Cancer Stem Cell: A rogue responsible for tumor development and metastasis

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Abstract
Cancer stem cells are a small population of cells in a tumor. They have the ability to self-renew and maintain the tumor. The most apt and accepted hypothesis for tumor development is Cancer Stem Cells. This review focuses on this concept of cancer stem cells, serving their purpose and leading to the development of tumor. There are many cell biomarkers which have been described for the identification and characterization of cancer stem cells. The most prominent of the cellular markers for the detection of cancer stem cells; CD133, CD44, ALDH-1 along with some others have been discussed in detail in this review.

Key Words: Clonal evolution, multi-potency, oncogenes, pre-cancerous stem cells, self-renewal, tumor suppressor genes

Introduction
Carcinogenesis is a complex and multi-step process. A normal cell is stressed and transformed into cancer cells. This often requires concordant expression of a number of genes, including multiple genetic and epigenetic changes in oncogenes, tumor-suppressor genes, cell-cycle regulators, cell adhesion molecules, DNA repair genes and genetic instability as well as telomerase activation.

Based on the heterogeneity of cancer cells, several models have been proposed to explain cancer development. The stochastic model claims that all cancer cells can reproduce phenotypically heterogeneous cell types in new tumors. However, this model cannot explain why cancer is highly heterogeneous. The cancer stem cell hypothesis may resolve the issue. It emphasizes that only a tiny population of cancer cells has the capability to produce phenotypically heterogeneous cells in new tumors; other cells only have limited proliferative capacity. Accordingly these cells have stem-like properties, having the capability of self-renewal and multi-potency of differentiation, and thus are called Cancer Stem Cells (CSCs).

If cancer stem cells are relatively refractory to therapies that have been developed to eradicate the rapidly dividing cells within the tumor that constitute the majority of the non-stem cell component of tumors, then they are unlikely to be curative and relapses would be expected. If correct, the cancer stem cell hypothesis would require that we rethink the way we diagnose and treat tumors, as our objective would have to turn from eliminating the bulk of rapidly dividing but terminally differentiated components of the tumor and be refocused on the minority stem cell population that fuels tumor growth. This explains why the cancer stem cell hypothesis is at the center of a rapidly evolving field that may play a pivotal role in changing how basic cancer researchers, clinical investigators, physicians, and cancer patients view cancer.

Though the idea of cancer stem cells is considered as a new concept in science, it was thought almost 35 years back in 1971 when they were called as leukemic stem cells. A small subset of cancer cells capable of extensive proliferation in leukemia and multiple myeloma were found and named as leukemic stem cells. Two possibilities were proposed: Either all leukemia cells had a low probability of proliferation and therefore all leukemia cells behave as LSC, or only a small subset was clonogenic. The later theory was favored by Dick and colleagues who were able to separate the LSC as CD34+ CD38- from patients’ samples. Recently, the cancer stem cells were also shown in the solid tumours such as breast cancer and brain tumours.

Cancer stem cells identification, isolation and characterization related discoveries and major research developments which have been highlighted in a consolidated form in Table 1.

However, this hypothesis is controversial and has been challenged by recent studies, which argue for a long-standing cancer model, well known as clonal evolution. The clonal evolution model claims that normal cells mutate and generate abnormal offspring that also mutate, forming a mass of genetically varied cancer cells. At least two hits of oncogenic mutation may be required. Practically, clonal evolution as a mechanism appears to underlie CSC development.

