-3 cells ($r = 0.99$, $P < 0.02$). Moreover, on the basis of methylation data, we demonstrate the potential of c-myc as a fetal DNA epigenetic marker for pre-eclamptic pregnancies. Thus we suggest a role for epigenetic mechanisms in regulating differential expression of c-myc and hTERT during placental development and use of the c-myc promoter region as a potential fetal DNA marker in the case of PE.

Rahmutulla, B., K. Matsushita, et al. "Alternative splicing of FBP-interacting repressor coordinates c-Myc, P27Kip1/cyclinE and Ku86/XRCC5 expression as a molecular sensor for bleomycin-induced DNA damage pathway." Oncotarget. 2014 May 15;5(9):2404-17.

The far-upstream element-binding protein-interacting repressor (FIR) is a c-myc transcriptional suppressor. FIR is alternatively spliced to lack the transcriptional repression domain within exon 2 (FIRDeltaexon2) in colorectal cancers. FIR and FIRDeltaexon2 form homo- or heterodimers that complex with SAP155. SAP155, a subunit of the essential splicing factor 3b subcomplex in the spliceosome, is required for proper P27Kip1 pre-mRNA splicing, and P27Kip1 arrests cells at G1. In contrast, FIR was co-immunoprecipitated with Ku86 and DNA-PKcs. siRNA against Ku86/Ku70 decreased FIR and P27Kip1 expression, whereas siRNA against FIR decreased Ku86/XRCC5 and P27Kip1 expression. Thus the mechanical interaction of FIR/FIRDeltaexon2/SAP155 bridges c-myc and P27Kip1 expression, potentially integrates cell-cycle progression and c-myc transcription in cell. Bleomycin(BLM) is an anticancer agent that introduces DNA breaks. Because DNA breaks generate the recruitment of Ku86/Ku70 to bind to the broken DNA ends, the possible involvement of FIR and Ku86/Ku70 interaction in the BLM-induced DNA damage repair response was investigated in this study. First, BLM treatment reduced SAP155 expression and increased FIR and FIRDeltaexon2 mRNA expression as well as the ratio of FIRDeltaexon2:FIR in hepatoblastoma cells (HLE and HLF). Second, FIR or FIRDeltaexon2 adenovirus vectors (Ad-FIR or Ad-FIRDeltaexon2) increased Ku86/Ku70 and P27Kip1 expression in vitro. Third, BLM decreased P27Kip1 protein expression, whereas increased P27Kip1 and gammaH2AX expression with Ad-FIRDeltaexon2. Together, the interaction of FIR/SAP155 modulates FIR splicing and involves in cell-cycle control or cell fate via P27Kip1 and c-myc in BLM-induced DNA damage pathway. This novel function of FIR splicing will contribute to clinical studies of cancer management through elucidating the mechanical interaction of FIR/FIRDeltaexon2/SAP155 as a potential target for cancer treatment.

Rajagopalan, V., M. Vaidyanathan, et al. "Pre-Clinical Analysis of Changes in Intra-cellular Biochemistry of Glioblastoma Multiforme (GBM) Cells Due to c-Myc Silencing." Cell Mol Neurobiol. 2014 Jul 24.

Glioblastoma Multiforme (GBM) is an aggressive form of brain Tumor that has few cures. In this study, we analyze the anti-proliferative effects of a new molecule JQ1 against GBMs induced in Wistar Rats. JQ1 is essentially a Myc inhibitor. c-Myc is also known for altering the biochemistry of a tumor cell. Therefore, the study is intended to analyze certain other oncogenes associated with c-Myc and also the change in cellular biochemistry upon c-Myc inhibition. The quantitative analysis of gene expression gave a co-expressive pattern for all the three genes involved namely; c-Myc, Bcl-2, and Akt. The cellular biochemistry analysis by transmission electron microscopy revealed high glycogen and lipid aggregation in Myc inhibited cells and excessive autophagy. The study demonstrates the role of c-Myc as a central metabolic regulator and Bcl-2 and Akt assisting in extending c-Myc half-life as well as in regulation of autophagy, so as to regulate cell survival on the whole. The study also demonstrates that transient treatment by JQ1 leads to aggressive development of tumor and therefore, accelerating death, emphasizing the importance of dosage fixation, and duration for clinical use in future.

Roderick, J. E., J. Tesell, et al. "c-Myc inhibition prevents leukemia initiation in mice and impairs the growth of relapsed and induction failure pediatric T-ALL cells." Blood. 2014 Feb 13;123(7):1040-50. doi: 10.1182/blood-2013-08-522698. Epub 2014 Jan 6.

Although prognosis has improved for children with T-cell acute lymphoblastic leukemia (T-ALL), 20% to 30% of patients undergo induction failure (IF) or relapse. Leukemia-initiating cells (LICs) are hypothesized to be resistant to chemotherapy and to mediate relapse. We and others have shown that Notch1 directly regulates c-Myc, a known regulator of quiescence in stem and progenitor populations, leading us to examine whether c-Myc inhibition results in efficient targeting of T-ALL-initiating cells. We demonstrate that c-Myc suppression by small hairpin RNA or pharmacologic approaches prevents leukemia initiation in mice by eliminating LIC activity. Consistent with its anti-LIC activity in mice, treatment with the BET bromodomain BRD4 inhibitor JQ1 reduces C-MYC expression and inhibits the growth of relapsed and IF pediatric T-ALL samples in vitro. These findings demonstrate a critical role for c-Myc in LIC maintenance and provide evidence that MYC inhibition may be an effective therapy for relapsed/IF T-ALL patients.

Rodrigues-Peres, R. M., S. Cadore, et al. "Tissue aluminum concentration does not affect the genomic stability of ERBB2, C-MYC, and CCND1 genes in breast cancer." Biol Trace Elem Res. 2013 Sep;154(3):345-51. doi: 10.1007/s12011-013-9751-3. Epub 2013 Jul 17.

It has long been hypothesized that body tissue uptake of aluminum may have biological implications in breast cancer. In vitro and in vivo studies have shown that aluminum may trigger genomic instability by interfering with DNA strands. The objective of this study was to examine the relationship between aluminum concentrations in the peripheral and central areas of breast tumors with the instability of three key genes in breast cancer, ERBB2, C-

MYC, and CCND1 and aneuploidy of the chromosomes harboring these genes. Tissue samples of 118 women treated for breast cancer were obtained. Evaluation of aluminum content was carried out using graphite furnace atomic absorption spectrometry. A tissue microarray slide containing the tumor samples was used in FISH assays to assess ERBB2, C-MYC, and CCND1 expressions as well as the statuses of their respective chromosomes 17, 8, and 11. Clinicopathological data were obtained from patient's records. Aluminum levels of >2.0 mg/kg were found in 20.3 and 22.1% of the central and peripheral breast tumor areas, respectively. Amplification and/or aneuploid-positive statuses for ERBB2/CEP17, C-MYC/CEP8, and CCND1/CEP11 were detected in 24, 36.7, and 29.3% of the tumors, respectively. We found that aluminum concentration was not related to these altered gene statuses. Our findings suggest that aluminum concentration does not affect genomic stability in breast tissues. Tissue microenvironment modifications, due to the presence of aluminum compounds, seem more appealing as a possible target for future studies to determine the implications of aluminum in breast carcinogenesis.

Schuhmacher, M. and D. Eick "Dose-dependent regulation of target gene expression and cell proliferation by c-Myc levels." Transcription. 2013 Aug 2;4(4). pii: 25907. Epub 2013 Aug 2.

The proto-oncogene c-myc encodes a basic helix-loop-helix leucine zipper transcription factor (c-Myc). c-Myc plays a crucial role in cell growth and proliferation. Here, we examined how expression of c-Myc target genes and cell proliferation depend on variation of c-Myc protein levels. We show that proliferation rates, the number of cells in S-phase, and cell size increased in a dose-dependent manner in response to increasing c-Myc levels. Likewise, the mRNA levels of c-Myc responsive genes steadily increased with rising c-Myc levels. Strikingly, steady-state mRNA levels of c-Myc target genes did not saturate even at highest c-Myc concentrations. These characteristics predestine c-Myc levels as a cellular rheostat for the control and fine-tuning of cell proliferation and growth rates.

Sekiguchi, N., K. Ootsubo, et al. "The impact of C-Myc gene-related aberrations in newly diagnosed myeloma with bortezomib/dexamethasone therapy." Int J Hematol. 2014 Mar;99(3):288-95. doi: 10.1007/s12185-014-1514-1. Epub 2014 Feb 5.

Recent studies have suggested that c-Myc over-expression may be a factor indicating poor prognosis in multiple myeloma (MM), although c-Myc gene-related abnormalities, including translocation and gene amplification, have not been fully investigated in the novel agent era. Additional chromosome 8 may be considered as aggressive disease in the 1990s. To clarify the impact of these aberrations, we retrospectively analyzed newly diagnosed MM (NDMM) and relapsed/refractory MM (RRMM) with bortezomib and dexamethasone induction therapy. In the present study, the high-risk group was defined as having at least one of the following present: non-hyperdiploidy, IgH/FGFR3, and del p53. Forty NDMM cases were analyzed. At the median follow-up duration of 14.1 months, 14 RRMM were recognized. The proportions of patients in the high-risk, c-Myc gene-related aberrations, and additional chromosome 8 groups at diagnosis were 45.5, 22.5, and 10 %, respectively. The proportions of patients who developed RRMM in the high-risk, c-Myc gene-related aberrations, and additional chromosome 8 groups were 41.7, 77.7, and 50 %, respectively. Furthermore, patients with c-Myc gene-related abnormalities tended to exhibit inferior progression-free survival (PFS), and those with c-Myc gene-related abnormalities and/or additional chromosome 8 showed statistically shorter PFS. Therefore, c-Myc gene-related abnormalities and additional chromosome 8 may be related to a poorer prognosis.

