Cancer Stem Cells

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ABSTRACT
This mini-review will discuss Cancer Stem Cells (CSCs) on their definition, history, characteristics, models, origin, tumorigenesis, targeting Cancer Stem Cells with nanomaterials, niche interactions, CSCs therapeutics, vaccination, the role of autophagy in CSCs, artificial intelligence, and clinical trials targeting CSCs.

Keywords: Cancer Stem Cells

Definition
Cancer stem cells (CSCs) are a subpopulation of cancer cells inside the cancer microenvironment niche that defines or constructs a reservoir of independent cells with the unique capability of self-renewal, multi-potent tumor-initiating properties and assembling various lineages of cancer cells.¹² The maintenance of CSCs is entirely controlled by the stroma and microenvironment.³ CSCs can perpetuate themselves within the tumor growth via auto restoration with tumor-initiating potential.⁴,⁵ CSCs are also known as tumor propagating cells (TPCs) and tumor-initiating cells (TICs).

History
The term CSCs was first introduced by Reya, et al in 2001.⁶ In 1963, Becker, et al, explained that some cells with self-renewal abilities could develop colonies or territories in the spleens.⁷ In 1964, Kleinsmith and Pierce discovered a small group of cancer cells in blood with extensive proliferation capabilities termed “leukemic stem cells”. They successfully observed subpopulations of cells with identical features and properties in various types of solid tumors, such as breast cancer.⁴

Characteristics
Cancer stem cells (CSCs) have different characteristics from normal stem cells (NSCs). CSCs have various properties. For example, they have the tumorigenic capacity, are indefinite and extensive self-renewal, are rarely found in tumors, have abnormal karyotypes, and have identical surface markers as typical stem cells less mitotically active than other cancer cells, differ in phenotypical progeny.⁸,⁹ Apart from self-renewal, CSCs also have essential roles...
in regulatory and cellular processes, such as apoptosis, heterogeneity, metastasis, immune intransigence (resistance), and connected to chemoresistance and/or radioresistance (Figure 1).3

CSCs are generated from NSCs, progenitor, or precursor cells where epigenetic mutations exist (Figure 2).3 Only CSCs can sustain and form a tumor and are impervious to standard therapies. Conventional therapies can reduce tumor size; if they can eradicate CSCs, they should be more powerful to annihilate the tumor. Developmental pathways such as Notch, Wnt/β-catenin, and Hedgehog perform instrumentally in cancers and are frequently transformed and are involved in CSCs regulation.12 It is still an accustomed strategy to isolate CSCs by fluorescence-activated cell sorting (FACS) and scrutinize their biological features.13

Normal stem cells (NSCs) also have various properties, such as organogenic capacity, self-renewal, rarely found in normal adult tissues, having normal karyotypes, being able to be identified based on surface markers, being primarily silent, being able to engender normal progeny with restricted proliferative potential.11,14

Models

Basically, according to a non-stem tumor (traditional) model, every cell in a tumor can initiate a new tumor. Recently, based on models of tumor heterogeneity, there are two concepts. First, tumor cells have heterogeneous characteristics; most cells can proliferate extensively and create novel tumors. Second, tumor cells are heterogeneous, and only the CSCs subset can proliferate extensively and produce novel tumors.15

Somewhat similar is the heterogeneity model of cancer with two general models. First, all cancer cells are promising CSCs but have a low possibility of propagation in clonogenic assays. Second, only a tiny definable subset of cancer cells are CSCs that can propagate continually.16

Origin

The concept of CSCs can answer some enigmatic questions about cancer growth. However, it is important to know the origin of the CSCs; two fundamental factors need to be understood. First, a series of mutations are required for one cell to become cancerous. Second, stem cells need to overcome various genetic barriers to both proliferation and self-renewal capabilities.4,17,18