Emerging Concept of pCSCs
It has been identified that a new type of cancer cell from murine lymphoma, represents an early stage of CSC development but similar to pre-cancer in clinical origin, having the potentials of both benign and malignant differentiation. Therefore, it was named as ‘pCSCs’. Theoretically, all cells that are hit by carcinogens have the potential to develop into Tumor Initiating Cells (TICs). Practically, the cellular processes of TIC → pCSC → CSC → cancer should parallel the histological process of hyperplasia/metaplasia (TIC) → pre-cancerous lesions (pCSC) → malignant lesions (CSC → cancer) [Figure 1]. While clonal evolution disconnects the molecular basis of cancer development, the CSC hypothesis pinpoints the same cellular origin of the primary, metastatic and recurrent cancer. The gap between these two models can be resolved with identification of pCSCs. The existence of pCSCs in tumors strongly implies that CSC can be derived from the precursors through a mechanism of clonal evolution, or that the target cells of clonal evolution are the precursors of CSCs. Preliminary studies suggest that the progression of pCSCs to CSCs is associated with
First study on cancer stem cells – First identified and isolated

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<th>Year</th>
<th>Discovery</th>
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<tr>
<td>2003</td>
<td>Breast cancer stem cells discovered at the U-M Comprehensive Cancer Centre.</td>
<td>Al-Hajj <em>et al.</em>, 2003</td>
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<td>2005</td>
<td>First evidence for human bone cancer stem cells (USA).</td>
<td>Gibbs <em>et al.</em>, 2005</td>
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<td>2005</td>
<td>Prostate cancer stem cells isolated.</td>
<td>Collins <em>et al.</em>, 2005</td>
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<tr>
<td>2007</td>
<td>Pancreatic cancer stem cells identified for the first time.</td>
<td>Li <em>et al.</em>, 2007</td>
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Table 1: Cancer stem cells – First identified and isolated – Time line

Tumor neo-vascularization is critical for tumor growth, invasion and metastasis, which has been considered to be mediated by a mechanism of angiogenesis. However, histopathological studies have suggested that tumor cells might be the progenitor for tumor vasculature. It has been reported that in the pCSC-derived tumors, most blood vessels were derived from pCSCs. Some pCSCs constitutively expressed vasculogenic receptor, VEGFR-2, which can be up-regulated by hypoxia and angiogenesis-promoting cytokines such as GM-CSF, Flt3 ligand, and IL-13. The pCSCs are much more potent in tumor vasculogenesis than the differentiated tumor monocytic cells (TMCs) from the same tumor, which had comparable or even higher capacity to produce some vascular growth factors, suggesting that the potential tumor vasculogenesis of pCSCs is associated with their intrinsic stem-like property. Consistently tumor vasculogenesis was also observed in human cancers such as cervical cancer and breast cancer and xenograft lymphoma. Studies indicate that pCSCs can serve as tumor vasculogenic stem/progenitor cells (TVPCs), and may explain why anti-angiogenic cancer therapy trials are facing challenge.

**Cancer Stem Cell Markers**

**CD133**

The novel cell-membrane protein CD133, whose biological function is although not well understood, has been identified...
as a marker of a subset of neural stem cells in the adult central nervous system as well as of glioblastoma stem-like cells.\textsuperscript{[27,22]} CD133\textsuperscript{+} cancer stem cells have a capacity for unlimited self-renewal, as well as the ability to initiate and drive tumor progression in an animal model.\textsuperscript{[72]} Cancer and normal stem cells share the same self-renewal mechanisms, such as the Bmi-1 and Wnt canonical pathways.\textsuperscript{[73,74]} CD133\textsuperscript{+} cells expressed higher levels of CD90, CD44, Nestin, Msi1, MELK, GLI1 and PTCH. Particularly, Bmi-1, PSC, SHH, OCT4 and Snail were only expressed on CD133\textsuperscript{+} cells; none of the five genes were detectable on CD133\textsuperscript{–} tumor cells.\textsuperscript{[75]} CD133\textsuperscript{+} cancer stem cells are significantly resistant to four tested chemotherapeutic agents, including temozolomide, carboplatin, VP16 and Taxol than autologous CD133\textsuperscript{–} cells.\textsuperscript{[75]} One of the important mechanisms of drug resistance is the expression of ATP-binding cassette transporter protein, such as BCRP1. CD133\textsuperscript{+} cells express higher levels of BCRP1, which indicate that BCRP1 may also play an important part in the drug resistance of CD133\textsuperscript{+} cells.\textsuperscript{[76]} BCRP1 over-expressing tumor cells; however, are only resistant to mitoxantrone, Adriamycin, daunorubicin, etoposide, topotecan, and irinotecan. They are not resistant to Taxol and vincristine.\textsuperscript{[77]} Therefore, it has been proposed that both anti-apoptosis factors and BCRP1 contribute the drug resistant property on CD133\textsuperscript{+} cancer stem cells.\textsuperscript{[75]}