Seo, A. N., J. M. Yang, et al. "Clinicopathologic and prognostic significance of c-MYC copy number gain in lung adenocarcinomas." Br J Cancer. 2014 May 27;110(11):2688-99. doi: 10.1038/bjc.2014.218. Epub 2014 May 8.

BACKGROUND: c-MYC copy number gain (c-MYC gain) has been associated with aggressive behaviour in several cancers. However, the role of c-MYC gain has not yet been determined in lung adenocarcinomas classified by genetic alterations in epidermal growth factor receptor (EGFR), KRAS, and anaplastic lymphoma kinase (ALK) genes. We investigated the clinicopathologic and prognostic significance of c-MYC gain for disease-free survival (DFS) and overall survival (OS) according to EGFR, KRAS, and ALK gene status and stages in lung adenocarcinomas. METHODS: In 255 adenocarcinomas resected in Seoul National University Bundang Hospital from 2003 to 2009, fluorescence in situ hybridisation (FISH) with c-MYC probe and centromeric enumeration probe 8 (CEP8) was analysed using tissue microarray containing single representative core per each case. EGFR (codon 18 to 21) and KRAS (codon 12, 13, and 61) mutations were analysed by polymerase chain reaction and direct sequencing method from formalin-fixed, paraffin-embedded tissue sections. ALK rearrangement was determined by FISH method. c-MYC gain was defined as >2 copies per nucleus, chromosome 8 gain as 3 copies per nucleus, and gain of c-MYC:CEP8 ratio (hereafter, c-MYC amplification) as 2. RESULTS: We observed c-MYC gain in 20% (51 out of 255), chromosome 8 gain in 5.5% (14 out of 255), c-MYC amplification in 2.4% (6 out of 255), EGFR mutation in 49.4% (118 out of 239), KRAS mutation in 5.7% (7 out of 123), and ALK rearrangement in 4.9% (10 out of 205) of lung adenocarcinomas. c-MYC gain was observed in 19% (22 out of 118) of patients with lung adenocarcinomas with an EGFR mutation, but not in any patients with a KRAS mutation, or an ALK rearrangement. c-MYC gain (but not chromosome 8 gain or c-MYC amplification) was an independent poor-prognostic factor in the full cohort of lung adenocarcinoma (P=0.022, hazard ratio (HR)=1.71, 95% confidence interval (CI), 1.08-2.69 for DFS; P=0.032, HR=2.04, 95% CI, 1.06-3.91 for OS), as well as in stage I subgroup (P=0.023, HR=4.70, 95% CI, 1.24-17.78 for DFS; P=0.031, HR=4.65, 95% CI, 1.15-18.81 for OS), and in EGFR-mutant subgroup (P=0.022; HR=2.14; 95% CI, 1.11-4.10 for DFS). CONCLUSIONS: c-MYC gain (but not chromosome 8 gain or c-MYC amplification) was an independent poor-prognostic factor for DFS and OS in lung adenocarcinomas, both in full cohort and stage I cancer, and possibly for DFS in EGFR-mutant adenocarcinomas. Additional studies are required to determine if patients with lung adenocarcinoma with c-MYC gain are candidates for additional first-line treatment to mitigate their increased risk for disease progression and death.

Seo, H. K., K. O. Ahn, et al. "Antitumor activity of the c-Myc inhibitor KSI-3716 in gemcitabine-resistant bladder cancer." Oncotarget. 2014 Jan 30;5(2):326-37.

Intravesical instillation of chemotherapeutic agents is a well-established treatment strategy to decrease recurrence following transurethral resection in non-muscle invasive bladder cancer. Gemcitabine is a recently developed treatment option. However, the curative effects of gemcitabine are far from satisfactory due to de novo or acquired drug resistance. In a previous study, we reported that intravesical administration of the c-Myc inhibitor KSI-3716 suppresses tumor growth in an orthotopic bladder cancer model. Here, we explored whether KSI-3716 inhibits gemcitabine-resistant bladder cancer cell proliferation. As expected from the in vitro cytotoxicity of gemcitabine in several bladder cancer cell lines, gemcitabine effectively suppressed the growth of KU19-19 xenografts in nude mice, although all mice relapsed later. Long-term in vitro exposure to gemcitabine induced gemcitabine-specific resistance. Gemcitabine-resistant cells, termed KU19-19/GEM, formed xenograft tumors even in the presence of 2 mg/kg gemcitabine. Interestingly, KU19-19/GEM cells up-regulated c-Myc expression in the presence of the gemcitabine and resisted to the gemcitabine, however was suppressed by the KSI-3716. The sequential addition of gemcitabine and KSI-3716 inhibited gemcitabine-resistant cell proliferation to a great extent than each

drug alone. These results suggest that sequential treatment with gemcitabine and KSI-3716 may be beneficial to bladder cancer patients.

Severino, V., A. Farina, et al. "Secretome profiling of differentiated neural mes-c-myc A1 cell line endowed with stem cell properties." Biochim Biophys Acta. 2013 Nov;1834(11):2385-95. doi: 10.1016/j.bbapap.2012.12.005. Epub 2012 Dec 12.

Neural stem cell proliferation and differentiation play a crucial role in the formation and wiring of neuronal connections forming neuronal circuits. During neural tissues development, a large diversity of neuronal phenotypes is produced from neural precursor cells. In recent years, the cellular and molecular mechanisms by which specific types of neurons are generated have been explored with the aim to elucidate the complex events leading to the generation of different phenotypes via distinctive developmental programs that control self-renewal, differentiation, and plasticity. The extracellular environment is thought to provide instructive influences that actively induce the production of specific neuronal phenotypes. In this work, the secretome profiling of differentiated neural mes-c-myc A1 (A1) cell line endowed with stem cell properties was analyzed by applying a shotgun LC-MS/MS approach. The results provide a list of secreted molecules with potential relevance for the functional and biological features characterizing the A1 neuronal phenotype. Proteins involved in biological processes closely related to nervous system development including neurites growth, differentiation of neurons and axonogenesis were identified. Among them, proteins belonging to extracellular matrix and cell-adhesion complexes as well as soluble factors with well established neurotrophic properties were detected. The presented work provides the basis to clarify the complex extracellular protein networks implicated in neuronal differentiation and in the acquisition of the neuronal phenotype. This article is part of a Special Issue entitled: An Updated Secretome.

Sheth, A., S. Escobar-Alvarez, et al. "Inhibition of human mitochondrial peptide deformylase causes apoptosis in c-myc-overexpressing hematopoietic cancers." Cell Death Dis. 2014 Mar 27;5:e1152. doi: 10.1038/cddis.2014.112.

Inhibition of human mitochondrial peptide deformylase (HsPDF) depolarizes the mitochondrial membrane, reduces mitochondrial protein translation and causes apoptosis in Burkitt's lymphoma. We showed that HsPDF mRNA and protein levels were overexpressed in cancer cells and primary acute myeloid leukemia samples. Myc regulates mitochondria and metabolism; we also demonstrated c-myc regulated the expression of HsPDF, likely indirectly. Inhibition of HsPDF by actinonin blocked mitochondrial protein translation and caused apoptotic death of myc-positive Burkitt's lymphoma, but not myc-negative B cells. Inhibition of mitochondrial translation by chloramphenicol or tetracycline, structurally different inhibitors of the mitochondrial ribosome, which is upstream of deformylase activity, followed by treatment with actinonin, resulted in reversal of the biochemical events and abrogation of the apoptosis induced by actinonin. This reversal was specific to inhibitors of HsPDF. Inhibition of HsPDF resulted in a mitochondrial unfolded protein response (increased transcription factors CHOP and CEB/P and the mitochondrial protease Lon), which may be a mechanism mediating cell death. Therefore, HsPDF may be a therapeutic target for these hematopoietic cancers, acting via a new mechanism.

Shi, Y., X. Xu, et al. "tRNA synthetase counteracts c-Myc to develop functional vasculature." Elife. 2014 Jun 17;3:e02349. doi: 10.7554/eLife.02349.

Recent studies suggested an essential role for seryl-tRNA synthetase (SerRS) in vascular development. This role is specific to SerRS among all tRNA synthetases and is independent of its well-known aminoacylation function in protein synthesis. A unique nucleus-directing domain, added at the invertebrate-to-vertebrate transition, confers this novel non-translational activity of SerRS. Previous studies showed that SerRS, in some unknown way, controls VEGFA expression to prevent vascular over-expansion. Using in vitro, cell and animal experiments, we show here that SerRS intervenes by antagonizing c-Myc, the major transcription factor promoting VEGFA expression, through a tandem mechanism. First, by direct head-to-head competition, nuclear-localized SerRS blocks c-Myc from binding to the VEGFA promoter. Second, DNA-bound SerRS recruits the SIRT2 histone deacetylase to erase prior c-Myc-promoted histone acetylation. Thus, vertebrate SerRS and c-Myc is a pair of 'Yin-Yang' transcriptional regulator for proper development of a functional vasculature. Our results also discover an anti-angiogenic activity for SIRT2.DOI: http://dx.doi.org/10.7554/eLife.02349.001.

