Cancer Stem Cells - An Overview

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ABSTRACT
Cancer stem cells (CSC) have the ability to self-renew and are present in most tissues including breast, brain, lung, prostates, testis, ovary, esophagus, colon, and liver. Their origin is yet to be discovered, though a series of hypotheses have been proposed in this regard. CSCs play a role in not only the creation of cancer but also in its evolution, metastasis, and recurrence. CSCs have an important role in cancer therapy and the resistance towards chemotherapeutical agents. Acquisition of stemness involves epithelial–mesenchymal transition (EMT), in which epithelial cells are transformed into a mesenchymal phenotype characterized by increased capacities for migration, invasiveness, and resistance to apoptosis. EMT may also contribute to metastasis by driving dissemination of mesenchymal CSCs to distant locations, whereupon the CSCs revert to an epithelial phenotype to support metastatic tumor growth. Several different approaches to treatment aimed at overcoming the intrinsic resistance of CSCs to conventional therapies are currently being developed. These include agents targeting tumorigenic pathways, such as JAK2/STAT3 and PI3K/mTOR, and immunotherapies, including vaccines and natural killer cells employed to induce a T-cell response.

Keywords: Cancer stem cells, Metastasis, Recurrence, Resistance, Tumor microenvironment.


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INTRODUCTION
Cancer stem cell (CSC) hypothesis assumes the hierarchical cellular structure of a tumor, analogous to normal tissue. The three basic functional groups of cells are stem cells, progenitor cells, and mature cells.1 Stem cells are a minor population. They are able to self-renew and differentiate toward mature cells.1 Stem cells rarely divide to give descendant stem cells or progenitor cells. The latter (also known as progenitors or transit-amplifying cells) proliferate intensively.

Their descendants have a more restricted potential and are able to differentiate toward a certain type of mature cells. Progenitors have reduced the capacity of self-renewal with a limited number of divisions, in contrast to stem cells which can divide throughout the lifespan of the organism.3 Mature cells are the last stage of cellular development. Having lost the ability to divide, they contribute to the role of the tissue which they form. Normal tissue is characterized by a fixed number of cells. Dying mature cells are replaced by newborn mature cells derived from progenitors. This process is strictly controlled by mutual interactions between every cell forming the tissue. The delicate equilibrium is disturbed in carcinogenesis. Cancer progenitor proliferation gets out of control and the number of cells increases, which is one of tumor defining features.

CSC are cells that drive tumorigenesis, as well as giving rise to a large population of differentiated progeny that make up the bulk of the tumor, but that lack tumorigenic potential. CSCs have been identified in a variety of human tumors, as assayed by their ability to initiate tumor growth in immunocompromised mice.4,5 Further characterization studies have demonstrated that gene expression profiles in breast cancer correlate with patient prognosis, and brain CSCs are specifically resistant to radiation through DNA damage repair. In addition, specific signaling pathways play a functional role in CSC self-renewal and/or differentiation, and early studies indicate that CSCs are associated with a microenvironmental niche.6-8

ORIGIN OF CSCs
The fundamental concept underlying the CSC hypothesis is that not all tumor cells in a cancer are equal.9 The CSC hypothesis is fundamentally based on the application of stem cell concepts derived from embryogenesis to understand the tumorigenic process.

The following are key features of the CSC hypothesis:
1. Only a small fraction of the cancer cells within a tumor have tumorigenic potential when transplanted into immunodeficient mice,
2. The CSC subpopulation can be separated from the other cancer cells by distinctive surface markers,
3. Tumors resulting from the CSCs contain the mixed tumorigenic and non-tumorigenic cells of the original tumor, and

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4. The CSC subpopulation can be serially transplanted through multiple generations, indicating that it is a self-renewing population. Therefore, CSCs are capable of self-renewal and differentiating into other distinctive cells that make up the tumor mass.\[^9\]

**ORAL CSCs**

It is found that CSCs also play a central role in the pathogenesis and progression of carcinomas of head-and-neck squamous cell carcinoma (HNSCC), including oral SCC (OSCC), have been found. Early tissue culture studies showed that only a subpopulation of OSCC cells can form expanding tumor colonies, suggesting that human OSCC may contain some form of stem cells and it was subsequently shown that only a small subpopulation of the cells in OSCC corresponds to tumor-initiating cells concept that the tumor mass is a mixture of (a) CSCs dividing themselves to feed the tumor’s growth, (b) transient amplifying cells that divide themselves a few times before maturing into, and (c) differentiated tumor cells that do not contribute to tumor growth.\[^5,7\]

The isolation of CSCs from oral cancers has mainly been performed with the CD44 marker that was initially used to isolate breast cancer CSCs. CD44 is an adhesion molecule that binds itself to hyaluronan, and its expression is necessary for the maintenance of the CSC properties. CSCs lose their “stemness” when CD44 is experimentally reduced to 44. However, a problem with CD44 and also with all other CSC has therefore been sought. Aldehyde dehydrogenase 1 (ALDH1) is an intracellular through the oxidation of aldehydes, and ALDH-positive cells in HNSCC are reported to have typical CSC behavior and increased tumorigenic ability. The combination of CD44 with other markers, such as ALDH1, may improve the specificity of CSCs’ recognition and isolation.\[^8\]

**ISOLATION AND IDENTIFICATION OF CSCs**

The isolation of the minority of CSCs from mass tumor tissues or cell lines and the identification of the stem-like CSCs by diverse methods will be quite important to researches of tumor initiation, tumor development, and tumor diagnostics and therapeutics. Since CSCs and normal stem cells have much in common, we can also use the stem cell properties, such as the expression of specific surface markers, to isolate and identify CSCs.

