

Cancer and Prostate Epithelial Stem Cell

Mark H Smith

Queens, New York 11418, USA
mark20082009@gmail.com

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

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1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start by the abnormal cells grow out of control. Cancers can cause serious illness and death.

A living body can be made up of trillions of living cells. Normal the living body cells grow, divide, and die in an orderly procedure. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries, and other growths stop.

Cancer cells are the cells that grow out of control. Cancer cells can also invade other tissues. Growing out of control and invading other tissues are what makes a cell a cancer cell. In some cases, the cells become cancer cells because of DNA damage.

Literatures

Regenbrecht, C. R., M. Jung, et al. (2008). "The molecular basis of genistein-induced mitotic arrest and exit of self-renewal in embryonal carcinoma and primary cancer cell lines." *BMC Med Genomics* 1: 49.

BACKGROUND: Genistein is an isoflavonoid present in soybeans that exhibits anti-carcinogenic properties. The issue of genistein as a potential anti-cancer drug has been addressed in some papers, but comprehensive genomic analysis to elucidate the molecular mechanisms underlying the effect elicited by genistein on cancer cells have not been performed on primary cancer cells, but rather on transformed cell lines. In the present study, we treated primary glioblastoma, rhabdomyosarcoma, hepatocellular carcinoma and human embryonic carcinoma cells (NCCIT) with mu-molar concentrations of genistein and assessed mitotic index, cell morphology, global gene expression, and specific cell-cycle regulating genes. We compared the expression profiles of NCCIT cells with that of the

cancer cell lines in order to identify common genistein-dependent transcriptional changes and accompanying signaling cascades. **METHODS:** We treated primary cancer cells and NCCIT cells with 50 μM genistein for 48 h. Thereafter, we compared the mitotic index of treated versus untreated cells and investigated the protein expression of key regulatory self renewal factors as OCT4, SOX2 and NANOG. We then used gene expression arrays (Illumina) for genome-wide expression analysis and validated the results for genes of interest by means of Real-Time PCR. Functional annotations were then performed using the DAVID and KEGG online tools. **RESULTS:** We found that cancer cells treated with genistein undergo cell-cycle arrest at different checkpoints. This arrest was associated with a decrease in the mRNA levels of core regulatory genes, PBK, BUB1, and CDC20 as determined by microarray-analysis and verified by Real-Time PCR. In contrast, human NCCIT cells showed over-expression of GADD45 A and G (growth arrest- and DNA-damage-inducible proteins 45A and G), as well as down-regulation of OCT4, and NANOG protein. Furthermore, genistein induced the expression of apoptotic and anti-migratory proteins p53 and p38 in all cell lines. Genistein also up-regulated steady-state levels of both CYCLIN A and B. **CONCLUSION:** The results of the present study, together with the results of earlier studies show that genistein targets genes involved in the progression of the M-phase of the cell cycle. In this respect it is of particular interest that this conclusion cannot be drawn from comparison of the individual genes found differentially regulated in the datasets, but by the rather global view of the pathways influenced by genistein treatment (Regenbrecht, Jung et al. 2008).

Kasper, S. (2008). "Exploring the origins of the normal prostate and prostate cancer stem cell." *Stem Cell Rev* 4(3): 193-201.

Prostate epithelial stem cells (PSCs) are primed by the urogenital mesenchyme to initiate bud formation and branching morphogenesis, ultimately culminating in a glandular structure composed of luminal, basal and neuroendocrine cells. Identity of this cell has remained elusive however cell populations enriched for cells exhibiting stem cell characteristics express the stem cell markers CD133(+), alpha2beta1(hi), CD44 and Sca-1 along with embryonic stem cell factors including Oct-1, Nanog, Sox2 and nestin. Androgens are critical to prostate organogenesis and play a major role in normal prostate function and the development of prostate cancer. Cell lineage is another variable in the development of prostate cancer. This review discusses the embryonic prostate stem cell niche, normal prostate development, isolation and characterization of normal prostate and prostate cancer stem cells, and current concepts on the origin of prostate cancer (Kasper 2008).

Hombach-Klonisch, S., T. Paranjothy, et al. (2008). "Cancer stem cells as targets for cancer therapy: selected cancers as examples." *Arch Immunol Ther Exp (Warsz)* **56**(3): 165-80.

