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## Cancer stem cells and metastasis

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A great deal of excitement has been created in the area of stem cells, with the hope that many currently incurable diseases may in time become curable. Both embryonic and adult stem cells research has recently produced successful results, which may become subjects for drug discovery and disease diagnosis. In spite of significant progress in the early detection and treatment of this malignant disease, "cancer" currently available therapeutic regimens are constrained in their ability to completely eradicate tumors or to prevent recurrence and progression to metastasis. Tumors and distant metastasis often recur, even after completion of therapy. Moreover, existing therapies are relatively non-specific and highly toxic, often killing normally proliferating cells as well as tumor cells. Therefore new cellular and mechanistic insights are needed to decipher why current preventive and therapeutic interventions have limited efficacy, and why tumor metastasis recurs.

The biology of cancer initiation and progression is a very dynamically complex process which involves multiple sequential steps leading to cellular changes, altered signaling pathways, metabolic events and epigenetic alterations. In order to understand these changes at the molecular level, several "omics" based approaches have been utilized. Key signaling pathways involved in cell growth, differentiation and apoptosis have been identified and the expression profiling of specific genes and microRNAs that regulate the expression of these genes involved in these pathways have given us the clue to this phenomena.

One area of increasing importance in the new millennium is the discovery of cancer stem cells (CSCs), a sub-set of tumor generating cells capable of self renewal and of generating pro-genitors and mature cancer cells. Recent research studies describe the occurrences of specific set of "tumor initiating" ("tumor stem") cells within every tissue types in mammals that transform under certain cell signaling pathways into malignant population resulting in aggressive invasiveness, drug resistance and relapse or metastasis of these cancers. Several aspects of cancer stem cell biology could be extremely important in understanding the basis for the limitations in current cancer therapies since modern strategies for cancer drug development do not address cancer from stem cells perspective. The cancer stem cells are resistant to chemotherapy and therefore gives rise to metastasis.

Cancer stem cells are rare cells within tumors with the ability to self-renew and give rise to the phenotypically diverse tumor cell population to drive tumorigenesis. Stanford Scientists (Irv Weissman, MD 1991) isolated human leukemia and human breast cancer stem cells, their efforts are now close to isolating stem cells for brain cancer, ovarian cancer, melanoma and bladder cancer. Dr. Clarke's laboratory was the first to identify cancer stem cells in a solid tumor, breast cancer (Proc Natl Acad Sci USA 100; 3983-8, 2003). His laboratory has subsequently identified cancer stem cells in other solid tumors. These findings can be exploited to improve the outcome of patients with cancers of epithelial origin, the major cause of cancer-related mortality. Earlier using flow cytometry and the mouse model of self renewal, acute

myeloid leukemia stem cells were discovered in 1994. Since then several cancer stem cells have been identified including chronic myeloid, leukemia, breast cancer, multiple myeloma, brain tumor, and prostate cancer.

Of particular significance is the discovery that newly developed and affective drug gleevec was found to be resistance to chronic myeloid leukemia stem cells, leading to the proposal that cancer stem cells (CSCs) should be real target for drug discovery with the hope with the new therapeutics will be able to eradicate the disease. All cancer cells are potential cancer stem cells but have a low probability of proliferation in clonogenic assays. Certain oncogenic mutations within cancer stem cells could permit them to adapt to a different niche, again letting them to increase their numbers and expand their territory. Mutations might allow them to become independent of niche signals altogether, lifting environmental controls on both self-renewal and proliferation.

From initial descriptions on the occurrence of cancer stem cells by Bonnet and Dick using subpopulations of human leukemia cells, much has been achieved in this area. Description of CD34 and absence of CD38 (CD34+/CD38-) as biomarkers, was just the beginning and the list of specific markers have been growing with their structural elucidation and biochemical characterization. The assumption is that the subset of stem cells that can become malignant and show resistance to drugs is very minimal in number (e.g., human leukemia, where as low as 1 CSC occurs in every 10,000 normal cells). The success in finding a cure largely depends on identifying the finite genetic and biochemical reasons triggering CSCs towards uncontrolled growth while circumventing signals that maintain normal cell growth and homeostasis. The results from research globally indicate that there could be several variations within CSC populations and the reasons for this variation are not fully known. It has been proved that several signaling pathways are involved in normal stem cell transformation to CSCs. Several research efforts are underway across the globe for understanding the finite molecular mechanisms regulating signaling networks that orchestrate stemness to evaluate if CSC signaling can be blocked without