Srivastava, J., A. Siddiq, et al. "Astrocyte elevated gene-1 (AEG-1) and c-Myc cooperate to promote hepatocarcinogenesis." Hepatology. 2014 Jul 28. doi: 10.1002/hep.27339.

Astrocyte elevated gene-1 (AEG-1) and c-Myc are overexpressed in human hepatocellular carcinoma (HCC) functioning as oncogenes. AEG-1 is transcriptionally regulated by c-Myc and AEG-1 itself induces c-Myc by activating Wnt/beta-catenin signaling pathway. We now document cooperation of AEG-1 and c-Myc in promoting hepatocarcinogenesis by analyzing hepatocyte-specific transgenic mice expressing either AEG-1 (Alb/AEG-1), c-Myc (Alb/c-Myc) or both (Alb/AEG-1/c-Myc). WT and Alb/AEG-1 mice did not develop spontaneous HCC. Alb/c-Myc mice developed spontaneous HCC without distant metastasis while Alb/AEG-1/c-Myc mice developed highly aggressive HCC with frank metastasis to the lungs. Induction of carcinogenesis by N-nitrosodiethylamine (DEN) significantly accelerated the kinetics of tumor formation in all groups. However, in Alb/AEG-1/c-Myc the effect was markedly pronounced with lung metastasis. In vitro analysis showed that Alb/AEG-1/c-Myc hepatocytes acquired increased proliferation and transformative potential with sustained activation of pro-survival and epithelial-mesenchymal transition (EMT) signaling pathways. RNA-sequencing analysis identified a unique gene signature in livers of Alb/AEG-1/c-Myc mice that was not observed when either AEG-1 or c-Myc was overexpressed. Specifically Alb/AEG-1/c-Myc mice overexpressed maternally imprinted non-coding RNAs, such as Rian, Meg-3 and Migr, which are implicated in hepatocarcinogenesis. Knocking down these ncRNAs significantly inhibited proliferation and invasion by Alb/AEG-1/c-Myc hepatocytes. Conclusion: Our studies reveal a novel cooperative oncogenic effect of AEG-1 and c-Myc that might explain the mechanism of aggressive HCC. Alb/AEG-1/c-Myc mice provide a useful model to understand the molecular mechanism of cooperation between these two oncogenes and other molecules involved in hepatocarcinogenesis. This model might also be of use for evaluating novel therapeutic strategies targeting HCC. (Hepatology 2014;).

Sun, S., P. Sun, et al. "Downregulation of microRNA-155 accelerates cell growth and invasion by targeting c-myc in human gastric carcinoma cells." Oncol Rep. 2014 Sep;32(3):951-6. doi: 10.3892/or.2014.3288. Epub 2014 Jun 24.

MicroRNAs (miRNAs) are a recently discovered class of small non-coding RNAs that regulate gene expression. miRNAs can contribute to cancer development and progression and are differentially expressed in normal tissue and cancer. In the present study, our aim was to investigate the expression of miR-155 in gastric cancer and to explore the mechanisms by which it influences gastric cancer cells. The level of miR-155 in 52 gastric carcinoma and corresponding non-tumor tissues was quantified by real-time reverse transcriptase-polymerase chain reaction. We used the data from EdU, CASY and cell adhesion assays to show how the expression of miR-155 affects viability and proliferation in SGC-7901 cancer cells. We also performed functional assays using the 3'-untranslated region (3'-UTR) of the c-myc gene as a miR-155 target in a luciferase reporter assay system. Our results indicated that miR-155 is downregulated in both human gastric carcinoma tissues and

SGC-7901 cells. The high expression level of miR-155 may significantly downregulate cancer cell viability, proliferation and attachment. The level of miR-155 could influence endogenous c-myc expression in SGC-7901 cells, and may decrease its expression by binding to 3'-UTR of c-myc. In conclusion, our results suggest that miR-155 is extensively involved in the cancer pathogenesis of gastric carcinoma and support its function as recessive cancer genes. c-myc is an important miR-155 target gene.

Tao, J., X. Zhao, et al. "c-MYC-miRNA circuitry: a central regulator of aggressive B-cell malignancies." Cell Cycle. 2014 Jan 15;13(2):191-8. doi: 10.4161/cc.27646. Epub 2014 Jan 6.

MYC (c-Myc) deregulation has been frequently associated with aggressive lymphomas and adverse clinical outcome in B-cell malignancies. MYC has been implicated in controlling the expression of miRNAs, and MYC-regulated miRNAs affect virtually all aspects of the hallmarks of MYC-driven lymphomas. Increasing evidence has indicated that there is significant cross-talk between MYC and miRNAs, with MYC regulating expression of a number of miRNAs, resulting in widespread repression of miRNA and, at the same time, MYC being subjected to regulation by miRNAs, leading to sustained MYC activity and the corresponding MYC downstream pathways. Thus, these combined effects of MYC overexpression and downregulation of miRNAs play a central regulatory role in the MYC oncogenic pathways and MYC-driven lymphomagenesis. Here, we provide biological insight on the function of MYC-regulated miRNAs, the mechanisms of MYC-induced miRNA repression, and the complicated feedback circuitry underlying lymphoma progression, as well as potential therapeutic targets in aggressive B-cell lymphomas.

Torres, L. C., L. D. Kulikowski, et al. "Disruption of the CREBBP gene and decreased expression of CREB, NFkappaB p65, c-JUN, c-FOS, BCL2 and c-MYC suggest immune dysregulation." Hum Immunol. 2013 Aug;74(8):911-5. doi: 10.1016/j.humimm.2013.04.024. Epub 2013 May 2.

Genomic aberrations in the CREBBP (CREB-binding protein - CREBBP or CBP) gene such as point mutations, small insertions or exonic copy number changes are usually associated with Rubinstein-Taybi syndrome (RTs). In this study, the disruption of the CREBBP gene on chromosome 16p13.3, as revealed by CGH-array and FISH, suggests immune dysregulation in a patient with the Rubinstein Taybi syndrome (RTs) phenotype. Further investigation with Western blot techniques demonstrated decreased expression of CREB, NFkappaB, c-Jun, c-Fos, BCL2 and cMyc in peripheral blood mononuclear cells, thus indicating that the CREBBP gene is essential for the normal expression of these proteins and the regulation of immune responses.

Tsai, L. H., J. Y. Wu, et al. "The MZF1/c-MYC axis mediates lung adenocarcinoma progression caused by wild-type lkb1 loss." Oncogene. 2014 May 5. doi: 10.1038/onc.2014.118.

Liver kinase B1 (LKB1) loss in lung adenocarcinoma is commonly caused by genetic mutations, but these mutations rarely occur in Asian patients. We recently reported wild-type LKB1 loss via the alteration of NKX2-1/p53-axis-promoted tumor aggressiveness and predicted poor outcomes in cases of lung adenocarcinoma. The mechanistic action of wild-type LKB1 loss within tumor progression remains unknown. The suppression of MYC by LKB1 controls epithelial organization; therefore, we hypothesize that MYC expression can be increased via wild-type LKB1 loss and promotes tumor progression. Here, MYC transcription is upregulated by LKB1-loss-mediated MZF1 expression. The wild-type LKB1-loss-mediated MZF1/MYC axis is responsible for soft-agar growth, migration and invasion in lung adenocarcinoma cells. Moreover, wild-type LKB1 loss-induced cell invasiveness was markedly suppressed by MYC inhibitors (10058-F4 and JQ1). Patients with low-LKB1/high-MZF1 or low-LKB1/high-MYC tumors have shorter overall survival and relapse-free-survival periods than patients with high-LKB1/low-MZF1 or high-LKB1/low-MYC tumors. In summary, MZF1-mediated MYC expression may promote tumor progression, resulting in poor outcomes in cases of lung adenocarcinoma with low-wild-type-LKB1 tumors.Oncogene advance online publication, 5 May 2014; doi:10.1038/onc.2014.118.

Urbanek-Olejnik, K., M. Liszewska, et al. "Changes of c-Myc and DNMT1 mRNA and protein levels in the rat livers induced by dibutyl phthalate treatment." Toxicol Ind Health. 2013 Dec 5.

