Review Article

Cancer stem cells

From characterization to therapeutic implications

Nehad M. Alajez, *MSc, PhD.*

ABSTRACT

تفترض نظرية الخلايا الجذعية السرطانية أو المشار إليها أحياناً بنظرية الخلايا السرطانية المنشئة أن أورام السرطان منظمة بشكل هرمي، حيث تتواجد الخلايا الجذعية السرطانية على قمة الهرم. يمكن تعريف الخلايا الجذعية السرطانية وظيفياً من خلال قدرتها على تجديد الذات والتمايز لإعادة إنشاء الشكل الهرمي للسرطان الذي جاءت منه. وتشير نتائج الأبحاث الطبية التي قمنا بجمعها إلى أن الخلايا الجذعية السرطانية قد تكون ذلك الجزء من الورم الذي يقاوم العلاجات التقليدية للسرطان، لذلك تقدم نظرية الخلايا الجذعية السرطانية رؤية جديدة لتفسر أسباب تفاقم مرض السرطان والانتكاس الذي يحدث أحياناً بعد العلاج. سنقوم في هذا المقال بتقديم ومناقشة آخر الأبحاث المنشورة في هذا المجال مع التركيز على أثر هذه النظرية على مرض السرطان من الناحية السريرية.

The cancer stem cell (CSC), or alternatively referred to as the tumor initiating cell (TIC) model, proposes that human cancers are organized in a hierarchical structure with the CSC at the apex. Cancer stem cells are functionally defined by their ability to self-renew, and to recapitulate the hierarchy of the original tumor from which they were derived. Emerging data from the literature suggest that CSCs might be the fraction within the tumor that resists conventional therapies; hence, the CSC paradigm provides new insight into tumor progression and relapse. Herein, we provide literature review of the CSC model, with emphasis on the translational and clinical implications of this model.

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From the Department of Anatomy, Stem Cell Unit, College of Medicine, King Saud University, Riyadh, Kingdom of Saudi Arabia.

Address correspondence and reprint request to: Dr. Nehad M. Alajez, Department of Anatomy, Stem Cell Unit, College of Medicine, King Saud University, PO Box 2925, Riyadh 11461, Kingdom of Saudi Arabia. Tel. +966 (1) 4679421. Fax. +996 (1) 4671300. E-mail: nalajez@ksu.edu.sa

In normal tissues, cell division is a complex cellular process that is tightly regulated at several levels, hence, a delicate balance between cell death and cell division is essential to maintain the dynamic steady state of the organ, and the overall health of the organism. When normal cells accumulate sufficient genetic and epigenetic alterations leading to the over-expression of tumor promoting genes (oncogenes), and the down-regulation of tumor suppressor genes, this fine regulation of cell division is lost, leading to cellular transformation and cancer development. Therefore, cancer can be described as a group of diseases, in which normal cells lose their ability to regulate cell proliferation manifested by uncontrolled cellular growth at the primary site, and is oftentimes presented with metastasis. Despite recent advances in cancer management and therapy, cancer remains the second leading cause of death worldwide, underscoring the need for better understanding of tumor biology and therapy failure. Genetic, epigenetic, and the tumor microenvironment have all been implicated in tumorigenicity; however, the exact cellular and molecular mechanism(s) that drive disease progression and patient relapse are still largely unknown. Tumor heterogeneity is a hallmark of cancer, which has been the subject of heavy investigation by several research groups. In addition to intertumor (between different tumors) heterogeneity, a number of studies have clearly demonstrated significant intratumor (within the same tumor) heterogeneity at the gene expression and functional levels.[1-4] Therefore, 2 models have been described to explain the functional heterogeneity of tumors.[5] The stochastic model proposes that all tumor cells are biologically equivalent, which could potentially be endowed with tumor initiating activity due to intrinsic and/or extrinsic factors. On the

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other hand, the cancer stem cell (CSC), or also referred to as the tumor initiating cell (TIC) model, proposes that tumors are heterogeneous, but only a small fraction of the tumor cells (CSC) is tumorigenic. In this review, we provide historical overview of the CSC model and its therapeutic implications.