It is becoming increasingly evident that cancer constitutes a group of diseases involving altered stem-cell maturation/differentiation and the disturbance of regenerative processes. The observed malignant transformation is merely a symptom of normal differentiation processes gone astray rather than the primary event. This review focuses on the role of cancer stem cells (CSCs) in three common but also relatively under-investigated cancers: head and neck, ovarian, and testicular cancer. For didactic purpose, the physiology of stem cells is first introduced using hematopoietic and mesenchymal stem cells as examples. This is followed by a discussion of the (possible) role of CSCs in head and neck, ovarian, and testicular cancer. Aside from basic information about the pathophysiology of these cancers, current research results focused on the discovery of molecular markers specific to these cancers are also discussed. The last part of the review is largely dedicated to signaling pathways active within various normal and CSC types (e.g. Nanog, Nestin, Notch1, Notch2, Oct3 and 4, Wnt). Different elements of these pathways are also discussed in the context of therapeutic opportunities for the development of targeted therapies aimed at CSCs. Finally, alternative targeted anticancer therapies arising from recently identified molecules with cancer-(semi-)selective capabilities (e.g. apoptin, Brevinin-2R) are considered (Hombach-Klonisch, Paranjothy et al. 2008).

Shafee, N., C. R. Smith, et al. (2008). "Cancer stem cells contribute to cisplatin resistance in Brca1/p53-mediated mouse mammary tumors." *Cancer Res* **68**(9): 3243-50.

The majority of BRCA1-associated breast cancers are basal cell-like, which is associated with a poor outcome. Using a spontaneous mouse mammary tumor model, we show that platinum compounds, which generate DNA breaks during the repair process, are more effective than doxorubicin in Brca1/p53-mutated tumors. At 0.5 mg/kg of daily cisplatin treatment, 80% primary tumors (n = 8) show complete pathologic response. At greater dosages, 100% show complete response (n = 19). However, after 2 to 3 months of complete remission following platinum treatment, tumors relapse and become refractory to successive rounds of treatment. Approximately 3.8% to 8.0% (mean, 5.9%) of tumor cells express the normal mammary stem cell markers, CD29(hi)24(med), and these cells are tumorigenic, whereas CD29(med)24(-/lo) and CD29(med)24(hi) cells have diminished tumorigenicity or are nontumorigenic, respectively. In partially platinum-responsive primary transplants, 6.6% to 11.0% (mean, 8.8%) tumor cells are CD29(hi)24(med); these populations significantly increase to 16.5% to 29.2% (mean, 22.8%; P < 0.05) in platinum-refractory secondary tumor transplants. Further, refractory tumor cells have greater colony-forming ability than the primary transplant-derived cells in the presence of cisplatin. Expression of a normal stem cell marker, Nanog, is decreased in the CD29(hi)24(med) populations in the secondary transplants. Top2A expression is also down-regulated in secondary drug-resistant tumor populations and, in one case, was accompanied by genomic deletion of Top2A. These studies identify distinct cancer cell populations for therapeutic targeting in breast cancer and implicate clonal evolution and expansion of cancer stem-like cells as a potential cause of chemoresistance (Shafee, Smith et al. 2008).

Tang, Y., K. Kitisin, et al. (2008). "Progenitor/stem cells give rise to liver cancer due to aberrant TGF-beta and IL-6 signaling." *Proc Natl Acad Sci U S A* **105**(7): 2445-50.

Cancer stem cells (CSCs) are critical for the initiation, propagation, and treatment resistance of multiple cancers. Yet functional interactions between specific signaling pathways in solid organ "cancer stem cells," such as those of the liver, remain elusive. We report that in regenerating human liver, two to four cells per 30,000-50,000 cells express stem cell proteins Stat3, Oct4, and Nanog, along with the prodifferentiation proteins TGF-beta-receptor type II (TBR2) and embryonic liver fodrin (ELF).

Examination of human hepatocellular cancer (HCC) reveals cells that label with stem cell markers that have unexpectedly lost TBR1 and ELF. *elf(+/-)* mice spontaneously develop HCC; expression analysis of these tumors highlighted the marked activation of the genes involved in the IL-6 signaling pathway, including IL-6 and Stat3, suggesting that HCC could arise from an IL-6-driven transformed stem cell with inactivated TGF-beta signaling. Similarly, suppression of IL-6 signaling, through the generation of mouse knockouts involving a positive regulator of IL-6, Inter-alpha-trypsin inhibitor-heavy chain-4 (ITIH4), resulted in reduction in HCC in *elf(+/-)* mice. This study reveals an unexpected functional link between IL-6, a major stem cell signaling pathway, and the TGF-beta signaling pathway in the modulation of mammalian HCC, a lethal cancer of the foregut. These experiments suggest an important therapeutic role for targeting IL-6 in HCCs lacking a functional TGF-beta pathway (Tang, Kitisin et al. 2008).