We investigated the relationship between dibutyl phthalate (DBP)-induced hypomethylation of the c-Myc promoter region (as evident in our early study) and the expression of c-Myc and DNMT1 genes (at messenger RNA (mRNA) and protein level) in the rat liver. Male Wistar rats received DBP in 1, 3, or 14 daily doses of 1800 mg kg-1 body weight. Levels of DNMT1, c-Myc mRNA, and proteins were detected using real-time polymerase chain reaction and Western blot analysis, respectively. Our findings indicate that DBP caused an increase in mRNA levels of c-Myc at all time points. The results showed that protein levels of c-Myc in rat liver also increased significantly by DBP treatment, which were more pronounced at last time point (after 14 doses). Furthermore, overexpression of DNMT1gene have been found after one dose of DBP, which was confirmed at the protein level by Western blot analysis. Reduced levels of DNMT1mRNA and proteins (3 and 14 doses) were coordinated with depletion DNA synthesis (reported previously). Based on our previous results and those presented here, the following conclusion could be drawn: (1) DBP exerted biological activity through epigenetic modulation of c-Myc gene expression; (2) it seems possible that DBP-induced active demethylation of c-Myc gene through mechanism(s) linked to generation of reactive oxygen species by activated c-Myc; and (3) control of DNA replication was not directly dependent on c-Myc transcriptional activity and we attribute this finding to DNMT1gene expression which was tightly coordinated with DNA synthesis.

Valero, M. L., F. J. Cimas, et al. "E1a promotes c-Myc-dependent replicative stress: implications in glioblastoma radiosensitization." Cell Cycle. 2014 Jan 1;13(1):52-61. doi: 10.4161/cc.26754. Epub 2013 Oct 11.

The E1a gene from adenovirus is known to be a potent inducer of chemo/radiosensitivity in a wide range of tumors. However, the molecular bases of its radiosensitizer properties are still poorly understood. In an attempt to study this effect, U87MG cells, derived from a radio-resistant tumor as glioblastoma, where infected with lentivirus carrying E1a gene developing an acute sensitivity to ionizing radiation. The induction of radiosensitivity correlated with a marked G 2/M phase accumulation and a potent apoptotic response. Our findings demonstrate that c-Myc plays a pivotal role in E1a-associated radiosensitivity through the induction of a replicative stress situation, as our data support by genetic approaches, based in interference and overexpression in U87MG cells. In fact, we present evidence showing that Chk1 is a novel transcriptional target of E1a gene through the effect exerted by this adenoviral protein onto c-Myc. Moreover, c-Myc upregulation also explains the marked phosphorylation of H2AX associated to E1a expression in the absence of DNA damage. Indeed, all these observations were applicable to other experimental models, such as T98G, LN-405 and A172, rendering the same pattern in terms of radiosensitivity, cell cycle distribution, upregulation of Chk1, c-Myc, and phosphorylation pattern of H2AX. In summary, our data propose a novel mechanism to explain how E1a mediates radiosensitivity through the signaling axis E1a-->c-Myc--> replicative stress situation. This novel mechanism of E1a-mediated radiosensitivity could be the key to open new possibilities in the current therapy of glioblastoma.

Vander Griend, D. J., I. V. Litvinov, et al. "Conversion of androgen receptor signaling from a growth suppressor in normal prostate epithelial cells to an oncogene in prostate cancer cells involves a gain of function in c-Myc regulation." Int J Biol Sci. 2014 Jun

10;10(6):627-42. doi: 10.7150/ijbs.8756. eCollection 2014.

In normal prostate, androgen-dependent androgen receptor (AR) signaling within prostate stromal cells induces their secretion of paracrine factors, termed "andromedins" which stimulate growth of the epithelial cells. The present studies demonstrate that androgen-dependent andromedin-driven growth stimulation is counter-balanced by androgen-induced AR signaling within normal adult prostate epithelial cells resulting in terminal G0 growth arrest coupled with terminal differentiation into DeltaNp63-negative, PSA-expressing secretory luminal cells. This cell autonomous AR-driven terminal differentiation requires DNA-binding of the AR protein, is associated with decreases in c-Myc m-RNA and protein, are coupled with increases in p21, p27, and SKP-2 protein expression, and does not require functional p53. These changes result in down-regulation of Cyclin D1 protein and RB phosphoryation. shRNA knockdown documents that neither RB, p21, p27 alone or in combination are required for such AR-induced G0 growth arrest. Transgenic expression of a constitutive vector to prevent c-Myc down-regulation overrides AR-mediated growth arrest in normal prostate epithelial cells, which documents that AR-induced c-Myc down-regulation is critical in terminal growth arrest of normal prostate epithelial cells. In contrast, in prostate cancer cells, androgen-induced AR signaling paradoxically up-regulates c-Myc expression and stimulates growth as documented by inhibition of both of these responses following exposure to the AR antagonist, bicalutamide. These data document that AR signaling is converted from a growth suppressor in normal prostate epithelial cells to an oncogene in prostate cancer cells during prostatic carcinogenesis and that this conversion involves a gain of function for regulation of c-Myc expression.

Vindrieux, D., G. Devailly, et al. "Repression of PLA2R1 by c-MYC and HIF-2alpha promotes cancer growth." Oncotarget. 2014 Feb 28;5(4):1004-13.

Loss of secreted phospholipase A2 receptor (PLA2R1) has recently been found to render human primary cells more resistant to senescence whereas increased PLA2R1 expression is able to induce cell cycle arrest, cancer cell death or blockage of cancer cell transformation in vitro, suggesting that PLA2R1 displays tumor suppressive activities. Here we report that PLA2R1 expression strongly decreases in samples of human renal cell carcinoma (RCC). Knockdown of PLA2R1 increases renal cancer cell tumorigenicity supporting a role of PLA2R1 loss to promote in vivo RCC growth. Most RCC result from Von Hippel-Lindau (VHL) tumor suppressor loss-of-function and subsequent gain-of-function of the oncogenic HIF-2alpha/c-MYC pathway. Here, by genetically manipulating VHL, HIF-2alpha and c-MYC, we demonstrate that loss of VHL, stabilization of HIF-2alpha and subsequent increased c-MYC activity, binding and transcriptional repression, through induction of PLA2R1 DNA methylation closed to PLA2R1 transcriptional start site, results in decreased PLA2R1 transcription. Our results describe for the first time an oncogenic pathway leading to PLA2R1 transcriptional repression and the importance of this repression for tumor growth.

Wahlstrom, T., S. Belikov, et al. "Chromatin dynamics at the hTERT promoter during transcriptional activation and repression by c-Myc and Mnt in Xenopus leavis oocytes." Exp Cell Res. 2013 Dec 10;319(20):3160-9. doi: 10.1016/j.yexcr.2013.07.004. Epub 2013 Jul 13.

The transcription factors c-Myc and Mnt regulate gene expression through dimerization with Max and binding to E-boxes in target genes. While c-Myc activates gene expression via recruitment of histone modifying complexes, Mnt acts as a transcriptional repressor. Here, we used the Xenopus leavis oocyte system to address the effect of c-Myc and Mnt on transcription and chromatin remodeling over the E-box region in the human telomerase reverse transcriptase (hTERT) promoter. As expected we found elevated and decreased levels of hTERT transcription upon exogenously expressed c-Myc/Max and Mnt/Max, respectively. In addition, we confirmed binding of these heterodimers to both E-boxes already enriched with H3K9ac and H4K16ac. These chromatin marks were further enhanced upon c-Myc/Max binding followed by increased DNA accessibility in the E-box region. In contrast, Mnt/Max inhibited Myc-induced transcription and mediated repression through complete chromatin condensation and deacetylation of H3K9 and H4K16 across the E-box region. Importantly, Mnt was able to counteract c-Myc mediated activation even when expressed at low levels, suggesting Mnt to act as a strong repressor by closing the chromatin structure. Collectively our data demonstrate that the balance between c-Myc and Mnt activity determines the transcriptional outcome of the hTERT promoter by modulation of the chromatin architecture.

Walczynski, J., S. Lyons, et al. "Sensitisation of c-MYC-induced B-lymphoma cells to apoptosis by ATF2." Oncogene. 2014 Feb 20;33(8):1027-36. doi: 10.1038/onc.2013.28. Epub 2013 Feb 18.

Transcription factors ATF2 (activating transcription factor 2) and ATF7 (activating transcription factor 7) are highly homologous members of the activator protein 1 (AP-1) family. Their activities are growth factor and stress stimulated and they strictly require phosphorylation by mitogen-activated protein (MAP) kinases for their transcriptional functions. In samples of human B-cell lymphomas as well as Emu-Myc-driven mouse B-cell lymphomas, we find that ATF2 as well as MAP kinase c-Jun N-terminal kinase (JNK) are significantly up-regulated compared with normal human B-cell lines and mouse B cells, respectively. The B cell-specific deletion of ATF2 and ATF7 in mice results in significantly accelerated onset of Emu-Myc-induced lymphoma. In addition, loss of ATF2/7 desensitises Emu-Myc lymphoma cells to spontaneous as well as stress-induced apoptosis. Our results therefore suggest that c-MYC induces stress-mediated activation of ATF2 and ATF7 and that these transcription factors regulate apoptosis in response to oncogenic transformation of B cells.