Neural stem cells (NSCs) express nestin and CD133, and differentiate into neurons, astrocytes and oligodendrocytes at a clonal level.\textsuperscript{[78]} An important characteristic of NSCs, not fully understood, is their migratory ability and their tropism to brain pathology. High expression levels of functional chemokine receptor CXCR4 have been found on human neural stem cells.\textsuperscript{[79]} Thus, CXCR4 may play a significant role in directing NSC migration during CNS development. Similar to normal NSCs, CD133\textsuperscript{–} cancer stem cells showed 337.8 times increase on the expression levels of CXCR4 than did CD133\textsuperscript{–} cells, which suggests CD133\textsuperscript{–} cancer stem cells have higher capability of migration and may play an important role in glioma invasion.\textsuperscript{[75]} Cell lines derived from CD133\textsuperscript{+} CSC showed neurosphere-like growth.\textsuperscript{[27,77,80-83]} However, some cell lines derived from primary glioblastomas grew as adherent spheres within a dense network of differentiated cells and were maintained by CD133\textsuperscript{–} cells that display infinite potential for self-renewal. Pluri-potency was confirmed by expression of neuronal, astrocytic, and oligodendroglial lineage markers.\textsuperscript{[83]} To confirm that the small subpopulation of CD133\textsuperscript{–} tumor cells is rightly referred to as CSC, evidence for their selective capability to drive tumor growth \textit{in vivo} is needed. Because there is no surface marker allowing the separation of CD133\textsuperscript{–} CSC from CD133\textsuperscript{+} cells lacking stem cell properties, experiments similar to those done with the purified CD133\textsuperscript{+} CSC subset are not feasible yet.\textsuperscript{[72]} The observation that adherent CD133\textsuperscript{+} cell cultures are tumorigenic \textit{in vivo}, whereas CD133\textsuperscript{–} cells from neurosphere-like CD133\textsuperscript{+} CSC lines do not form tumors in nude mice, is the strongest currently obtainable evidence for the existence of CD133\textsuperscript{–} CSC consequently referred to as CD133\textsuperscript{–} CSC. Because only the total number of adherent CD133\textsuperscript{+} cells injected into immunodeficient mice is known, how many CD133\textsuperscript{–} CSCs are required to induce tumor formation \textit{in vivo} cannot be determined.\textsuperscript{[84]}

