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Stem cells in the etiology and treatment of cancer

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Using approaches first applied in human leukemias, recent progress has been made in the identification of putative cancer stem cells in several different carcinomas and other solid cancers. Additional studies have suggested that cancer stem cells may be derived not only from transformation of quiescent, long-term stem cells but also from short-lived progenitors that then obtain the ability to undergo self-renewal. Therefore, the heterogeneity observed in many types of human cancers may reflect both the activation of specific oncogenes and/or loss of specific tumor suppressor genes and the different stem and/or progenitor cell populations in which these genetic or epigenetic events occur. Similarities have been observed in the pathways regulating stem cell homing and metastasis, and increasing evidence also suggests that treatment failure and the recurrence of human cancer may reflect the intrinsic quiescence and drug resistance of cancer stem cells.

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Introduction

The concept that stem cells might be important in the etiology of cancer originated more than a century ago (reviewed in [1]). In the past two decades, there has been increasing evidence that tumors might also contain cancer stem cells, rare cells with indefinite proliferative potential that account for the growth of tumors and which might be resistant to conventional therapies. By definition, an adult stem cell is a cell that comes from a given organ, has long-term replicative potential and possesses the ability to both self-renew and differentiate into the cellular components of that organ [2]. This unique property of stem cells to undergo self-renewal divisions is tightly regulated in normal organogenesis, and the de-regulation of self-renewal might be one of the key events involved in carcinogenesis.

Evidence for the existence of cancer stem cells, a limited population of tumor cells also capable of self-renewal and responsible for giving rise to all components of a heterogeneous tumor, was first demonstrated in acute myelogenous leukemia (AML). In pioneering studies by John Dick and his colleagues, it was shown that only a minority of the leukemic cells exhibited the necessary pluripotency to reconstitute tumors in the bone marrow of NOD–SCID (non-obese diabetic–severe combined immunodeficiency) mice [3,4]. Subsequently, a landmark study in 2003 provided proof of principle using mouse models, by demonstrating that inhibiting tumor stem cell self-renewal after deletion of the polycomb gene *Bmi1* could prevent leukemic recurrence [5•].

Until recently, the identification of solid tumor stem cells has remained elusive. In studies of human leukemic cancer stem cells, investigators used FACS (fluorescence-activated cell-sorting) with a set of unique cell surface markers to isolate a subpopulation of tumor cells; these cells were then transplanted into immuno-compromised NOD–SCID mice. Using an analogous approach, Michael Clarke and colleagues employed cell surface markers to isolate a subpopulation of highly tumorigenic breast cancer cells from several human breast cancers, primarily from metastatic pleural effusions [6].

These studies have engendered a great deal of interest both with the scientific community and with clinicians, because they represent a paradigm shift for the development of new cancer treatments. The cancer stem cell hypothesis fundamentally alters the way that we look at cancer recurrence. Using the terms ''cancer stem cells'' or ''tumor stem cells'' to search PubMed for the five-year period between 2001 and the present generates more than 700 citations for articles and reviews. Approximately two years ago, Michael Clarke and his colleagues published a review in *Current Opinion in Genetics & Development*, entitled ''Therapeutic implications of cancer stem cells'' [7]. Thus, our review focuses on progress in this rapidly exploding field over the past two years and discusses several key questions that remain to be answered.

Origin of cancer stem cells

There are several fundamental questions yet to be resolved: what is the cell of origin of cancer stem cells? Are they derived only from transformation of quiescent, long-term stem cells or can short-lived progenitors regain the ability to undergo self-renewal? Because the hematopoietic stem cell lineages are the best characterized, these questions have been addressed primarily in studies of the origin of leukemias. Evidence from the study of AML has revealed that stem-like leukemia-initiating cells that are obtained from various subtypes of

AML exhibiting different stages of differentiation share similar cell-surface markers with the normal long-term hematopoietic stem cells, suggesting that the cancer stem cells originated from the transformed normal stem cells and not from the more committed progenitors [3,8]. This hypothesis has been supported also by functional assays showing that leukemic stem cells, in a similar fashion to hematopoietic stem cells, are arranged as a hierarchy of cells with different self-renewal capacities [9].