Wang, B., S. H. Hsu, et al. "Reciprocal regulation of microRNA-122 and c-Myc in hepatocellular cancer: role of E2F1 and transcription factor dimerization partner 2." Hepatology. 2014 Feb;59(2):555-66. doi: 10.1002/hep.26712. Epub 2013 Dec 20.

c-Myc is a well-known oncogene frequently up-regulated in different malignancies, whereas liver-specific microRNA (miR)-122, a bona fide tumor suppressor, is down-regulated in hepatocellular cancer (HCC). Here we explored the underlying mechanism of reciprocal regulation of these two genes. Real-time reverse-transcription polymerase chain reaction (RT-PCR) and northern blot analysis demonstrated reduced expression of the primary, precursor, and mature miR-122 in c-MYC-induced HCCs compared to the benign livers, indicating transcriptional suppression of miR-122 upon MYC overexpression. Indeed, chromatin immunoprecipitation (ChIP) assay showed significantly reduced association of RNA polymerase II and histone H3K9Ac, markers of active chromatin, with the miR-122 promoter in tumors relative to the c-MYC-uninduced livers, indicating transcriptional repression of miR-122 in c-MYC-overexpressing tumors. The ChIP assay also demonstrated a significant increase in c-Myc association with the miR-122 promoter region that harbors a conserved noncanonical c-Myc binding site in tumors compared to the livers. Ectopic expression and knockdown studies showed that c-Myc indeed suppresses expression of primary and mature miR-122 in hepatic cells. Additionally, Hnf-3beta, a liver enriched transcription factor that activates miR-122 gene, was suppressed in c-MYC-induced tumors. Notably, miR-122 also repressed c-Myc transcription by targeting transcriptional activator E2f1 and coactivator Tfdp2, as evident from ectopic expression and knockdown studies and luciferase reporter assays in mouse and human hepatic cells. CONCLUSION: c-Myc represses miR-122 gene expression by associating with its promoter and by down-regulating Hnf-3beta expression, whereas miR-122 indirectly inhibits c-Myc transcription by targeting Tfdp2 and E2f1. In essence, these results suggest a double-negative feedback loop

between a tumor suppressor (miR-122) and an oncogene (c-Myc).

Wang, C. Y., G. Y. Chiou, et al. "Induced pluripotent stem cells without c-Myc reduce airway responsiveness and allergic reaction in sensitized mice." Transplantation. 2013 Dec 15;96(11):958-65. doi: 10.1097/TP.0b013e3182a53ef7.

BACKGROUND: Allergic disorders have increased substantially in recent years. Asthma is characterized by airway damage and remodeling. Reprogramming induced pluripotent stem cells (iPSCs) from adult somatic cells transfected by Oct-4/Sox-2/Klf-4, but not c-Myc, has shown the potential of embryonic-like cells. These cells have potential for multilineage differentiation and provide a resource for stem cell-based utility. However, the therapeutic potential of iPSCs without c-Myc (iPSC-w/o-c-Myc) in allergic diseases and airway hyperresponsiveness has not been investigated. The aim of this study was to evaluate the therapeutic effect of iPSC-w/o-c-Myc transplantation in a murine asthma model. METHODS: BALB/c mice were sensitized with alum-adsorbed ovalbumin (OVA) and then challenged with aerosolized OVA. Phosphate-buffered saline or iPSC-w/o-c-Myc was then intravenously injected after inhalation. Serum allergen-specific antibody levels, airway hyperresponsiveness, cytokine levels in spleen cells and bronchoalveolar lavage fluid (BALF), and cellular distribution in BALF were then examined. RESULTS: Treatment with iPSC-w/o-c-Myc effectively suppressed both Th1 and Th2 antibody responses, which was characterized by reduction in serum allergen-specific IgE, IgG, IgG1, and IgG2a levels as well as in interleukin-5 and interferon-gamma levels in BALF and in OVA-incubated splenocytes. Meanwhile, regulatory cytokine, interleukin-10, was enhanced. Transplantation of iPSC-w/o-c-Myc also significantly attenuated cellular infiltration in BALF and allergic airway hyperresponsiveness. However, no tumor formation was observed 6 months after transplantation. CONCLUSIONS: Administration of iPSC-w/o-c-Myc not only inhibited Th1 inflammatory responses but also had therapeutic effects on systemic allergic responses and airway hyperresponsiveness. iPSC-w/o-c-Myc transplantation may be a potential modality for treating allergic reactions and bronchial asthma.

Wang, J., A. Elahi, et al. "The interplay between histone deacetylases and c-Myc in the transcriptional suppression of HPP1 in colon cancer." Cancer Biol Ther. 2014 Sep 1;15(9):1198-207. doi: 10.4161/cbt.29500. Epub 2014 Jun 11.

HPP1 (hyperplastic polyposis protein 1), a tumor suppressor gene, is downregulated by promoter hypermethylation in a number of tumor types including colon cancer. c-Myc is also known to play a role in the suppression of HPP1 expression via binding to a promoter region cognate E-box site. The contribution of histone deacetylation as an additional epigenetic mechanism and its potential interplay with c-Myc in the transcriptional regulation of HPP1 are unknown. We have shown that the treatment of the HPP1-non-expressing colon cancer cell lines, HCT116 and DLD-1 with HDAC inhibitors results in re-expression of HPP1. RNAi-mediated knockdown of c-Myc as well as of HDAC2 and HDAC3 in HCT116 and of HDAC1 and HDAC3 in DLD-1 also resulted in significant re-expression of HPP1. Co-immunoprecipitation (IP), chromatin IP (ChIP), and sequential ChIP experiments demonstrated binding of c-Myc to the HPP1 promoter with recruitment of and direct interaction with HDAC3. In summary, we have demonstrated that c-Myc contributes to the epigenetic regulation of HPP1 via the dominant recruitment of HDAC3. Our findings may lead to a greater biologic understanding for the application of targeted use of HDAC inhibitors for anti-cancer therapy.

Wang, J., X. Ma, et al. "Evaluation of the antitumor effects of c-Myc-Max heterodimerization inhibitor 100258-F4 in ovarian cancer cells." J Transl Med. 2014 Aug 21;12(1):226.

Epithelial ovarian carcinoma is the most lethal gynecological cancer due to its silent onset and recurrence with resistance to chemotherapy. Overexpression of oncogene c-Myc is one of the most frequently encountered events present in ovarian carcinoma. Disrupting the function of c-Myc and its downstream target genes is a promising strategy for cancer therapy. Our objective was to evaluate the potential effects of small-molecule c-Myc inhibitor, 10058-F4, on ovarian carcinoma cells and the underlying mechanisms by which 10058-F4 exerts its actions. Using MTT assay, colony formation, flow cytometry and Annexin V FITC assays, we found that 10058-F4 significantly inhibited cell proliferation of both SKOV3 and Hey ovarian cancer cells in a dose dependent manner through induction of apoptosis and cell cycle G1 arrest. Treatment with 10058-F4 reduced cellular ATP production and ROS levels in SKOV3 and Hey cells. Consistently, primary cultures of ovarian cancer treated with 10058-F4 showed induction of caspase-3 activity and inhibition of cell proliferation in 15 of 18 cases. The response to 10058-F4 was independent the level of c-Myc protein over-expression in primary cultures of ovarian carcinoma. These novel findings suggest that the growth of ovarian cancer cells is dependent upon c-MYC activity and that targeting c-Myc-Max heterodimerization could be a potential therapeutic strategy for ovarian cancer.

Wang, L., X. Zhang, et al. "c-Myc-mediated epigenetic silencing of MicroRNA-101 contributes to dysregulation of multiple pathways in hepatocellular carcinoma." Hepatology. 2014 May;59(5):1850-63. doi: 10.1002/hep.26720. Epub 2014 Mar 27.

The MYC oncogene is overexpressed in hepatocellular carcinoma (HCC) and has been associated with widespread microRNA (miRNA) repression; however, the underlying mechanisms are largely unknown. Here, we report that the c-Myc oncogenic transcription factor physically interacts with enhancer of zeste homolog 2 (EZH2), a core enzymatic unit of polycomb repressive complex 2 (PRC2). Furthermore, miR-101, an important tumor-suppressive miRNA in human hepatocarcinomas, is epigenetically repressed by PRC2 complex in a c-Myc-mediated manner. miR-101, in turn, inhibits the expression of two subunits of PRC2 (EZH2 and EED), thus creating a double-negative feedback loop that regulates the process of hepatocarcinogenesis. Restoration of miR-101 expression suppresses multiple malignant phenotypes of HCC cells by coordinate repression of a cohort of oncogenes, including STMN1, JUNB, and CXCR7, and further increases expression of endogenous miR-101 by inhibition of PRC2 activation. In addition, co-overexpression of c-Myc and EZH2 in HCC samples was closely associated with lower expression of miR-101 ($P < 0.0001$) and poorer prognosis of HCC patients ($P < 0.01$). CONCLUSIONS: c-Myc collaborates with EZH2-containing PRC2 complex in silencing tumor-suppressive miRNAs during hepatocarcinogenesis and provides promising therapeutic candidates for human HCC.

Wang, R., D. Q. Chen, et al. "Acquisition of radioresistance in docetaxel-resistant human lung adenocarcinoma cells is linked with dysregulation of miR-451/c-Myc-survivin/rad-51 signaling." Oncotarget. 2014 Aug 30;5(15):6113-29.