CD133 has been identified as a stem cell marker for human leukemia, brain tumors, and prostrate cancer. Also, only a small proportion (<5%) of cells in the Hep-2 cell line expressed CD133. CD133\textsuperscript{+} cells possess a marked capacity for self renewal, extensive proliferation, and multi-lineage differentiation potency \textit{in vitro}. Thus, CD133 is one of the markers for cancer stem cells in human laryngeal tumors.\textsuperscript{[85]} Colon cancer stem cells are believed to originate from a rare population of putative CD133\textsuperscript{–} intestinal stem cells. A small subset of colon cancer cells express CD133, and only these CD133\textsuperscript{+} cancer cells are capable of tumor initiation.\textsuperscript{[86]} CD133\textsuperscript{+} colonic tumor cells express epithelial cell adhesion molecule (EpCAM). Similarly, CD133\textsuperscript{+} is widely expressed by human primary colon cancer epithelial cells, whereas the CD133\textsuperscript{–} population is composed mostly of stromal and inflammatory cells. Conversely, CD133 expression does not identify the entire population of epithelial and tumor-initiating cells in human metastatic colon cancer. Indeed, both CD133\textsuperscript{–} and CD133\textsuperscript{+} metastatic tumor subpopulations formed colonospheres in \textit{in vitro} cultures and were capable of long-term tumorigenesis in a NOD/SCID serial xenotransplantation model. Moreover, metastatic CD133\textsuperscript{+} cells form more aggressive tumors and express typical phenotypic markers of cancer-initiating cells, including CD44 (CD44\textsuperscript{+},CD44\textsuperscript{+}), whereas the CD133\textsuperscript{–} fraction is composed of CD44\textsuperscript{+}CD44\textsuperscript{+} cells. CD133 expression is not restricted to intestinal stem or tumor-initiating cells, and during the metastatic transition, CD133\textsuperscript{+} tumor cells might give rise to the more aggressive CD133\textsuperscript{–} subset, which is also capable of tumor initiation in NOD/SCID mice.\textsuperscript{[86]}

Prospectively isolated CD133\textsuperscript{+} cells and/or side population (SP) cells in endometrial cancer were capable of initiating tumor formation and of recapitulating the phenotype of the original tumor, and therefore are candidate for endometrial cancer stem cells.\textsuperscript{[87]} High expression of CD133 has also been reported in 4T1 mouse breast cancer cells.\textsuperscript{[88]} Identification of a cancer stem cell population has been reported in Hepatocellular Carcinoma characterized by their CD133 phenotype.\textsuperscript{[89]} Human pancreatic cancer tissue contains cancer stem cells defined by CD133 expression that are exclusively tumorigenic and highly resistant to standard chemotherapy. In the invasive front of pancreatic tumors, a distinct subpopulation of CD133\textsuperscript{+} CXCR4\textsuperscript{+} cancer stem cells was identified that determines the metastatic phenotype of the individual tumor.\textsuperscript{[90]} CD133 expression defines a NOD/SCID tumor initiating subpopulation of cells in human ovarian cancer that may be an important target for new chemotherapeutic strategies aimed at eliminating ovarian cancer.\textsuperscript{[91]} CD133 has also been used to identify normal and cancer stem cells from several different tissues, such as renal epithelial or kidney cancer cells [Figure 2].\textsuperscript{[92]}

\textbf{CD200}

Recently the glycoprotein CD200, expressed within the innate immune system and other tissues and cells, was shown...
to be involved in tolerance. CD200 co-expression with stem cell markers found on prostate, breast, brain, and colon cancers has been described. This is the first report describing an immunomodulatory molecule on epithelial cancer stem cells. This important finding suggests a mechanism by which a tumor might evade immune system detection [Figure 3].

**CD117**

Gastrointestinal stromal tumors (GISTs) represent a distinct and the most important subset of mesenchymal tumors of the GI tract. These tumors are both phenotypically and genotypically different from true leiomyomas and usually express CD34, a hematopoietic progenitor cell antigen. CD34 however, is also present in a wide variety of fibroblastic and endothelial cell tumors. CD117, the c-kit proto-oncogene product is expressed in subsets of hematopoietic stem cells, mast cells, melanocytes, and interstitial cells of Cajal of the GI tract. CD117 was almost always (85%) expressed in both benign and malignant GISTs. CD117 was observed both in the spindle cell and epithelioid subtypes of GISTs in all locations. In addition to reacting with the CD34+ GISTs, CD117 was positive in some CD34- cases. These results indicate that CD117 is a specific marker for GIST among tumors that occur in the GI tract and adjacent regions. CD117 expression also separates GISTs from true leiomyomas and gastric schwannomas. The sphere-forming cells isolated from primary ovarian cancer tissues have the characterization of cancer stem cell as they had the properties of self-renewal, over expression of stem cell marker genes Nanog, Oct-4, Sox-2, nestin, ABCG2, CD (133) and CD (117) [Figure 4].