compromising normal tissue renewal so that cancer can be eliminated or permanently inhibited. As these reports are very few, there is a need for more taking up research on cancer stem cells. The first conclusive evidence for cancer stem cells was published in 1997 in Nature Medicine. Bonnet and Dick, isolated a subpopulation of leukaemic cells that express a specific surface marker CD34, but lack the CD138 marker. The authors established that the CD34+/CD138- subpopulation is capable of initiating tumors in NOD/SCID mice that is histologically similar to the donor. The ground-breaking discovery of CSC provided evidence for a revisit to the theory of cancer stem cells, which has long-term implications for the efficient and lasting elimination of cancer.

This paradigm shift involves a change from viewing the malignant tumor as a perpetually mutating mass of clonogenic cells to seeing it as an organ mistakenly created by mutations that disrupt cell-signaling pathways in stem cells. Multiple signaling pathways such as Wnt/ $\beta$ -catenin, BMPs, Notch, PTEN, and Sonic hedgehog, and gene products of the Bmi1 have been proved to be involved in the normal stem cell self-renewal. The dysregulation of such pathways could result in the proliferation of CSCs in malignancies. However, dysregulation does not necessarily mean up-regulation or down-regulation of a certain product; it could also indicate selection and activation of a certain pathway through direct mutations or SNP changes. The Bmi1, however, is also expressed in normal stem cells to induce self-renewal. Another example is the genes that encode for APC and  $\beta$ -catenin. These genes are highly expressed in normal stem cells, but they are mutated in colon cancer. The stem cell signaling pathways define and signify the role of the niche, the microenvironment in which the stem cells home to and mature. Tissue regeneration or self-renewal depends on the regulation of proliferation-promoting signals (such as Wnt signaling) versus proliferation-inhibiting signals (such as BMP antigrowth signal) that stem cells receive in the niche. Thus, CSCs may rise from dominant growth-promoting signals in the altered niche, or from intrinsic mutations that make them self-sufficient and independent of the microenvironment.

Differences between normal stem cells and cancer stem cells may provide novel therapeutic targets. This article tries to reason-out the failures of cancer therapies and highlights the new avenues of research which is seen in the theory of "Cancer Stem-cells". Inhibition of self-renewal in CSCs but not in normal stem cells could result in more effective treatments. Mutations might allow stem cells to become independent of niche signals altogether, lifting environmental controls on both self-renewal and proliferation. These oncogenic mutations within CSCs could permit them to adapt to a different niche, again letting them to increase their numbers and expand their territory. Michigan State University researchers have found that a certain gene, expressed within a human adult stem cell, could hold the key to not only offering new hope to cancer patients, but also to answering the question of how cancer originates. The discovery that the gene – known as oct-4 – is expressed in normal adult stem cells, by MSU's James Trosko and colleagues, is detailed in the February issue of *Carcinogenesis* (2006) one of the world's top cancer-research journals. It was already known that the oct-4 gene was located in embryonic stem cells as well as tumor cells, but researchers were uncertain whether it was expressed in adult stem cells. The oct-4 gene is a "regulatory" gene, one whose job is to control the expression of other genes. Forced expression of Bmi1 and constitutively active beta-catenin mutant similarly promoted the self-renewal of hepatic stem/progenitor cells. The transplantation of Bmi1- or beta-catenin-transduced cells clonally expanded from single hepatic stem/progenitor cells produced tumors. These experiments highlight the important roles of Bmi1 and the Wnt/beta-catenin pathway in regulating the self-renewal of normal or cancer stem cells in liver.

Normal tissue stem cells are naturally resistant to chemotherapeutic agents - they have various pumps (such as MDR) that pump

out xenobiotics and drugs, and they also have a slow rate of cell turnover (chemotherapeutic agents naturally target rapidly replicating cells and CSCs escape being targeted- being slow growing). Transformed hematopoietic stem/progenitor cells with an enhanced or acquired self-renewal capability function as leukemic stem cells. In a variety of solid cancers, stem/progenitor cells could be also targets of carcinogenesis. Differences between normal stem cells and CSCs may provide novel therapeutic targets. Inhibition of self-renewal in CSCs but not in normal stem cells could result in more effective treatments. Although the in-vivo cancer diagnosis has not significantly changed for the past three decades, however, in the future it might be possible to trace all cancer cells, including the CSCs to make it possible to for a disease free survival.

A new hope for cancer patients!!!!

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