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A concise review on the definitions of cancer stem cells

Abstract

Although the notion of proposing and investigating cells that might possess a vague biological capacity of "Stamm (phylum)" could be traced back to the late nineteenth century, such endeavors were mainly focused on searching for cells capable to produce the germline or the entire blood system. Influenced by the original reasoning tracks, contemporary research outcomes not only scientifically engendered definitions of stem cells for normal developmental and metabolic biology processes but also definitively outlined this concept for varied pathological cell events including oncogenesis. However, due to the complexity and fundamental life-origin mechanisms involved, presently there are ongoing debates regarding the conceptual essentials of stem cell-like tumor initiation cells. This paper aims to give a succinct review about the evolvement of the concepts and current definitions of cancer stem cells (CSCs).

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Background

It has been viewed in the field of developmental cell biology that one of the earliest academics who proposed the nomenclature of "stem cell" was Ernst Haeckel (1834-1919). He, in a set of published lecture notes, described protozoa (i.e., unicellular organisms) as "stammzellen" (stem cells) for their phylogenetic potential to give rise to all cell types needed to form different biological species.[1,2] The reasoning was largely based on the analytical tracking of the embryological developments of fertilized egg cells. This together with findings in research work on hematopoiesis and leukemia in the beginning of the 20th century led to more specific characterization of stem cells, emphasizing a central capacity of self-renewal and phenotypic differentiation.

Also during the late 19th century, scholars speculated that either malformation or tumorigenesis might be caused by errors of embryonic developmental cells, inferring possible links between embryonic stem cells and normal or cancer-like growth.[3] Around the period of World War II, important elements of embryonic theory of tumor formation (e.g., the displacement of embryonic cells) were challenged by experimental evidence.[4] In the 1950s and early 1960s, it was the systematically expanded investigations on murine teratomas cells that promoted isolation and basic characterization of mouse embryonic stem cells. This helped to engender the stem cell theory of cancer.[5] Efforts in the following years resulted in tangible isolation and *in vitro* maintenance of mouse embryonic stem cells in the early 1980s.[6,7] Taken together with uncovering human neural stem cells[8] and human embryonic stem cells,[9,10] these advancements opened the contemporary chapter of stem cell research.

Interestingly, the modern course of teratoma-triggered stem cell research was paralleled with that of the conceptual establishment of the cancer stem cell identity in the 1960s. As examples, Kleinsmith & Pierce[5] reported that donor embryonal carcinoma cells could differentiate into somatic tissues and embryonal carcinoma as well.[5] It was found that merely 0.1-1% cells in mouse myeloma could actually form clones *in vitro*; after transplantation in NOD/SCID mice, only 1-4% of the leukemia cells grew into colonies in the spleen.[11] The data, in certain degrees, were similar to what was observed in irradiated mice after administration of bone marrow cells, in that nodules were also found in post-mortem spleens. In fact, the nodule number was found to be proportional to the dose of bone marrow cells injected. The investigators concluded that each individual nodule might be a cell colony derived from a single hematopoietic stem cell (i.e., colony-forming unit - CFU).[12] These results combinatorially suggested a possibility that a very small fraction of tumor cells might be responsible for tumorigenic, i.e., stem cell-like tumor initiating activities, further validating the cancer stem cell concept.

In the middle 1970s, the afore-described work was instrumental for helping formulate the clonal evolution theory of cancer growth, with the latter being additionally enriched by the discovery that most human cancers were linked with mutations in oncogenes and tumor suppressor genes.[13] For instance, the clonal evolution model for colon cancer proposed by Fearon & Vogelstein[14] described that the progression from early adenoma to invasive carcinoma might result from the stepwise acquisition of mutations in specific oncogenes.[14] Conceivably, the biology of clonal evolution offered a genetic underpin in regards to a subpopulation of tumor cells' ever escalating malignant behavior detected in a given solid tumor mass. Whereas colon cancers exhibited a generally linear tumor evolution with stepwise genetic mutations with inactivation of APC (adenomatous polyposis coli) as the most common gene mutation,[14] breast cancers manifest discernible levels of intratumor heterogeneity (e.g., HER2 amplification, mutant PIK3CA, etc.).[15] Moreover, oncological heterogeneity was identified in leukemia. Researchers found that almost all subtypes of acute myeloid leukemia (AML) could develop in immunodeficient mice following engraftment of $CD34^{+}CD38^{-}$ fractions of AML cells (i.e., acute myelogenous leukemia stem cells: LSCs); frequency analysis determined that LSCs are present on the order of one per million tumor cells.[16]

The concept of CSC (cancer stem cell)/TSC (tumor stem cell) was systematically evaluated and proposed at the beginning of the 21st century, which was built upon the hypothesis that developmental

signaling pathways governing regular stem cells may also work for CSC.[17] The modernized concept defines CSCs as rare tumor cells that hold infinitive potential for self-renewal, being primary driving force of tumorigenesis. Indeed, only as few as ~100 $CD44^{+}CD2^{4-/low}$ lineage cells isolated from solid breast cancer in humans were required to form neoplastic masses in the mouse, showing sharp contrast in tumorigenic power between CSCs and tumor cells of other phenotypes that failed to grow tumor even under thousands fold higher quantities.[18] The consensus definition of a CSC was first reached at the 2006 American Association of Cancer Research Workshop on Cancer Stem Cell, i.e., CSCs should possess the properties of tumorogenicity, self-renewal capacity, multi-lineage differentiation potential to generate the heterogeneous lineages of cancer cells that comprise the tumor, continuous passage ability, and unique and reliable surface markers.[19,20]