Cancer stem cell model. Experiments performed in the early 1960s demonstrated that the frequency of the tumor-forming cells in a murine tumor model was very low,[6] but not until recent years when technical advances allowed us to isolate populations of tumor cells based on the expression of specific surface marker, it was then feasible to demonstrate that transplantation of only a small fraction of tumor cells with defined surface markers was sufficient to establish tumor in vivo. Therefore, the landmark work carried out by Dr. John Dick group was the first to demonstrate without ambiguity that in human acute myelocytic leukemeia (AML), leukemia cells with the phenotype CD34+CD38- were the fraction capable of initiating and maintaining leukemia in non-obese diabetic/severe combined immunodeficient (NOD/SCID) mice.[7,8] Thereafter, CSC or alternatively referred to, as the tumor initiating cell (TIC) concept has emerged. By definition, a CSC has to fulfill 2 criteria. First, it has the capacity to self-renew, which is oftentimes measured by serial transplantation in immunocompromised mice, or using an in vitro sphere forming assay under low attachment culture conditions. And second, it has the capacity to differentiate and recapitulate the hierarchy of the original tumor from which they were derived, with the CSC at the apex of this hierarchy (**Figure 1a**).[9] Using a similar paradigm to that utilized in leukemia, Al-Hajj et al[10] were the first to identify the CSCs from solid tumor by defining CD44+CD24-/lowLin- phenotype as the fraction of human breast cancer that harbors the CSC population. Since then, the past several years witnessed huge interest in the CSC field, which led to the isolation and characterization of the CSCs from several other human cancers including the brain, prostate, colon, pancreas, head and neck, liver, ovarian, lung, melanoma, and human B-precursor acute lymphocytic leukemia (B-ALL).[11-22] An up-to-date list of the surface markers used to isolate the CSCs from different human cancers is provided in **Table 1**.

Cellular origin of the cancer stem cell. Cancer stem cells are functionally defined by their ability to sustain and propagate the tumor, however, the cellular origin of the CSC remains elusive. Initially, it was hypothesized that CSC might arise from a normal stem cell based on the assumption that normal stem cell are the ideal candidate for transformation, given their longevity, which allows them to accumulate sufficient genetic hits and to transform.[9] Emerging data from the literature

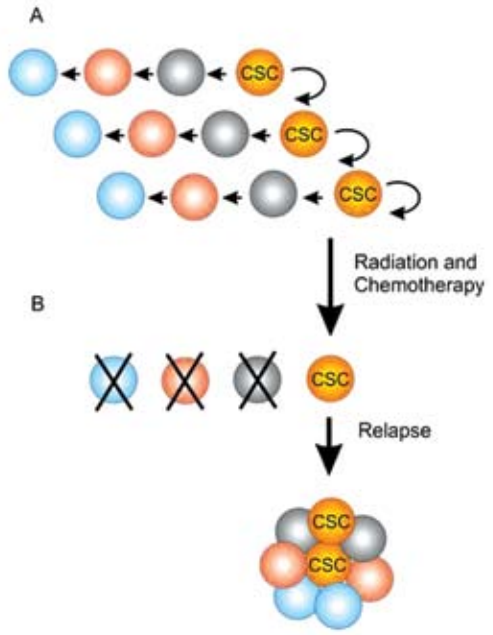

Figure 1 - Schema depicting the hierarchical organization of tumors as per the CSC model. **a)** According to the CSC model, tumors are maintained by a rare population of tumor cells (CSC), which has the capacity to self-renew (curved arrow) and to differentiate (horizontal arrow) and give rise to the bulk of the tumor. **b)** CSCs are thought to be the fraction within the tumor that resists conventional therapies, recapitulate the original hierarchy of the tumor, and cause relapse.

Table 1 - Surface markers used to isolate the cancer stem sells (CSC) from different human cancers.

Tumor site	CSC marker
AML[8]	$CD34^+CD38^-$
Breast[10]	$CD44^+CD24^{-/low}Lin^-$
Prostate[15]	$CD44^+\alpha_2\beta_1^{hi}CD133^+$
Brain[11]	$CD133^+$
Colon[12]	$CD133^+$
Colon[13]	$EpCAM^{high}CD44^+$
Head and neck[18]	$CD44^+$
Pancreas[16]	$CD44^+CD24^+ESA^+$
Pancreas[17]	$CD133^+$
Lung[14]	$CD133^+$
Liver[19]	$CD90^+$
Liver[58]	CD133+
Melanoma[20]	ABCB5
Melanoma[59]	$CD20^+$
Melanoma[60]	$CD271^+$
Melanoma[61]	$CD133^+$
Ovarian[21]	$CD44^+CD117^+$
B-precursor acute lymphocytic leukemia (B-ALL)[22]	$CD34^+CD38^{+/-}CD19^+$

