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REVIEW

Cancer stem cells: a potential target for cancer therapy

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Abstract Current evidence indicates that a subpopulation of cancer cells, named cancer stem cells (CSCs) or tumor-initiating cells, are responsible for the initiation, growth, metastasis, therapy resistance and recurrence of cancers. CSCs share core regulatory pathways with normal stem cells; however, CSCs rely on distinct reprogrammed pathways to maintain stemness and to contribute to the progression of cancers. The specific targeting of CSCs, together with conventional chemotherapy or radiotherapy, may achieve stable remission or cure cancer. Therefore, the identification of CSCs and a better understanding of the complex characteristics of CSCs will provide invaluable diagnostic, therapeutic and prognostic targets for clinical application. In this review, we will introduce the dysregulated properties of CSCs in cancers and discuss the possible challenges in targeting CSCs for cancer treatment.

Keywords Cancer-initiating cell · Self-renewal · Tumorigenesis · Tumor metastasis

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Introduction

Cancer stem cells (CSCs), or tumor-initiating cells, are a subset of cancer cells with the abilities to self-renew and differentiate and to drive the growth and metastasis of tumors, whereas the majority of cancer cells have only limited proliferative potential [1, 2]. CSCs were first identified in acute myeloid leukemia (AML) [3, 4] and were subsequently discovered in breast cancer [5] and other types of solid tumors. A distinctive repertoire of cell surface markers are used to identify and enrich CSCs from human tumor tissues and cancer cell lines (Table 1). Compared to low-tumorigenic bulk cancer cells and normal stem cells, CSCs exhibit dysregulated signaling pathways and abnormal phenotypes. Recent studies have demonstrated that CSCs are involved in the initiation, growth, metastasis, therapy resistance and recurrence of human cancers [1, 2]. Here, we summarize the characteristics of CSCs in cancers and discuss the possibility of targeting CSCs as a therapeutic strategy for the treatment of human cancers.

Dysregulated self-renewal and differentiation capacities of CSCs

Normal stem cells have evolved various defense mechanisms to prevent tumor development. Normal stem cells also exhibit regulated life cycles that include tightly controlled self-renewal and committed lineage differentiation. Current evidence demonstrates that dysfunction of self-renewal- and differentiation-related genes endows normal stem cells and/or their differentiated progeny with the capacity for continuous self-renewal and dysregulated differentiation, which may promote the bypass of certain protective

Table 1 Cancer stem cell markers in tumors

Types of tumor	CSC markers	References
Breast cancer	CD44+CD24−, ALDH1+	[5, 6]
Glioblastoma	CD133+, CD15+	[7, 8]
Colon cancer	LGR5+, CD133+, CD44+v6	[9–11]
Liver cancer	CD24+, CD133+, CD90+	[12, 13]
Lung cancer	CD133+, ALDH1+	[14, 15]
Leukemia	CD34+CD38−, CD117	[16–18]
Melanoma	CD20+, CD271+	[19, 20]
Gastric cancer	CD44+, Lgr5+	[21, 22]
Ovarian cancer	CD44+CD117+, CD133+	[23, 24]
Pancreatic cancer	CD44+CD24+EpCAM+	[25]
Prostate cancer	CD44, TRA-1-60+CD151+CD166+	[26, 27]
Head and neck cancer	CD44+, c-MET+	[28, 29]
Osteosarcoma	CD133+, CD117+Stro-1+	[30, 31]
Chondrosarcoma	CD133+	[32]
Synovial sarcoma	CD133+	[33]
Ewing's sarcoma	CD133+, ALDH+	[34, 35]
Rhabdomyosarcoma	CD133+	[36]

mechanisms in cells, ultimately resulting in cancers. Combined p53 and PTEN mutations can promote c-Myc activation to enhance self-renewal capacity and impair differentiation of glioblastoma-initiating cells [37]. CSCs can be established by overexpressing H-Ras (L61) in p53-deficient neural stem cells, while Sox11 prevents tumorigenesis of CSCs by inducing neural differentiation [38]; however, only a fraction of cancer cells display the capacity to give rise to cancer cells in the long term [39]. Similar to normal stem cells, CSCs also display a committed differentiation ability. Glioblastoma stem cells (GSCs) can differentiate into astrocytes, oligodendrocytes or neurons [40] (Fig. 1). Interestingly, GSCs can transdifferentiate into vascular endothelial cells and pericytes to support vessel function and tumor growth [41–44].