By contrast, studies by Weissman and colleagues have suggested that not only the long-term hematopoietic stem cells but also the committed short-lived myeloid progenitors can be transformed and give rise to tumors with comparable latencies, phenotypes and gene expression profiles [10–12]. For example, short-lived myeloid progenitors transduced with the *MLL–ENL* (mixed-lineage leukemia–eleven nineteen leukemia) fusion oncogene gave rise to AML with similar latencies compared with those of prospectively isolated stem cells. These experiments performed using mouse models have been extended to the granulocyte-macrophage progenitors isolated from patients at several different stages of chronic myelogenous leukemia (CML). These studies revealed that activation of β-catenin in CML granulocyte-macrophage progenitors enhanced their self-renewal potential and leukemic activity. A similar conclusion was obtained by Huntley *et al.* [13•], who studied the transformation of committed myeloid progenitors with the leukemic oncogene *MOZ–TIF2* (monocytic leukemia zinc finger protein–transcriptional intermediary factor 2). Similar to the previous studies with *MLL–ENL*, *MOZ–TIF2*, but interestingly not *BCR-ABL* (Breakpoint cluster region–Abelson), was able to induce AML, which could be serially transplanted. Thus, these results support the hypothesis that some, but not all, leukemia oncogenes can confer self-renewal properties to both the committed progenitors and mediate their transformation to leukemia. These studies also suggest that the heterogeneity observed in many types of human cancers may reflect the activation of specific oncogenes and/or loss of specific tumor suppressor genes and the different stem and/or progenitor cell populations in which these genetic or epigenetic events occur [14].

Extension of these studies to solid tumors has been hampered by the lack of detailed markers to characterize cell lineages in both normal tissues and tumors derived from these tissues. Nevertheless, in lung [15], brain [16–18] and prostate [19] — to list a few examples — a variety of different cell surface markers have been identified that enable the functional isolation of stem and/or progenitor cells that can initiate tumorigenesis. Somewhat surprisingly, a subpopulation of highly tumorigenic cells has been isolated also from several immortalized cancer cell lines [20–22].

Drug resistance in stem cells

Stem cells potentially can undergo self-renewal and differentiation throughout the entire lifetime of the organism. Thus, it is not surprising that members of a self-defense system against xenobiotics — members such as ATP-binding cassette transporters — are highly expressed in stem cells. For example, the breast cancer resistance protein (BCRP–ABCG2), a specific ATP-binding cassette transporter, is expressed in a variety of stem cells, such as hematopoietic stem cells, and its expression was greatly reduced in more committed cells as a function of differentiation [23]. Cancer stem cells are believed to maintain this property. Thus, side population (SP) cells, which efflux Hoechst dye, have been suggested to be frequently involved in human AML and may be a target for leukemic transformation [24]. More recently, it has been shown that BCRP was highly expressed in $CD34^+/CD38^-$ cells, a proposed stem cell subpopulation from human normal bone marrow and bone marrow from AML patients, and was actively involved in the drug efflux [25]. Such SP cells also have been identified from a variety of primary cancers, including brain, breast and lung cancer, as well as cancer cell lines [26•]. Research shows that they are enriched in the putative cancer stem cells, and are responsible for the resistance to chemotherapy [27].

ATP-binding cassette protein family members, such as ABCG2, ABCB1/MDR-1 (multi-drug resistance-1), ABCC1, and ABCA2, have been reported to be responsible for the SP phenotype [28,29]. However, $ABCG2^+$ and $ABCG2^-$ cells generated from several cancer cell lines, including those of prostate, breast and glioma, showed similar tumorigenicity [22]. Therefore, further studies need to be done to correlate the expression of other ATP-binding cassette transporters, their contribution to the SP phenotype, and their functional role in the resistance of stem cells to chemotherapy.

Cancer stem cells and clinical significance

Another fundamental question that remains to be answered is, ''what are the key differences between signaling pathways in normal and cancer stem cells that might provide a therapeutic window?'' Elucidation of the mechanisms responsible for the recurrence of the malignant disease is one of the crucial issues in cancer research. In some cancers, such as breast cancers, 25% of recurrences may occur after a period of 10 years, and the properties of these tumors are almost always similar to those of the primary tumors [30,31]. Cancer stem cells, although they may only comprise a very small proportion of the cells within a tumor, are believed to be relatively quiescent, therefore avoiding the toxicity of the anticancer drugs that target the rapidly dividing cells. In addition to the tumor suppressor gene *PTEN* [35] and the polycomb gene *Bmi1* [36], molecular signaling pathways that play a role in normal stem cell self-renewal —

pathways such as Wnt [32], Hh [33] and Notch [34] — also actively participate in cancer development.