AML - acute myelocytic leukemeia, Lin - lineage surface markers, EpCAM - epithelial cell adhesion molecule, ESA - epithelial specific antigen, ABCB5-ATP - binding cassette beta 5

however, suggest that the CSC model could be bi-directional. In an elegant study conducted by Jamieson et al,[23] activation of the beta-catenin pathway in the granulocyte-macrophage progenitor (GMP) population during the crisis phase in chronic myelocytic leukemia (CML) was shown to enhance the self-renewal potential of GMP cells, making them the likely origin of CSC in CML. In another study, Mani et al[24] assessed the contribution of epithelial-mesenchymal transition (EMT), which is a process oftentimes activated during cancer progression and metastasis to CSC development. Interestingly, the authors observed that induction of EMT in an immortalized human mammary epithelial tumor model led to the acquisition of a CSC-like phenotype, suggesting a possible role for EMT in CSC development. In an independent study,[25] normal and cancerous differentiated human mammary epithelial cells were shown to spontaneously switch into a stem-like state in vitro and in vivo, further supporting the de-differentiation model. This concept is also supported by the finding that normal differentiated somatic cells could be easily reprogrammed, and induced to de-differentiate into stem cell-like state by the re-expression of defined set(s) of genes.[26] Therefore, it is conceivable to state that CSC in different human cancers could arise from a normal stem cell that accumulated sufficient genetic hits, or/and from a more differentiated cell that acquired a self-renewal potential.

Controversies over CSC model. Despite the existence of substantial evidence in the literature documenting the isolation and characterization of CSCs from different human cancers, there are still some controversies over this paradigm. Cancer stem cells are functionally defined by their ability to form tumor when serially transplanted into immunocompromised mice, therefore, the question remains as to whether the so called "CSC" are indeed the population of cells that drive tumor progression in humans, or whether those cells just happen to be more adapted to growing in the NOD/SCID host because of a permissive microenvironment. This debate initially arose from the finding that in melanoma patients, when using a more permissive mouse model, the NOD/SCID interleukin-2 receptor gamma chain null (NOD/SCID IL2Rg-/-), for the transplantation experiment, the frequency of the CSCs was found to be much higher than previously reported in the literature.[20,27] In fact, the authors demonstrated that even a single melanoma cell could form a tumor when transplanted into this more permissive mouse model in 27% of the cases. In another attempt to address this controversy, a recent study[28] compared the frequency of CSC in pancreatic, lung, and head and neck cancers when using the traditional NOD/SCID versus the NOD/SCID IL2Rg-/- model as the recipient, and found an almost 10-fold increase in the frequency of CSC when using the more permissive NOD/SCID-LI2Rg-/-mouse model. Interestingly enough however, the frequency of CSCs within those tumors was still relatively rare (<1 in 2500 cells), which further supported the CSC model.

Clinical relevance of the cancer stem cells model. The CSC model clearly demonstrated the existence of a hierarchical organization within most human cancers and demonstrated the capability of the CSC to initiate tumors in immunodeficient mice, however, it took several years before sufficient data emerged in support of the clinical relevance of the CSC model. Using 2 breast cancer cell lines, it was shown that the CD44+/CD24-/low population is the fraction that has inherent resistance to ionizing radiation (IR) manifested by reduced levels of reactive oxygen species (ROS), and less accumulation of DNA lesions post IR.[29] Similarly and using a Glioma CSC model, the CD133+ fraction was shown to resist IR by preferential activation of the DNA damage response pathway.[30] In concordance with that, recent clinical data demonstrated significant increase in the CD44+CD24-/low fraction in a cohort of breast cancer patients, 12 weeks post neoadjuvant chemotherapy.[31] In an independent study, Creighton et al[32] demonstrated significant enrichment for a gene-signature derived from the CD44+CD24-/low CSC fraction in a cohort of breast cancer patients undergoing conventional endocrine and chemotherapy. Significant association between the expression of CD133 CSC marker and worse clinical outcome had been reported in brain, liver, and colorectal cancers.[33-35] Significant association between the expression of CD44, a marker for head and neck CSC, and disease progression was also reported.[36] Collectively, these data suggested a plausible role for CSCs in therapy failure and in driving disease progression (**Figure 1b**).