**CD90**

CD90 is a potential marker of liver CSCs, and the concomitantly expressed CD44 modulates the biological activity of the CD90+ CSCs. The presence of local and circulating CSCs implies the aggressive phenotype of liver malignancy, in which the CD90+ CD44+ cells contribute prominently to its aggressiveness and metastasis. The prevention of local and systemic tumor formation by CD44 blockade highlights the potential of CD44 as a therapeutic target for CD90+ CSCs. The differential gene expression profiles of CSCs and normal stem cells suggest the importance of these genes in hepatocarcinogenesis. The identification of local and circulating CSCs provides a cellular basis of liver cancer development, recurrence, and metastasis and will favor the design of future therapeutic strategies [Figure 5].

**ALDH-1**

ALDH is a detoxifying enzyme responsible for the oxidation of intracellular aldehydes, thereby mediating self-protection and resistance to some alkylating agents used in cancer therapy. Besides, ALDH is implicated in the biology of normal stem cells through its role in metabolism of retinol to retinoic acid, which initiates a program of cellular differentiation. Therefore, ALDH has been suggested as a marker for isolating normal stem cells and lately also CSCs from several tumor types. ALDH1+ cells displayed radio resistance and represented a reservoir for generating tumors. ALDH1+ lineage cells showed evidence of having epithelial-mesenchymal transition (EMT) shifting and endogenously co-expressed Snail. Furthermore, the knockdown of Snail expression significantly decreased the expression of ALDH1, inhibited cancer stem-like properties, and blocked the tumorigenic abilities of CD44+ CD24+ ALDH1+ cells. Finally, in a xenotransplanted tumorigenicity study, it was confirmed that the treatment effect of chemoradiotherapy for ALDH1+
could be improved by Snail siRNA. Therefore, it is likely that ALDH1 is a specific marker for the cancer stem-like cells of head and neck squamous cell carcinoma.\(^{100}\)

Stem-like ALDH (hi) CD44\(^+\) CD24\(^-\) and ALDH (hi) CD44\(^+\) CD133\(^+\) cells may be important mediators of breast cancer metastasis.\(^{101}\) Breast cancer stem cells identified as ALDH1\(^+\), but not CD44\(^+/\)CD24\(^-\), play a significant role in resistance to chemotherapy. Thus, ALDH1 seems to be a more significantly predictive marker than CD44\(^+\)/CD24\(^-\) for the identification of breast cancer stem cells in terms of resistance to chemotherapy.\(^{102}\) The metastatic behavior of inflammatory breast cancer may be mediated by a cancer stem cell component that displays ALDH enzymatic activity. ALDH1 expression represents the first independent prognostic marker to predict metastasis and poor patient outcome in inflammatory breast cancer.\(^{103}\)

ALDH1 is a tumor stem cell-associated marker in lung cancer.\(^{104}\) The existence of a hierarchical organization in hepato-cellular carcinoma bearing tumorigenic potential revealed in the order of CD133\(^+\) ALDH\(^+\) CD133\(^+\) ALDH\(^-\) CD133\(^-\) ALDH\(^-\). ALDH, expressed along CD133, can more specifically characterize the tumorigenic liver CSC population [Figure 6].\(^{105}\)

CD44

Al Hajj and his group made experiments using a model in which human breast cancer cells were grown in immunocompromised mice, they found that only a minority of breast cancer cells had the ability to form new tumors. They prospectively identified and isolated the tumorigenic cells as CD44\(^+\) CD24\(^-\) Lineage-\ in eight of nine patients. As few as 100 cells with this phenotype were able to form tumors in mice, whereas tens of thousands of cells with alternate phenotypes failed to form tumors. The tumorigenic subpopulation could be serially passaged: Each time cells within this population generated new tumors containing additional CD44\(^+\) CD24\(^-\) Lineage- tumorigenic cells as well as the phenotypically diverse mixed populations of non-tumorigenic cells present in the initial tumor.\(^{16}\)