Schulz, W. A. and M. J. Hoffmann (2007). "Transcription factor networks in embryonic stem cells and testicular cancer and the definition of epigenetics." *Epigenetics* 2(1): 37-42.

The stem cell phenotype of human and murine ES cells has recently been shown to be maintained by a self-stabilizing network of transcription factors, NANOG, OCT4, and SOX2. These factors maintain their own and each other's transcription, activating, by combinatorial interactions, genes responsible for the ES cell phenotype while repressing genes required for differentiation. This 'core circuitry' interacts with an 'expanded circuitry' encompassing signal transduction and chromatin regulator proteins. During ES cell differentiation the crucial transcription factors are down-regulated by epigenetic mechanisms, including DNA methylation. Aberrant activation of the ES transcription factor network elicited by increased dosage of an embryonic gene cluster at 12p including NANOG, together with additional genetic and epigenetic alterations, appears to be a crucial event in the genesis of testicular germ cell cancers. Intriguingly, the ES cell transcription factor network fits current as well as past definitions of 'epigenetic' (Schulz and Hoffmann 2007).

Clark, A. T. (2007). "The stem cell identity of testicular cancer." *Stem Cell Rev* 3(1): 49-59.

Testicular germ cell tumors account for 1% of all cancers, and are the most common malignancies to affect males between the ages of 15 and 34. Understanding the pathogenesis of testis cancer has been challenging because the molecular and cellular events that result in the formation of germ cell tumors

are hypothesized to occur during human fetal development. In this review, the molecular pathways involved in human testis cancer will be presented based on our research in human embryonic stem cells (hESCs), and also research using animal models. Testis germ cell tumors are unique in that the normal germ cell from which the tumor is derived has distinct stem cell characteristics that are shared with pluripotent hESCs. In particular, normal fetal germ cells express the core pluripotent transcription factors NANOG, SOX2 and OCT4. In contrast to hESCs, the germ line is not pluripotent. As a result, germ cell tumorigenesis may arise from loss of germ line-specific inhibitors which in normal germ cells prevent overt pluripotency and self-renewal and when absent in abnormal germ cells, result in the conversion to germ line cancer stem cells. At the conclusion of this review, a model for the molecular events involved in germ cell tumor formation and the relationship between germ cell tumorigenesis and stem cell biology will be presented (Clark 2007).

Wilson, H., M. Huelsmeyer, et al. (2008). "Isolation and characterisation of cancer stem cells from canine osteosarcoma." *Vet J* 175(1): 69-75.

There is increasing evidence that cancer is a stem cell disease. This study sought to isolate and characterise cancer stem cells from canine osteosarcoma. One human and three canine cell lines were cultured in non-adherent culture conditions using serum-starved, semi-solid media. Primitive sarcosphere colonies from all cell lines were identified under these conditions and were characterised using molecular and cytochemical techniques for embryonic stem cell markers. Expression of the embryonic stem cell-associated genes *Nanog*, *Oct4* and *STAT3* indicated a primitive phenotype. Sarcospheres could be reproduced consistently when passaged multiple times and produced adherent cell cultures when returned to normal growth conditions. Similarities between human and canine osteosarcoma cell lines add credence to the potential of the dog as a model for human disease (Wilson, Huelsmeyer et al. 2008).

Gu, G., J. Yuan, et al. (2007). "Prostate cancer cells with stem cell characteristics reconstitute the original human tumor in vivo." *Cancer Res* 67(10): 4807-15.

Cancer may arise from a cancer stem/progenitor cell that shares characteristics with its normal counterpart. We report the reconstitution of the original human prostate cancer specimen from epithelial cell lines (termed HPET for human prostate epithelial/hTERT) derived from this sample. These tumors can be described in terms of Gleason score, a classification not applied to any of the transgenic mouse models currently developed to mimic human

disease. Immunohistochemical and Western blot analyses indicate that they do not express androgen receptor or p63, similar to that reported for prostate stem cells. These cell lines also express embryonic stem markers (Oct4, Nanog, and Sox2) as well as early progenitor cell markers (CD44 and Nestin) in vitro. Clonally derived HPET cells reconstitute the original human tumor in vivo and differentiate into the three prostate epithelial cell lineages, indicating that they arise from a common stem/progenitor cell. Serial transplantation experiments reconstitute the tumors, suggesting that a fraction of parental or clonally derived HPET cells have self-renewal potential. Thus, this model may enhance our understanding of human tumor development and provide a mechanism for studying cancer stem/progenitor cells in differentiation, tumorigenesis, preclinical testing, and the development of drug resistance (Gu, Yuan et al. 2007).

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