Chemoresistant tumors usually fail to respond to radiotherapy. However, the mechanisms involved in chemo- and radiotherapy cross resistance are not fully understood. Previously, we have identified microRNA (miR)-451 as a tumor suppressor in lung adenocarcinoma (LAD). However, whether miR-451 plays critical roles in chemo- and radiotherapy cross resistance in LAD is unclear. Here, we established two docetaxel-resistant LAD cell models (SPC-A1/DTX and H1299/DTX), and showed that miR-451 was significantly downregulated in docetaxel-resistant LAD cells. Gain - and loss - of - function assays indicated that re-expression of miR-451 could reverse radioresistance of docetaxel-resistant LAD cells both in vitro and in vivo through promoting apoptosis and DNA double-strand breaks (DSBs). The proto-oncogene c-Myc was identified as a direct target of miR-451, and re-expression of miR-451 inhibited survivin and rad-51 expression by reducing the amount of c-Myc protein binding to their promoters. Silencing of c-Myc could phenocopy the effects of miR-451 upregulation, and

restoration of c-Myc could partially rescue the effect of miR-451 upregulation on radiosensitivity of docetaxel-resistant LAD cells. Therefore, dysregulation of miR-451/c-Myc-survivin/rad-51 signaling is responsible for radioresistance of docetaxel-resistant LAD cells, and targeting it will be a potential strategy for reversing chemo- and radiotherapy cross resistance of LAD patients.

Wang, W. L., Y. T. Yeh, et al. "Regulation of fibrillar collagen-mediated smooth muscle cell proliferation in response to chemical stimuli by telomere reverse transcriptase through c-Myc." Biomaterials. 2014 Apr;35(12):3829-39. doi: 10.1016/j.biomaterials.2014.01.049. Epub 2014 Feb 5.

Human telomerase reverse transcriptase (hTERT) and oncogene c-Myc have been shown to regulate cell proliferation. Our previous studies demonstrated that fibrillar collagen mediates vascular smooth muscle cell (SMC) cycle progression and proliferation in response to platelet-derived growth factor (PDGF)-BB and interleukin (IL)-1beta. However, whether hTERT and c-Myc are involved in these fibrillar collagen-mediated SMC responses remain unclear. The present study elucidated the regulatory role of hTERT and c-Myc in PDGF-BB/IL-1beta-induced cell cycle progression in SMCs on fibrillar collagen and its underlying mechanisms. Our results showed that PDGF-BB and IL-1beta exert synergistic effects to induce hTERT expression, but not its activity, in human arterial SMCs on fibrillar collagen. This PDGF-BB/IL-1beta-induced up-regulation of hTERT contributes to cell cycle progression in SMCs through the up-regulation of cyclin-dependent kinase-6 and down-regulations of p27(KIP1) and p21(CIP1). In addition, PDGF-BB/IL-1beta induces up-regulation of c-Myc in SMCs on fibrillar collagen; this response is mediated by the increased binding of hTERT, which can form complexes with TPP1 and hnRNPK, to the guanine-rich region of the c-Myc promoter and consequently contributes to cell cycle progression in SMCs on fibrillar collagen. Moreover, the PDGF-BB/IL-1beta-induced hTERT and c-Myc expressions are regulated by phosphatidylinositol 3-kinase/Akt in SMCs on fibrillar collagen. Our findings provide insights into the mechanisms by which hTERT and c-Myc regulates SMC cell cycle progression and proliferation on fibrillar collagen in response to chemical stimuli.

Wu, D. W., N. Y. Hsu, et al. "c-Myc suppresses microRNA-29b to promote tumor aggressiveness and poor outcomes in non-small cell lung cancer by targeting FHIT." Oncogene. 2014 Jun 9;0. doi: 10.1038/onc.2014.152.

The dual role of the microRNA-29 (miR-29) family in tumor progression and metastasis in solid tumors has been reported. Evidence for the role of miR-29 in tumor malignancy and its prognostic value in overall survival (OS) and relapse-free survival (RFS) in non-small cell lung cancer (NSCLC) remains conflicting. Mechanistic studies presented herein demonstrated that c-Myc suppressed the expression of miR-29b, promoting soft agar growth and invasion capability in lung cancer cells. Interestingly, the decrease in the expression of miR-29b by c-Myc is responsible for soft agar growth and invasiveness mediated by FHIT loss due to promoter methylation. Among patients, low expression of miR-29b and FHIT was more common in tumors with high c-Myc expression than in tumors with low c-Myc expression. Kaplan-Meier and Cox regression analysis showed that tumors with high c-Myc, low miR-29b and low FHIT expression had shorter OS and RFS periods than their counterparts. In conclusion, the decrease in the expression of miR-29b by c-Myc may be responsible for FHIT loss-mediated tumor aggressiveness and for poor outcome in NSCLC. Therefore, we suggest that restoration of the miR-29b expression using the c-Myc inhibitor might be helpful in suppressing tumor aggressiveness mediated by FHIT loss and consequently improving outcomes in NSCLC patients with tumors with low expression of FHIT.Oncogene advance online publication, 9 June 2014; doi:10.1038/onc.2014.152.

Wu, H., Z. Li, et al. "PKM2 depletion induces the compensation of glutaminolysis through beta-catenin/c-Myc pathway in tumor cells." Cell Signal. 2014 Nov;26(11):2397-405. doi: 10.1016/j.cellsig.2014.07.024. Epub 2014 Jul 17.

The metabolic activity in cancer cells primarily rely on aerobic glycolysis. Besides glycolysis, some tumor cells also exhibit excessive addition to glutamine, which constitutes an advantage for tumor growth. M2-type pyruvate kinase (PKM2) plays a pivotal role in sustaining aerobic glycolysis, pentose phosphate pathway and serine synthesis pathway. However, the participation of PKM2 in glutaminolysis is little to be known. Here we demonstrated that PKM2 depletion could provoke glutamine metabolism by enhancing the beta-catenin signaling pathway and consequently promoting its downstream c-Myc-mediated glutamine metabolism in colon cancer cells. Treatment with 2-deoxy-d-glucose (2-DG), a glycolytic inhibitor, got consistent results with the above. In addition, the dimeric form of PKM2, which lacks the pyruvate kinase activities, plays a critical role in regulating beta-catenin. Moreover, we found that overexpression of PKM2 negatively regulated beta-catenin through miR-200a. These insights supply evidence that glutaminolysis plays a compensatory role for cell survival upon glucose metabolism impaired.

Wu, Q., T. Chen, et al. "Microwave-assisted synthesis of arene ruthenium(II) complexes [(eta(6)-RC(6)H(5))Ru(m-MOPIP)Cl]Cl (R = -H and -CH(3)) as groove binder to c-myc G4 DNA." Dalton Trans. 2014 Jun 28;43(24):9216-25. doi: 10.1039/c3dt53635a.

Two arene Ru(II) complexes coordinated by 2-(3-methoxyphenyl)imidazole[4,5-f][1,10]phenanthroline, [(eta(6)-RC6H5)Ru(m-MOPIP)Cl]Cl (R = H, ; R = CH3, 2), have been prepared under microwave irradiation; the crystal structure of 2 exhibits a typical "piano stool" conformation, with bond angles for N1-Ru1-Cl1 86.02 (14) degrees and N2-Ru1-Cl1 84.51 (14) degrees . The Ru-C distance for the Ru atom bound to the benzene ring is about 0.2178(8) nm, and the average Ru-N distance for Ru atom to the two chelating N atoms is about 0.2092(4) nm. The evaluation of in vitro anticancer activities revealed that these synthetic Ru(II) complexes selectively inhibited the growth of HepG2 hepatocellular carcinoma cells, with low cytotoxicity toward LO2 human normal liver cells. The results demonstrated that the complexes exhibited great selectivity between human cancer and normal cells by comparing with the ligand m-MOPIP. Furthermore, complexes 1 and 2 could bind to c-myc G4 DNA in groove binding mode in promising affinity, and the insertion of the methyl groups in the arene ligand contributed to strengthen the binding affinity. This was also confirmed by molecular docking calculation and (1)H NMR analysis which showed that both 1 and 2 can bind in the loop constructed by A6-G9 and G21-A25 base pairs in c-myc G4 DNA to block the replication of c-myc oligomer. Taken together, these results suggest that arene Ru(II) complexes display application potential as small molecule inhibitors of c-myc G4 DNA.

Xia, S., J. Ma, et al. "Prostaglandin E2 promotes the cell growth and invasive ability of hepatocellular carcinoma cells by upregulating c-Myc expression via EP4 receptor and the PKA signaling pathway." Oncol Rep. 2014 Oct;32(4):1521-30. doi: 10.3892/or.2014.3393. Epub 2014 Aug 7.

Hepatocellular carcinoma (HCC) represents a major health problem worldwide. Prostaglandin E2 (PGE2), the predominant product of cyclooxygenase-2, has been implicated in hepatocarcinogenesis. However, the underlying molecular mechanisms remain to be further elucidated. c-myc, a cellular proto-oncogene, is activated or overexpressed in many types of human cancer, including HCC. The present study was designed to investigate the internal relationship and molecular mechanisms between PGE2 and c-Myc in HCC, and to define its role in HCC cell growth and invasion. Our results showed that PGE2 significantly upregulated c-Myc expression at both the mRNA and protein levels, and knockdown of c-Myc blocked PGE2-induced HCC cell growth and invasive ability in human HCC Huh-7 cells. The effect of PGE2 on c-Myc expression was mainly through the

EP4 receptor, and EP4 receptor-mediated c-Myc protein upregulation largely depended on de novo biosynthesis of c-Myc mRNA and its protein. EP4 receptor signaling activated GS/AC and increased the intracellular cAMP level in Huh-7 cells. The adenylate cyclase (AC) activator forskolin mimicked the effects of the EP4 receptor agonist on c-Myc expression, while the AC inhibitor SQ22536 reduced EP4 receptor-mediated c-Myc upregulation. These data confirm the involvement of the GS/AC/cAMP pathway in EP4 receptor-mediated c-Myc upregulation. Moreover, the phosphorylation levels of CREB protein were markedly elevated by EP4 receptor signaling, and by using specific inhibitor and siRNA interference, we demonstrated that PKA/CREB was also involved in the EP4 receptor-mediated c-Myc upregulation. In summary, the present study revealed that PGE2 significantly upregulates c-Myc expression at both mRNA and protein levels through the EP4R/GS/AC/cAMP/PKA/CREB signaling pathway, thus promoting cell growth and invasion in HCC cells. Targeting of the PGE2/EP4R/c-Myc pathway may be a new therapeutic strategy to prevent and cure human HCC.