Breast cancer cells with CD44\(^+\)/CD24\(^-\) subpopulation express higher levels of pro-invasive genes and have highly invasive properties.\(^{106}\) The prevalence of CD44\(^+\)/CD24\(^-\)\hi\ tumor cells in breast cancer may not be associated with clinical outcome and survival but may favor distant metastasis.\(^{107}\) Role of CD 44 in colon cancer has also been established as it has been found out that ESA\(^\ast\) -CD44\(^\ast\) -CD133\(^\ast\) -ESA\(^\ast\) cells are SW480-colon cancer-like cancer stem cells.\(^{108}\) In prostate cancer stem cells have a CD44\(^+\)/α\β\hi\) CD133\(^+\) phenotype. Approximately 0.1% of cells in any tumor expressed this phenotype, and there was no correlation between the number of CD44\(^+\)/α\β\hi\) CD133\(^+\) cells and tumor grade.\(^{28}\) A minority population of CD44\(^+\) cancer cells, which typically comprise <10% of the cells in a head and neck squamous cell carcinoma tumor, but not the CD44\(^-\) cancer cells, gave rise to new tumors \emph{in vivo}. Immunohistochemistry revealed that the CD44\(^+\) cancer cells have a primitive cellular morphology and coexist with the basal cell marker Cytokeratin 5/14, whereas the CD44\(^-\) cancer cells resemble differentiated squamous epithelium and express the differentiation marker Involucrin.\(^{109}\)

Furthermore, the tumorigenic CD44\(^+\) cells differentially express the BMI1 gene, at both the RNA and protein levels. By immunohistochemical analysis, the CD44\(^+\) cells in the tumor express high levels of nuclear BMI1, and are arrayed in characteristic tumor microdomains.\(^{132}\) BMI1 has been demonstrated to play a role in self-renewal in other stem cell types and to be involved in tumorigenesis.\(^{23}\) Therefore, cells within the CD44\(^+\) population of human HNSCC possess the unique properties of cancer stem cells in functional assays for cancer stem cell self-renewal and differentiation and form unique histological micro domains that may aid in cancer diagnosis.\(^{12}\)

CD44\(^+\), CD133\(^+\), and CD24\(^+\) cells have some biological properties of cancer stem-like cells or are highly similar to the characteristics of cancer stem cells (CSC). These results provide an important method for identifying cancer stem-like cells in B16F10 cells and for further cancer target therapy.\(^{110}\) CD44\(^+\) gastric cancer cells showed increased resistance for chemotherapy or radiation-induced cell death. These results support the existence of gastric CSCs and may provide novel approaches to the diagnosis and treatment of gastric cancer [Figure 7].\(^{111}\)

**Conclusion**

At present, the shrinkage in the size of a tumor is considered as a response to the treatment. But, CSCs are...
resistant to treatment, therefore the identification of CSCs is necessary for better treatment. In this review we bring to light that CD133, CD44 and ALDH1 altogether can be used for the identification and characterization of cancer stem cells in tumors.

Integrating the hypothesis of cancer stem cells with the concept of clonal evolution hypothesis, by far looks the most appropriate. Benign differentiation leads to the pre-cancerous stem cells to maintain their howsoever small population, while differentiation on the malignant lines, leads to the formation of CSCs. From the concept of CSCs, now cancer may be considered as a cancer stem cell disorder rather than lump of undifferentiated cells. Although the origin of the cancer stem cells is yet to be defined, the concept of the pre-cancer stem cells (pCSCs) may allow new treatment options in the possible cure of the cancer.

Further research is required to be more focused, so as to identify and separate the cancer stem cells in various cancers other than what have been identified to date, from normal stem cells and other cancer cells. Also, there is a need to identify the differences between gene expression and pathways involved normal stem cells and CSCs, with the eventual goal of eliminating the residual disease and recurrence.

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