Current definitions of cancer stem cells

Research work underlined by the CSC concept has to date determined a whole variety of different sets of CSC markers. For examples, presently recognized markers for glioma CSCs are CD15, CD90, CD133, nestin, and integrin-α6; for ovarian CSCs, CD44, ALDH, CD117, CD133, and CD24; for malignant melanoma CSCs, ABCB5, ALDH1, CD20, CD133, and CD271; and for breast CSCs, ALDH1, CD44, CD24, CD90, and CD133. Overall, CD133 is one of the most commonly shared CSC markers among different types of malignant tumors. The fact additionally supports the speculation of the existence of a subpopulation of tumor cells as stem cell-like cancer initiation cells.[21]

Based on the current CSC models, researchers have been trying to more effectively elucidate causes of neoplasm recurrence, metastasis, and drug resistance. Since CSCs were observed to retain properties of hibernation and/or slow division, as well as resistance to conventional oncolytic treatments, they are postulated to play pivotal roles in tumor recurrence. Indeed, a sub-group of CSCs has been believed to act as tumor metastasis (or drug resistance)-initiating cells (MIC) for their tumorigenicity and migration capabilities (e.g., expression of EMT marker: Epithelial Mesenchymal Transition).[22]

Although the evidence keeps growing that progressively confirms the existence of CSCs, data questioning CSC validity as an oncological event have continuously been presented, primarily focusing on discrepancies observed regarding the biological characteristics, phenotypes, genetic profiles, and subpopulation proportions of the so called original CSCs. As examples, there were published results that experimentally demonstrated that all colonies derived from randomly selected single cells from murine lung and breast cancer cell lines could form tumors following allografting in histocompatible mice.[23] On the other hand, there are persistent frustrations felt by some conventional stem cell biologists who believe that fundamental developmental biology principles prevent application of the stem cell concept in characterizing oncological processes. Nevertheless, based on leading doctrines in the field the following points succinctly summarize the current definitions of CSCs.[24]

I. Cancer stem cells may directly derive from normal stem cells via genetic mutation. Thus, these cells have the ability for self-renewal and differentiation into all heterogeneous tumor cell phenotypes.

II. Cancer stem cells may directly derive from normal progenitor cells that may acquire stemness biology through further accumulation of genetic abnormalities and/or abnormal epigenetic modifications.Cancer stem cells may directly derive from normal developing or adult cells via genetic mutations. This hypothetic pathway is partially supported by the success in making the induced pluripotent stem cells (iPS) by introducing only four (or either less or more) transcription factors into adult cells to enable them to regain the ability of self-renewal and pluripotency. In fact, by stable expression of hTERT, H-RasV12, SV40LT and ST antigens, human skin fibroblasts could be reprogrammed *in vitro* to have properties of CSCs that, post transplantation, formed tumor cells showing pathological heterogeneity.[25]

III. Data analyses of thermal conditioning of glioblastoma cells[26] and mathematical modeling suggested that stem cell-like tumor initiation cells may not be a fixed population of neoplasm cells. Instead, CSC capacities including expressions of representative markers may likely be a group of transient oncological events occurring in a subpopulation of cancer cells when induced by (or interacting with) environmental, epigenetic, and genetic impacts.[26,27]

IV. Cancer stem cells can emerge under varied combinatorial regimens that comprise the aforementioned mechanisms.

With the introduction of the fourth and fifth definitions of CSC, data previously used as evidence to question real existence of the so called CSCs have now turned to be valuable to further enrich this concept. Specifically, it was reported that CSC composition ratio in given tumors could range from 0.2% to 82.5%. Moreover, using standardized limiting dilution assays researchers found that this ratio increased in breast cancers along their Stage I to Stage III progression. By contrast, for stage III-IV melanomas, tumorigenic cells ratio could remain around 30%.[28] Studies also showed that CSCs of the same tumor could carry overlapping, non-overlapping, or different characteristic markers.[29,30] Therefore, instead of being taken as evidence discrepancy against the CSC concept, such data corroborates the notion that the CSC features such as expression of representative markers may actually be a set of transient stem cell-like capabilities possessed by a selected population of cancer cells.[26,27] However, cautions and efforts are needed to further investigate the CSC-related oncological phenomena since there were reports suggesting that the specific molecular mechanisms underlying tumor cell stemness were unstable. Such observations of genetic instability indicate a real possibility that different new parental CSC lines may continuously be produced in certain types of malignant tumors, explaining why expressions of some CSC markers in certain tumor cells are time dependent.[31]

Summary

There appears to be adequate experimental and clinical data that validate the genetic, epigenetic, and phenotypic heterogeneity of cells in malignant tumors. Although questions remain in regards to the consistency and expression levels of CSC markers as well as complexity of CSC oncology, they have not been able to shake the foundation of the CSC concept. The current CSC model describes tumor generation capabilities of subpopulations of self-renewable and differentiable cells that drive tumor progression via producing genetic, epigenetic, and phenotypic heterogeneity. Conversely, based on the feature of "functional multipotency" identified in normal stem cells,[8,32] future studies should focus more on investigating functional capacity of CSCs, exploring consequences of non-genetic variability, rare clones, clonal dynamics, and functional interactions among CSC

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clones within a given tumor and/or with host microenvironment. Such undertakings will help illuminate the oncological and biological essentials of CSCs in terms of their impacts on the host, providing crucial targets for developing efficacious cancer therapies.

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Conflict of interest

The author declares no conflict of interest.

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