There are several theories on the origin of CSCs that lead to cancer. First, transforming stem cells, resulting in the growth and differentiation of the changed properties. Second is the transformation or renewal of an innate pool from previous precursors that regain properties with self-renewal characteristics. Third, the sequence of powerful mutations that change temporary-amplifying antecedent or extricated somatic cells between networks (so-called de-differentiation). Fourth, the process of circling bone-marrow-derived stem cells with the tissue-enduring cells.5,16
It is highly unlikely that all mutations occur along with the lifespan of a progenitor or mature cell. Therefore, CSCs can come from either the progenitor cells or the self-renewing normal stem cells that have acquired self-renewal ability due to mutations (Figure 3).18

The current CSC paradigm is that a sparse population of tumor cells with several characteristics as normal stem cells (NSCs) such as self-renewal and stemness are behind the tumorigenesis (initial formation of a tumor) and the advancement of various cancers in humans.13 While CSCs are found in multiple human cancers, it is crucial to know the origin of these cells. Reliable evidence proves that the plasticity of CSCs is a phenotypic characteristic and is influenced by a variety of protein signaling, a tumor-definite microenvironment, and specific or targeted transcription factors.21,22

This concept recommends that the various factors unique to each tumor have a dynamic balance and plasticity between cancer stem cells and non-cancer stem cells, thereby maintaining homeostasis in the subpopulation of tumor cells.23 Homeostasis change through de-differentiation (Figure 4) because of natural occurrence or as an outcome of medical therapy results in tumor aggressiveness, since both cancer stem cells and the dedifferentiated non-cancer stem cells to drug-induced cancer stem cells are more resistant to the common radiation and chemotherapy management.24

Tumorigenesis
CSCs are the prevailing cells for tumor initiation. The tumor initiation assay is a standard and well-accepted method to ponder the self-renewal of CSCs.26 Tumorigenesis is a process of oncogenic reprogramming. Many chromatin remodeling complexes are dysregulated in CSCs and cancer cells.27 The chromatin remodeling becomes a demanding target for CSC and cancer eradication as a driver factor in tumorigenesis.28 The SWI/SNF (mating type SWIt/Sucrose NonFermentable) chromatin remodeling complexes are muddled in CSC self-renewal and oncogenic reprogramming.29 The SWI/SNF complex can be assembled into BRM-contained SWI/SNF complex and the BRG1-contained SWI/SNF complex. The BRG1-contained SWI/SNF complex is elevated in liver tumorigenesis, in as much as the BRM-contained SWI/SNF complex is dwindled.30 This switch between BRG1- and BRM-contained SWI/SNF complex plays a fundamental aspect in liver CSC self-renewal and liver tumorigenesis.31

Targeting Cancer Stem Cells with Nanomaterials
New CSCs have been observed in nearly all cancer types, such as brain, colon, gastric, lung, pancreatic, prostate, etc. CSCs have several functional characteristics:
1. Specific signaling pathways and/or biomarkers can purify CSCs.
2. The capability to generate colonies in suspension culture conditions.
3. Resistant to radiation and chemotherapeutic agents.

Therefore, a considerable part of conventional treatments, e.g., radiation and chemotherapy, can execute most tumor cells but are unsuccessful in maintaining clinical results as resting CSCs can produce new colonies and invigorate tumors. Novel therapeutic approaches that selectively target cancer stem cells will advance cancer therapies.32,33

The CSCs can stimulate tumor development and be eminently resistant to typical treatments, such as radiotherapy and chemotherapy. Moreover, it leads to disease progression and the establishment of metastases. Thus, analyzing and selectively addressing signaling pathways and markers of CSCs are expedient therapeutic methods for managing numerous cancer types, regardless

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**Figure 4.** The implications cancer stem cells (CSCs) in the development and progression of tumors. CSCs are generated from the normal stem cells (NSCs) through tumorigenic transformation of several pathways such as Hh: hedgehog, epithelial-to-mesenchymal transition (EMT), and the reverse process mesenchymal-to-epithelial transition (MET). CSCs and drug-induced CSCs (Di-CSCs) are enriched following conventional chemotherapy treatment.25