Xiao, W., J. Wang, et al. "Mutual interaction between YAP and c-Myc is critical for carcinogenesis in liver cancer." Biochem Biophys Res Commun. 2013 Sep 20;439(2):167-72. doi: 10.1016/j.bbrc.2013.08.071. Epub 2013 Aug 28.

Yes-associated protein (YAP), the downstream effector of Hippo signaling pathway as well as c-Myc has been linked to hepatocarcinogenesis. However, little is known about whether and how YAP and c-Myc interacts with each other. In this study, we find YAP-c-Myc interaction is critical for liver cancer cell both in vitro and in vivo. Moreover, both c-Myc and YAP proteins are closely correlated in human liver cancer samples. Mechanistically, YAP promotes c-Myc transcriptional output through c-Abl. By contrast, c-Myc enhances protein expression independent of transcription. Taken together, our study uncovers a novel positive auto-regulatory feedback loop underlying the interaction between YAP and c-Myc in liver cancer, suggesting YAP and c-Myc links Hippo/YAP and c-Myc pathways, and thus may be helpful in the development of effective diagnosis and treatment strategies against liver cancer.

Xue, G., H. L. Yan, et al. "c-Myc-mediated repression of miR-15-16 in hypoxia is induced by increased HIF-2alpha and promotes tumor angiogenesis and metastasis by upregulating FGF2." Oncogene. 2014 Apr 7. doi: 10.1038/onc.2014.82.

Previous studies have established the link between aberrant microRNA (miRNA) expression and hypoxia in various neoplasms. However, how these hypoxia-related miRNAs modulate tumor progression is still unclear. Therefore, the patterns of miRNA in colorectal carcinoma cell lines in response to hypoxia or not were first screened and the hypoxia-induced repression of the miR-15-16 cluster was confirmed. Then, this repression was found to be associated with high tumor stage and poor prognosis in colorectal carcinoma and is shown to promote tumor angiogenesis and metastasis by the loss of restriction of its target gene, fibroblast growth factor-2 (FGF2). Moreover, the general and alterative promoters of the miR-15-16 host (deleted in lymphocytic leukemia 2, DLEU2) were mapped, and three c-Myc/Max binding sites in response to the hypoxia-induced repression of miR-15-16 were further identified. Finally, an enhanced stability of c-Myc/Max heterodimer promoted by increased hypoxia-inducible factor-2alpha (HIF-2alpha) was validated, and we also verified that the enhancement contributed to the hypoxia-induced repression of miR-15-16. In brief, the c-Myc-mediated transcriptional repression of miR-15-16 in hypoxia is induced by increased HIF-2alpha and promoted tumor angiogenesis and hematogenous metastasis by the further loss of post-transcriptional inhibition of FGF2. Our study provides a better understanding of the coping mechanisms in response to tumor hypoxia and may be helpful in developing an effective prognostic marker or treatment target against solid tumors.Oncogene advance online publication, 7 April 2014; doi:10.1038/onc.2014.82.

Yamashita, S., K. Ogawa, et al. "FOXO3a potentiates hTERT gene expression by activating c-MYC and extends the replicative life-span of human fibroblast." PLoS One. 2014 Jul 7;9(7):e101864. doi: 10.1371/journal.pone.0101864. eCollection 2014.

In our previous studies, we reported that SIRT1 prevents cellular senescence in human fibroblast, and that SIRT1-induced inhibition of cellular senescence is due to enhanced hTERT gene expression. In this study, we investigate the molecular mechanisms behind SIRT1-induced potentiation of hTERT transcription and show that FOXO3a functions downstream of SIRT1 and prevents the induction of cellular senescence by enhancing hTERT gene expression. Furthermore, we found that FOXO3a-induced potentiation of hTERT gene expression is regulated in a c-MYC/E-box dependent manner. In addition, we found that FOXO3a binds to the novel binding element in the c-MYC promoter, and this interaction activates the transcription of the c-MYC gene. The resulting increase in c-MYC leads to higher levels of c-MYC recruited to the hTERT promoter and, in turn, activates hTERT gene expression. Taken together, this pathway might constitute the molecular basis for the anti-senescence effects of SIRT1 and FOXO3a.

Yang, F., X. Xue, et al. "Long non-coding RNA GHET1 promotes gastric carcinoma cell proliferation by increasing c-Myc mRNA stability." FEBS J. 2014 Feb;281(3):802-13. doi: 10.1111/febs.12625. Epub 2014 Jan 15.

Long non-coding RNAs (lncRNAs), a recently characterized class of non-coding RNAs, have been shown to have important regulatory roles and are de-regulated in a variety of tumors. However, the contributions of lncRNAs to gastric carcinoma and their functional mechanisms remain largely unknown. In this study, we found that lncRNA gastric carcinoma high expressed transcript 1 (lncRNA-GHET1) was up-regulated in gastric carcinoma. The over-expression of this lncRNA correlates with tumor size, tumor invasion and poor survival. Gain-of-function and loss-of-function analyses demonstrated that GHET1 over-expression promotes the proliferation of gastric carcinoma cells in vitro and in vivo. Knockdown of GHET1 inhibits the proliferation of gastric carcinoma cells. RNA pull-down and immunoprecipitation assays confirmed that GHET1 physically associates with insulin-like growth factor 2 mRNA binding protein 1 (IGF2BP1) and enhances the physical interaction between c-Myc mRNA and IGF2BP1, consequently increasing the stability of c-Myc mRNA and expression. The expression of GHET1 and c-Myc is strongly correlated in gastric carcinoma tissues. Depletion of c-Myc abolishes the effects of GHET1 on proliferation of gastric carcinoma cells. Taken together, these findings indicate that GHET1 plays a pivotal role in gastric carcinoma cell proliferation via increasing c-Myc mRNA stability and expression, which suggests potential use of GHET1 for the prognosis and treatment of gastric carcinoma.

Ye, J., J. He, et al. "Generation of c-Myc transgenic pigs for autosomal dominant polycystic kidney disease." Transgenic Res. 2013 Dec;22(6):1231-9. doi: 10.1007/s11248-013-9707-6. Epub 2013 Mar 30.

After several decades of research, autosomal dominant polycystic kidney disease (ADPKD) is still incurable and imposes enormous physical, psychological, and economic burdens on patients and their families. Murine models of ADPKD represent invaluable tools for studying this disease. These murine forms of ADPKD can arise spontaneously, or they can be induced via chemical or genetic manipulations. Although these models have improved our understanding of the etiology and pathogenesis of ADPKD, they have not led to effective treatment strategies. The mini-pig represents an effective biomedical model for studying human diseases, as the pig's human-like physiological processes help to understand disease mechanisms and to develop novel therapies. Here, we tried to generate a transgenic model of ADPKD

in pigs by overexpressing c-Myc in kidney tissue. Western-blot analysis showed that c-Myc was overexpressed in the kidney, brain, heart, and liver of transgenic pigs. Immunohistochemical staining of kidney tissue showed that exogenous c-Myc predominantly localized to renal tubules. Slightly elevated blood urea nitrogen levels were observed in transgenic pigs 1 month after birth, but no obvious abnormalities were detected after that time. In the future, we plan to subject this model to renal injury in an effort to promote ADPKD progression.

Yoshida, G. J. and H. Saya "Inversed relationship between CD44 variant and c-Myc due to oxidative stress-induced canonical Wnt activation." Biochem Biophys Res Commun. 2014 Jan 10;443(2):622-7. doi: 10.1016/j.bbrc.2013.12.016. Epub 2013 Dec 11.

Cancer stem-like cells express high amount of CD44 variant8-10 which protects cancer cells from redox stress. We have demonstrated by immunohistochemical analysis and Western blotting, and reverse-transcription polymerase chain reaction, that CD44 variant8-10 and c-Myc tend to show the inversed expression manner in gastric cancer cells. That is attributable to the oxidative stress-induced canonical Wnt activation, and furthermore, the up-regulation of the downstream molecules, one of which is oncogenic c-Myc, is not easily to occur in CD44 variant-positive cancer cells. We have also found out that CD44v8-10 expression is associated with the turn-over of the c-Myc with the experiments using gastric cancer cell lines. This cannot be simply explained by the model of oxidative stress-induced Wnt activation. CD44v8-10-positive cancer cells are enriched at the invasive front. Tumor tissue at the invasive area is considered to be composed of heterogeneous cellular population; dormant cancer stem-like cells with CD44v8-10 (high)/ Fbw7 (high)/ c-Myc (low) and proliferative cancer stem-like cells with CD44v8-10 (high)/ Fbw7 (low)/ c-Myc (high).