For example, Bmi1 is required for maintenance of adult stem cells in some tissues because it represses genes such as *Ink4a* and *Arf* that induce premature cellular senescence and cell death [37,38]. Interestingly, an 11-gene signature has been derived by a comparison of genes involved in the Bmi1-driven pathway in neural stem cells with those involved in metastasis in the TRAMP (transgenic adenocarcinoma of the mouse prostate) mouse model of prostate cancer [39]. This signature has been suggested to represent a subset of highly malignant cancers with a high probability of recurrence. Although the prognostic significance of these studies remains to be validated, they do support the hypothesis that stem and/or progenitor cells may be responsible for both metastasis and cancer recurrence.

A comparison of the pathways regulating stem cell homing with those involved in metastasis may also provide important new insights into the mechanisms involved in both metastasis and quiescence. For example, the SDF1–CXCR4 (stromal cell-derived factor–CXC chemokine receptor 4) axis appears to be a pivotal regulator of not only trafficking of stem cells in the body but also of metastasis [40]. This has led to the hypothesis that migrating cancer stem cells are derived from normal stem cells by genetic alterations that influence both 'stemness' and epithelial–mesenchymal transition [41•]. In this regard, elevated Hh pathway activity has recently been reported to distinguish metastatic from localized prostate cancer [42•], potentially as a consequence of increased Smoothened expression. Furthermore, Beachy and his colleagues have suggested that *Bmi1* may be a downstream target of the Hh pathway.

So, is it possible to selectively target these pathways involved in cancer stem cell self-renewal? Treatment of mice, with Hh pathway inhibitors, such as cyclopamine [43] or cyclopamine analogs [44], inhibits the growth of medulloblastomas in both xenograft and genetically engineered mouse models, without any apparent toxicity. Thus, in the absence of tissue injury or inflammation, the Hh pathway may be inactive in most normal adult tissues [33], thus minimizing the toxicity of these inhibitors. Inhibition of the Notch pathway with specific gamma-secretase inhibitors provides another potential target to inhibit cancer stem cell self-renewal, although in this case a potential toxicity may be goblet cell metaplasia [45].

Additional approaches may include the identification of markers that are differentially expressed on cancer stem cells. For example, a $CD34^+/CD38^-$ subpopulation in hematopoietic stem cells and leukemic stem cells expressed different cellular markers, with Thy-1 and c-kit only expressed on hematopoietic stem cells [46,47], and IL-3 (interleukin-3) receptor α-chain uniquely on leukemic stem cells [48]. Further studies identifying cancer stem cells from different types of tumors and performing comparative gene expression profiles with their normal stem cells counterparts may help identify potential therapeutic targets. The key to these studies will derive from an understanding of the factors and pathways regulating normal development and stem cell renewal. For example, adult human stem cells, immortalized non-tumorigenic cells, and tumor cells and cell lines, but not differentiated cells, have been reported to express Oct-4 (Octamer-4), a transcription factor known to be important for pluripotency in embryonic stem cells [49]. Oct-4 expression has also been observed in highly tumorigenic $CD44^+/CD24^-$ breast cancer initiating cells [20]. Interestingly, overexpression of Oct-4 has been shown recently to result in dysplastic growths of epithelial tissues that normally depend on its continuous expression [50]. The significance of these observations in most human cancers remains to be determined.

Finally, it is also likely that differences between normal and cancer stem cells may reflect post-transcriptional as well as post-translational modifications. Thus, one potential target, which has been used to isolate tumorigenic breast cancer cells, is the adhesion receptor CD44, which displays extensive differential splicing in normal cells and tumors [51]. Thus, it is conceivable that cell surface epitopes, which differ on normal and cancer stem cells, may provide selective targets for antibody-based therapies.

Conclusions

Despite the explosion of new information and the exponential number of publications in the past few years in the 'cancer stem cell' field, much remains to be learned. There is a need for better cell-lineage markers for the multiple cell types present in most tissues, and for better reagents to facilitate the isolation of these cells in order to enable the identification of the cells of origin for the different subtypes of cancers. Little information is currently available about the nature of the stem cell niche and the pathways regulating quiescence and self-renewal in both normal tissue stem cells and cancer stem cells. In summary, although recent progress has been encouraging, the differences in signaling pathways in normal and cancer stem cells need to be elucidated to provide new therapeutic targets with the eventual goal of eliminating residual disease and recurrence.

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