**Figure 5.** The promising roles of nanoparticles targeting CSC-specific surface markers or signaling pathways.32
Presently, there is extensive excitement in the usage of nano-sized ingredients or materials for CSC-directed anticancer treatment. The modalities and novel therapy in the structure of nanoparticles (NPs)-targeting CSC-specific markers or signaling pathways are feasible or still being researched. The NPs’ surface has been created to effectively and meticulously target directly to the CSCs.\textsuperscript{32,34}

The schematic diagram encapsulates the promising aspects of NPs-targeting CSC-signaling pathways and specific markers in cancer treatments (Figure 5).\textsuperscript{32}

Recognition of CSC is feasible by several markers, such as CD44 and CD90 and CD133, Aldehyde Dehydrogenases (ALDH) marker, and specific signaling pathways, such as Hedgehog, Notch, TGF-\(\beta\) (Transforming growth factor-\(\beta\)) to advance the therapeutic consequences and therapy strategies.\textsuperscript{35}

Many types of research also recognized various kinds of NP-targeting CSCs, such as liposomes-based NPs, curcumin-based NPs, and NP-mediated hyperthermia. These nanoparticles (NP)-based therapeutic strategies support benefit over tiny molecule pharmaceutical agents-based therapeutic approaches.\textsuperscript{36}

Figure 6 exhibits the varied nanomaterial that targeted cancer stem cells.\textsuperscript{35}

Niche Interactions

The complicatedness of the tumor microenvironment leads to the most destructive solid tumors with their mutual characteristics. CSCs vigorously reconstruct, inhabit in, and in turn also are controlled by several essential features of those niches, rising to a dynamic-heterogeneous population within numerical reliances and expansive diversity of intransigence systems (Figure 7).\textsuperscript{37}

As long as directing a specific and targeted niche is adequate in several types of certain cancers, specifically in low-stadium tumors, therapy for many threatening solid tumors should be palliative. Moreover, their niches are neither static nor isolated. The vascularization area turns into a component of the hypoxic (low-oxygenated) area as many tumors outgrow their blood supply. Cells within the immune system endure throughout the different domains and display definite features and properties and functional interplay and communication towards niches.\textsuperscript{37}

Durability is an essential element of a tumor model as a self-sustaining ecosystem. Thus, the intratumoral interactions driving that resilience will be a necessary target for effective treatment. For example, angiogenesis inhibitors could inhibit VEGF signaling (e.g., bevacizumab) or CSC-derived pericytes (e.g., via BMX inhibition).\textsuperscript{37,38} Checkpoint inhibitors, e.g., PD-L1 or PD-1 antagonists (such as atezolizumab and nivolumab), have been used to target the bulk tumor of many solid cancers.\textsuperscript{39} Still, CSC-specific strategies need the characterization and targeting of additional immunosuppressive or checkpoint mechanisms. Cytokine signaling, such as interleukin-6 (IL6) production by endothelial cells or interleukin-4 by CSCs, mutually promotes CSC immunosuppression and maintenance.\textsuperscript{40} Perivascular CSC-specific molecules, such as CD109 in glioblastoma CSCs, can be utilized with strategies such as HIF inhibitors to target CSCs across multiples niches.\textsuperscript{37}

CSCs Therapeutics

Regardless of late improvements in cancer...
treatments, chemoresistance and severe side effects are still problematic. Currently, it was affirmed that a small subpopulation of CSCs inside the tumor mass has self-renewal capacity and supports resistance to cancer treatments. CSCs are regularly referred to as Tumor Initiating Cells (TICs), which are answerable for metastasis. At the point when the epithelial-mesenchymal transition (EMT) happens, CSCs relocate through the lymphatic and blood circulation, self-renew, and differentiate into different kinds of anomalous cancerous cells via other elements (e.g., Notch, TGF-beta, Shh, and Wnt/beta-catenin signaling). Progressive alteration in the cytochemical properties of CSCs limits the improvement of viable therapeutics besides against usually shared biomarkers that recognize and detach CSCs from normal stem cells and cancer. Accordingly, focusing on the CSC microenvironment can be effective therapeutics to forestall metastasis interceded by CSCs, such as changing ECM deposition, adjusting the acidic microenvironment, and neutralizing hypoxic conditions. The unique energy metabolism (such as glycolysis and OXPHOS) of CSCs is hoped to be another promising candidate for therapeutics. Table 1 summarizes promising compounds for forthcoming clinical CSC therapeutics.