Zakaria, M. K., I. Khan, et al. "Combination of hepatocyte specific delivery and transformation dependent expression of shRNA inducing transcriptional gene silencing of c-Myc promoter in hepatocellular carcinoma cells." BMC Cancer. 2014 Aug 10;14:582. doi: 10.1186/1471-2407-14-582.

BACKGROUND: A specific targeting modality for hepatocellular carcinoma (HCC) could ideally encompass a liver cell specific delivery system of a transcriptional unit that is active only in neoplastic cells. Sendai virosomes, derived from Sendai viral envelopes, home to hepatocytes based on the liver specific expression of asialoglycoprotein receptors (ASGPRs) which are recognized by the Sendai virosomal fusion (F) proteins. As reported earlier by us and other groups, transcriptional gene silencing (TGS) does not require continuous presence of the effector siRNA/shRNA molecule and is heritable, involving epigenetic modifications, leading to long term transcriptional repression. This could be advantageous over conventional gene therapy approaches, since continuous c-Myc inactivation is required to suppress hepatocarcinoma cells. METHODS: Exploiting such virosomal delivery, the alpha-fetoprotein (AFP) promoter, in combination with various tumour specific enhancers, was used to drive the expression of shRNA directed against ME1a1 binding site of the proto-oncogene c-Myc P2 promoter, in order to induce TGS in neoplastic liver cells. RESULTS: The dual specificity achieved by the Sendai virosomal delivery system and the promoter/enhancer guided expression ensured that the shRNA inducing TGS was active only in liver cells that had undergone malignant transformation. Our results indicate that such a bimodal therapeutic system induced specific activation of apoptosis in hepatocarcinoma cells due to heterochromatization and increased DNA methylation of the CpG islands around the target loci. CONCLUSIONS: The Sendai virosomal delivery system, combined with AFP promoter/enhancer expression machinery, could serve as a generalized mechanism for the expression of genes deleterious to transformed hepatocarcinoma cells. In this system, the epigenetic suppression of c-Myc could have an added advantage for inducing cell death in the targeted cells.

Zappasodi, R., A. Cavane, et al. "Pleiotropic antitumor effects of the pan-HDAC inhibitor ITF2357 against c-Myc-overexpressing human B-cell non-Hodgkin lymphomas." Int J Cancer. 2014 Nov 1;135(9):2034-45. doi: 10.1002/ijc.28852. Epub 2014 Mar 26.

Histone deacetylases (HDAC) extensively contribute to the c-Myc oncogenic program, pointing to their inhibition as an effective strategy against c-Myc-overexpressing cancers. We, thus, studied the therapeutic activity of the new-generation pan-HDAC inhibitor ITF2357 (Givinostat(R)) against c-Myc-overexpressing human B-cell non-Hodgkin lymphomas (B-NHLs). ITF2357 anti-proliferative and pro-apoptotic effects were analyzed in B-NHL cell lines with c-Myc translocations (Namalwa, Raji and DOHH-2), stabilizing mutations (Raji) or post-transcriptional alterations (SU-DHL-4) in relationship to c-Myc modulation. ITF2357 significantly delayed the in vitro growth of all B-NHL cell lines by inducing G1 cell-cycle arrest, eventually followed by cell death. These events correlated with the extent of c-Myc protein, but not mRNA, downregulation, indicating the involvement of post-transcriptional mechanisms. Accordingly, c-Myc-targeting microRNAs let-7a and miR-26a were induced in all treated lymphomas and the cap-dependent translation machinery components 4E-BP1, eIF4E and eIF4G, as well as their upstream regulators, Akt and PIM kinases, were inhibited in function of the cell sensitivity to ITF2357, and, in turn, c-Myc downregulation. In vivo, ITF2357 significantly hampered the growth of Namalwa and Raji xenografts in immunodeficient mice. Noteworthy, its combination with suboptimal cyclophosphamide, achieved complete remissions in most animals and equaled or even exceeded the activity of optimal cyclophosphamide. Collectively, our findings provide the rationale for testing the clinical advantages of adding ITF2357 to current therapies for the still very ominous c-Myc-overexpressing lymphomas. They equally provide the proof-of-concept for its clinical evaluation in rational combination with the promising inhibitors of B-cell receptor and PI3K/Akt/mTOR axis currently in the process of development.

Zhang, W., Q. Wang, et al. "MicroRNA-145 function as a cell growth repressor by directly targeting c-Myc in human ovarian cancer." Technol Cancer Res Treat. 2014 Apr;13(2):161-8. doi: 10.7785/tcrt.2012.500367. Epub 2013 Aug 2.

MiR-145 is reported to be significantly down-regulated in ovarian cancer. This study was aimed at elucidating the roles of miR-145 in regulating the biological behavior of epithelial ovarian cancer (EOC) cells. In this report, we find out that up-regulation of miR-145 in OVCAR-3 and SKOV-3 cells inhibit cell proliferation and promote cell apoptosis. We show that miR-145 directly target the c-Myc 3'-UTR. Moreover, ectopic expression of c-Myc reduces the inhibition of cell proliferation caused by miR-145 transfection. Cell cycle assay showed that up-regulation of miR-145 reduces S phase population, and restoration of c-Myc can rescue this reduction. These findings indicate that miR-145 inhibits cell proliferation and promotes cell apoptosis by targeting c-Myc 3'-UTR. Therefore, the result indicated that miR- 145 could be used as a potential therapeutic target in ovarian cancer.

Zhang, Y., L. Peng, et al. "Combinational delivery of c-myc siRNA and nucleoside analogs in a single, synthetic nanocarrier for targeted cancer therapy." Biomaterials. 2013 Nov;34(33):8459-68. doi: 10.1016/j.biomaterials.2013.07.050. Epub 2013 Aug 8.

The treatment of aggressive non-small-cell lung cancer (NSCLC) depends on the creation of new therapeutic regimens in clinical settings. In this study, we developed a Lipid/Calcium/Phosphate (LCP) nanoparticle that combines chemotherapy with gene therapy. By encapsulating a chemodrug, gemcitabine monophosphate (GMP), and siRNA specific to the undruggable cMyc oncogene (cMyc siRNA) into a single nano-sized vesicle and systemically administering them to nude mice, we achieved potent anti-tumor activity in both subcutaneous and

orthotopic models of NSCLC. The improvements in therapeutic response over either cMyc siRNA or GMP therapy alone, were demonstrated by the ability to effectively induce the apoptosis of tumor cells and the significant reduction of proliferation of tumor cells. The combination therapy led to dramatic inhibition of tumor growth, with little in vivo toxicity. Additionally, the current studies demonstrated the possibility of incorporating both nucleic acid molecules and phosphorylated small molecule drugs into the inner core of a single nanoparticle formulation. Co-encapsulation of an oncogene-modulating siRNA and a chemotherapeutic agent will allow simultaneous interruption of diverse anti-cancer pathways, leading to increased therapeutic efficacy and reduced toxicities.

Zhou, S. L., W. B. Yue, et al. "Autoantibody detection to tumor-associated antigens of P53, IMP1, P16, cyclin B1, P62, C-myc, Survivn, and Koc for the screening of high-risk subjects and early detection of esophageal squamous cell carcinoma." Dis Esophagus. 2013 Oct 21. doi: 10.1111/dote.12145.

The aim of this study was to evaluate the diagnostic values by detecting sera autoantibodies to eight tumor-associated antigens (TAAs) of P53, IMP1, P16, cyclin B1, P62, C-myc, Survivn and Koc full-length recombinant proteins for the screening of high-risk subjects and early detection of esophageal squamous cell carcinoma (ESCC). Enzyme-linked immunosorbent assay was used to detect autoantibodies against the eight selected TAAs in 567 sera samples from four groups, including 200 individuals with normal esophageal epithelia (NOR), 214 patients with esophageal basal cell hyperplasia (BCH), 65 patients with esophageal dysplasia (DYS), and 88 patients with ESCC. In addition, the expression of the eight antigens in esophageal tissues was analyzed by immunohistochemistry. Statistically significant distribution differences were identified among the four groups for each of the individual autoantibodies to six TAAs (P53, IMP1, P16, cyclin B1, P62, and C-myc); the detection rates of antoantibodies were positively correlated with the progression of ESCC. When autoantibody assay successively accumulated to six TAAs (P53, IMP1, P16, cyclin B1, P62, and C-myc), a stepwise increased detection frequency of autoantibodies was found in the four sera groups (6% in NOR, 18% in BCH, 38% in DYS, and 64% in ESCC, respectively), the risks to BHC, DYS, and ESCC steadily increased about 3-, 9-, and 27-folds. The sensitivity and the specificity for autoantibodies against the six TAAs in diagnosing ESCC reached up to 64% and 94%, respectively. The area under the receiver operating characteristic curve for the six anti-TAA autoantibodies was 0.78 (95% confidence interval 0.74-0.83). No more increasing in sensitivity was found with the addition of new anti-TAA autoantibodies. A combination detection of autoantibodies to TAAs might distinguish ESCC patients from normal individuals and the patients with esophageal precancerous lesions.

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