Up to now, we usually take advantage of these features, namely, the sphere forming ability in non-adherent medium, dye exclusion ability which is because of the over-expression of efflux transporters, expression of specific cell surface markers and signalling pathways, intracellular enzyme activity, and clonogenicity, to isolate the CSCs.\[^10-14\]

Thus, there are several *in vitro* assays to identify CSCs, such as sphere-forming assays,\[^15\] Hoechst Dye Exclusion (SPcells), detection enzymatic activity of ALDH1, detection of surface markers, signaling pathway identification, serial colony-forming unit assays (replating assays), label-retention assays, and migration assays.\[^16,17\]

However, *in vitro* assays alone are not enough to demonstrate that the cells we detect are CSCs, for normal stem cells, or progenitors may have the same characteristics as CSCs and these assays cannot show tumor propagation. Thus, *in vivo* assays are regarded as the gold standard, including serial transplantation in animal models, which can complement and enhance the ability of *in vitro* assays to identify CSCs. However, improved and optimized methods need to be developed to identify CSCs. However, improved and optimized methods need to be developed to identify CSCs.

**STEM CELLS AND HETEROGENEITY**

Tumors are heterogeneous, but the mechanisms underlying this are unclear. Heterogeneity may result from mutations occurring early or late in a stem cell’s maturation. For example, chronic myeloid leukemia is believed to derive from an early stem cell progenitor because its cytogenetic marker (BCR-ABL) is present in several cell lineages, for example, lymphoid, myeloid, and platelet cells. However, acute promyelocytic leukemia may result from an abnormality in a late stem cell progenitor in the myeloid lineage at the promyelocytic stage. Tumors derived from an early stem cell may develop a more heterogeneous phenotype and have an increased metastatic potential. Mutations in late progenitor stem cells may lead to tumors of a single cell type with reduced metastatic potential.\[^9\]

As recently shown in an experiment by Liu *et al.*, the mammary gland develops by differentiation from its mammary stem cell.\[^18\] A diverse range of breast cancers may, therefore, develop depending on where a mutation occurs in this pathway.\[^19\] Consequently, a stem cell model for estrogen receptor (ER) expression in breast cancer has been proposed, dividing breast cancer into three types, in an attempt to explain how ER-positive, ER-negative, or heterogenous receptor status tumors can be created by mutations in the stem cell or progenitor cell populations.\[^20,21\] In early fetal life, stem cells are ER negative, but presumably under the influence of environmental factors including estrogen, progenitor cells that are both ER positive and ER negative can be identified at various times during growth, in particular, during puberty and pregnancy.\[^22\]
Identification of gastric cancer

The identification of CSCs has potential therapeutic implications. As stem cells are important for tissue growth and repair, they have developed highly efficient mechanisms for resistance to apoptosis. Many have overexpression of antiapoptotic genes such as Bcl-2 and may express drug-resistance transporter proteins such as multidrug resistance and ABC transporters. These mechanisms permit normal stem cells to become resistant to chemotherapy. It has been proposed that CSCs also express these proteins at higher levels than the bulk population of tumor cells and may be more resistant to chemotherapeutic agents, permitting the repopulation of tumors after chemotherapy. Developing targeted therapies that are selectively toxic to CSCs while sparing normal stem cells may lead to more effective treatment options for eradicating this crucial population of cells.

There has been much interest in microarray analysis of tumors, allowing tumor subtyping, the development of prognostic and predictive markers, and the possibility of developing specific tumor treatments. The identification of stem cells in acute myeloid leukemia, breast cancers, and central nervous system tumors raises the possibility that decision-making on the basis of microarray analysis of the bulk tumor population may not be entirely appropriate because the gene expression profile of the CSC may be different to the rest of the tumors. By comparing gene expression profiles of CSCs, the bulk tumor cell population, normal stem cells and normal tissue, it may be possible to identify therapeutic targets that preferentially attack CSCs. Understanding CSC biology may lead to insights into the causes and treatment of tumor metastasis. The metastatic ability of a tumor cell may be related to properties of the stem cell of origin. For example, the cytokine receptor CXCR4 is expressed on hematopoietic stem cells and interacts with cytokines CXCL12/SCDF that are secreted by bone marrow stromal cells. This attracts hematopoietic stem cells to the bone marrow. The CXCR4 cytokine is also overexpressed on metastatic breast cancer cells.

CONCLUSIONS

The recognition of CSCs as a major component and driver of key processes in cancer progression, such as tumor growth, recurrence, metastasis, and treatment resistance, constitutes a landmark discovery in cancer research. The evolving CSC model is helping to explain a variety of unresolved questions, such as why the destruction of non-stem cancer cells of the tumor bulk may be associated with little or no improvement in patient outcomes. Recent discoveries concerning the centrality of CSC in cancer offer researchers a conceptual framework that is vital to decode previously unexplained processes in cancer pathophysiology and offers new approaches and new targets for cancer treatment.

REFERENCES