Therapeutic implications of the CSC model. If the CSC model is true, then what would be the impact of this model on us as scientists or clinicians? The BMI1 proto-oncogene has been implicated in regulating the self-renewal capability of normal and cancerous stem cells.[37,38] Interestingly, our group was the first to document a novel function for BMI1 in protecting tumor cells from ionizing radiation by regulating reactive oxygen species (ROS) levels in a P53-dependant manner.[39] Subsequently, a number of other groups have also implicated BMI1 in radiation resistance, and in the survival of neural and leukemic CSCs.[40,41] Therefore, targeting BMI1 might be a useful strategy to selectively target and sensitize CSCs to radiation therapy. Hambardzumyan et al[42] reported that medulloblastoma CSCs resist radiation therapy through activation of the PI3K/Akt pathway, and by undergoing transient p53-dependent cell cycle arrest post-radiation therapy.

Consistent with this model, pharmacological inhibition of the Akt pathway in a mammary tumor mouse model led to a significant inhibition of the canonical Wnt signalling and the DNA damage repair, thus enhancing the efficacy of radiation therapy.[43] The ATP-binding cassette subfamily G member 2 (ABCG2) protein has also been implicated in CSC resistance, whereas, its inhibition led to significant chemosensitization.[44] In another study, Zhao[45] reported successful eradication of CML by selective inhibition of the Hedgehog signalling pathway. In a breast cancer model, targeting the Notch pathway was shown to reduce the CD44+/CD24- proportion and to reduce brain metastasis.[46] Since CSC retain several properties of normal stem cells, Campos et al[47] assess the therapeutic potential of all-trans retinoic acid (ATRA) differentiation therapy in a glioma-like stem cell model. The authors reported that treating these cells with ATRA led to significant sensitization to radiation and chemotherapy and led to significant reduction in tumorigenicity.[47] Another successful therapeutic approach relied on the utilization of oncolytic viruses to target the CSC. We previously reported successful utilization of engineered vesicular stomatitis virus (VSV) to target nasopharyngeal carcinoma (NPC) sphere forming cells in vitro, and when combined with ionizing radiation, to completely eradicate established NPC tumors in vivo.[48] Subsequently, other research groups reported successful utilization of herpes simplex virus (HSV) to target glioblastoma, and reovirus to target breast CSC.[49,50] An alternative approach utilized global gene and microRNA expression profiling to identify key molecular pathways that governs CSCs survival and therapy resistance.[51-55] In one study, miR-200c was found to be down-regulated in normal and breast CSCs, whereas restoring the expression of this microRNA led to significant inhibition of breast CSC tumor formation capability in vivo, which interestingly was mediated by repression of BMI1, a novel bona fide target for miR-200c identified in the same study.[55] In the quest to identify novel molecular agents that selectively target epithelial CSCs, Gupta et al[56] performed high throughput screen and identified several compounds that exhibited anti-epithelial-CSC properties. One compound, salinomycin, was extremely efficient in preventing mammary epithelial tumor growth in vivo, which was associated with induction of tumor differentiation. Similarly, Dirk's group[57] performed high throughput screen against several glioma neural stem (GNS) line, and identified several modulators of the serotonin signalling pathway as potent inhibitors of GNS lines growth in vitro.

Perspective. The past several years had witnessed huge interest in the cancer stem cell field. Emerging data suggest that CSC is the fraction within the tumor that sustain the tumor and resist standard therapies; however, before the wide acceptance of a clinical relevance of the CSC model, more clinical data is needed in order to support the plausible role for CSC in driving disease progression, therapy resistance, and relapse. In many instances, the markers used to isolate the CSCs from solid tumors are not unique stem cell surface markers (in most of the cases CSCs are isolated based on the expression of CD44). For instance, in breast cancer, the frequency of the CD44+CD24-/low population could be up to 35% of the lineage negative fraction within any given patient tumor;[10] therefore, the challenge is to identifying unique surface markers specific for CSC, or to utilize a combination of several markers in order to isolate the true CSC fraction in high purity suitable for genetic analyses, which could ultimately lead to the identification of key molecular pathways unique to the CSC subset. There are several potential anti-CSC agents, which exhibited promising anti-CSC effects in preclinical models, few of which are currently being evaluated in the clinic (http://clinicaltrials.gov). One major concern is that CSCs might still develop resistance to such agents, therefore, a more efficient approach would likely rely on the combination of several anti-CSC agents targeting different molecular pathways critical for CSC survival and self renewal, which likely will have a better chance of eradicating the CSCs and curing the disease.

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