**Table 1. Summary of potential compounds for future clinical CSC therapy**

| Target                          | Name of Compound |
|---------------------------------|------------------|
| Acidosis/hypoxia                | Anthracyclines, Anthraquinones, Acriflavine, Vinca alkaloids, Cobalt, MLN4924, PT2385, PT2399, PT2977 |
| Wnt/beta-catenin                | Salinomycin, Pipeliner, Curcumin, Repertaxin, Panthenolide, B-Qunolinol, Berberine, XAV939, IWR, IWP, Pynvinum, icRT-3.5.14, CDDO6477 |
| HDAC                            | Veprosic acid, Vinronstat, Panobinostat, Belinostat |
| Metabolism                      | IAC-010759, ME-344, Etoromoxir, perhexiline, DCA, AR-12, BX795, BX912 |

**Table 2. Clinical trials targeting CSCs**

| Drug name                        | Mechanism          | Condition or disease | NCT Number    | Current Status      |
|----------------------------------|--------------------|----------------------|---------------|---------------------|
| Vismodegib (GDC-0449)            | Hedgehog Pathway Inhibitor | Ovarian Cancer       | NCT00959647   | Completed           |
| Hedyehight Pathway Inhibitor     | Basal Cell Carcinoma | NCT00959647          |               | Completed           |
| Hedyehight Pathway Inhibitor     | Metastatic Colorectal Cancer | NCT00959647          |               | Completed           |
| Sondegib (LDE225)                | Hedgehog Pathway Inhibitor | Medulloblastoma       | NCT01700174   | Completed           |
| BMS-833933                       | Hedgehog Pathway Inhibitor | Leukemia             | NCT021003171  | Completed           |
| MK-0752                          | Notch pathway inhibitors | Metastatic Breast Cancer | NCT06645333  | Completed           |
| RO4929097                        | Notch pathway inhibitors | Adenocarcinoma of the Pancreas | NCT01122901   | Terminated          |
| Nilotrigacestat (PF-03846014)     | Notch pathway inhibitors | Desmoid tumors/aggressive fibromatosis | NCT01981551   | Active, not recruiting |
| Cremigacaeat (LY339478)          | Notch signaling pathway | Neoplasms             | NCT01695005   | Completed           |
| Notch signaling pathway          | Lymphoma            | NCT01695005          |               | Completed           |
| Demizumab (OMP-21M18)            | Notch pathway inhibitors | Non-Small Cell Lung Cancer | NCT01189968   | Completed           |
| Ipafricept (OMP-S4F28)           | WNT pathway inhibitors | Stage IV Pancreatic Cancer | NCT02092363   | Completed           |
| WNT pathway inhibitors           | Pancreatic Cancer    | NCT02050178          |               | Completed           |
| Vantictumab (OMP-1885)           | WNT pathway inhibitors | Metastatic breast cancer | NCT01973309   | Completed           |
| PRT-724                          | Wnt signaling pathway blocking | Advanced Solid Tumors | NCT01020405   | Terminated           |
| AVID 200                         | TGF-β inhibitors     | Malignant solid tumor | NCT013834662  | Active, not recruiting |
| Fresolimab (GCT1008)             | TGF-β inhibitors     | Metastatic breast cancer | NCT01401062   | Completed           |
| TGF-β inhibitors                 | Stage IA Non-Small Cell Lung Carcinoma | NCT02581787 | Recruiting | |
| NIT793                           | TGF-β inhibitors     | MPN (Myeloproliferative Neoplasms) | NCT02947165   | Active, not recruiting |
| TGF-β inhibitors                 | Lung cancer          | NCT02947165          |               | Active, not recruiting |
| TGF-β inhibitors                 | Hepatocellular Cancer | NCT02947165          |               | Active, not recruiting |
| TGF-β inhibitors                 | Colorectal Cancer    | NCT02947165          |               | Active, not recruiting |
| Ruxolitinib                      | Pancreatic Cancer    | NCT02947165          |               | Active, not recruiting |
| JAK inhibitors                   | Metastatic breast cancer | NCT01348490          |               | Completed           |
| JAK inhibitors                   | Myeloproliferative neoplasms | NCT01348490          |               | Completed           |
| AZD4205                          | JAK inhibitors       | Advanced non-small cell lung cancer | NCT03450330   | Completed           |
| SAR245409                        | PI3K and mTOR inhibitors | Advanced or metastatic solid tumors | NCT01240460   | Completed           |
| Matzuumab (EMD 72000)            | EGFR inhibitors      | Non small cell lung carcinoma | NCT00753246   | Completed           |

Clinical trials evaluating drugs for the selective inhibition of cancer stem cells in different solid tumors and hematologic malignancies.
Cancer immunotherapy against CSCs.44 CSCs and may lead to novel avenues for first scientific spectacle of an off-the-shelf effects against multiple tumors recognized tissues and exerted tenacious antitumor the frequency of ALDHhigh CSCs in tumor IgG therapy, ND vaccination diminished responses.42 When united with anti-PD-L1 IgG therapy, ND vaccination diminished the frequency of ALDHHigh CSCs in tumor tissues and exerted tenacious antitumor effects against multiple tumors recognized to harbor CSCs.43 This endeavor performs the first scientific spectacle of an off-the-shelf nanoparticle-based vaccine strategy against CSCs and may lead to novel avenues for cancer immunotherapy against CSCs.44

Autophagy
Autophagy, a cellular self-digestion measure, is a novel cytotoxicptive interaction to expand tumor cell endurance under nutrient or growth factor starvation, hypoxia, and metabolic stress. It has a functional act in tumor advancement and arrangement. The tumor hypoxic surroundings may support the site for the enhancement or enlargement of the CSCs and ensuing expeditious tumor progression.45 Recently, CSCs have been deliberated to be one of the causes of deterioration of anticancer treatment, metastasis, recurrence, radioresistance, and chemoresistance. Autophagy may play a dual role in CSC-related resistance to anticancer therapy; it is responsible for cell fate determination and the targeted degradation of transcription factors through growth arrest. Autophagy advances drug resistance, dormancy, and stemness, and maintenance of CSCs. Various studies have also implied that autophagy can expedite the calamity of stemness in CSCs.46

Artificial Intelligence
Artificial intelligence (AI) enables machines to think like humans.47 AI challenges in biomedicine involve multiple aspects, such as study documentation, study design, and sample size, clarity of scope and goals, statistical evaluation, integration of prior knowledge, model interpretability.48 Recently, multiple omics-based AI diagnostic tools have already been clinically validated.49 DeepMind’s AlphaFold 2 is a significant advance in AI-based protein structure prediction.50 Shortly, AI plays a prominent role in biomedicine, i.e., biomarker discovery, drug discovery, and digital health monitoring.51

AI was trained to utilize fluorescence images of the Nanog-Green fluorescence protein, the expression cultivated in CSCs, and the phase-contrast images.52 The AI model segmented the CSC region in the phase contrast image of the tumor model and CSC cultures.53 The possibility of mapping CSC morphology to the condition of undifferentiation was demonstrated using deep-learning conditional generative adversarial networks (CGAN) workflows.54 Mitosis, nucleus, cell shape, and hemorrhage were distinguished automatically using convolutional neural networks (CNNs).55

Clinical Trials
Several clinical trials scrutinize the best cell target to fight cancer, including, but not limited to, CSCs, since CSCs are maintained by other cells containing tumor-associated macrophages (TAMs) (Table 2).56

Summary
Cancer stem cells (CSCs) are a subpopulation of cancer cells within cancer with the unique capability of self-renewal and multi-potent. Their maintenance is regulated by stroma and microenvironment. CSCs have diverse characteristics from normal stem cells. The fundamental factors in the origin of CSCs are mutations and various genetic barriers. Several clinical trials targeting CSCs were also revealed herein.

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