In addition to glioblastoma, the self-renewal and differentiation abilities of CSCs are also documented in other types of cancers. CSCs from prostate cancer specimens can differentiate into three prostate epithelial cell lineages and reconstitute the original human tumor in vivo [45]. Head and neck squamous cell carcinoma encompasses a subpopulation of $CD44^+$ cancer cells that can be serially passaged and that reproduce the original tumor heterogeneity. $CD44^+$ cells express high levels of BMI1, whereas $CD44^-$ cancer cells express the differentiation marker involucrin and resemble differentiated squamous epithelium cells [28]. Colon CSCs are able to form large lumen-containing colonies, which consist of three types of differentiated colon epithelial cells in three-dimensional

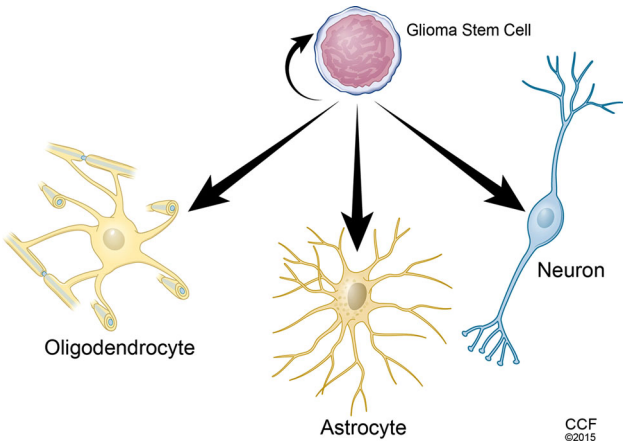

Fig. 1 Schema of glioblastoma stem cells (GSCs) displaying self-renewal and multiple-lineage differentiation. GSCs can maintain their stemness through self-renewal and differentiation into oligodendrocytes, astrocytes and neurons

matrigel culture. Some single cells from these colonies can reconstitute themselves and form tumors in immunodeficient mice [46]. Notably, CSC-derived differentiated cancer cells are usually major components of tumors and also play important roles in sustaining tumor growth.

Dysregulation of cell death in CSCs

In addition to sustained proliferation, cancer cells can disrupt the balance between proliferation and death by evading signals from apoptotic factors. Compared with other cells, CSCs are more resistant to apoptosis. $CD133^+$ colon CSCs secrete IL-4 to protect themselves from apoptosis [47]. When nutrition transport is prevented by blood vessel growth blockage, most colon cancer cells will die, while $CD133^+$ colon CSCs are apoptosis resistant [48]. Moreover, colon CSCs can escape the apoptosis stimulant by entering into a reversible quiescent state [49]; however, some treatment strategies can induce apoptosis sensitivity in CSCs. For example, the removal of phosphatase Wip1 inhibits APC-driven polyposis through lowering the threshold for p53-dependent apoptosis of colon CSCs [50]. BMI1 deficiency promotes cell death and delays cell cycle progression in lung cancers [51]. In conjunction with irradiation, TRAIL-expressing mesenchymal stem cells (MSCs) enhance glioma stem cells to undergo apoptosis [52]. Transient exposure of leukemia stem cells (LSCs) to a DNA methylation inhibitor causes an antitumor "memory" without immediate toxicity [53]. Delta12-prostaglandin-J3, an omega-3 fatty acid-derived metabolite, selectively targets LSCs for apoptosis in murine bone marrow and spleen [54]. Niclosamide inhibits the formation of spheroids and induces the apoptosis of breast CSCs [55].

CSCs and angiogenesis

Angiogenesis is considered as an important property of tumors and is required for tumor growth and metastasis. CSCs have the capacity to give rise to angiogenesis, whereas differentiated tumor cells are non-angiogenic [56]. CD105-positive renal CSCs release microvesicles to stimulate angiogenesis and the formation of premetastatic niches, which results in cancer cell metastasis to the lungs [57]. In glioblastoma, GSCs promote angiogenesis by secreting vascular endothelial growth factor (VEGF) and stromal-derived factor 1 (SDF-1) [58, 59] (Fig. 2). In contrast, VEGF promotes cancer stemness by stimulating angiogenesis in a paracrine manner and providing a perivascular niche for CSCs [60]. SDF-1 and its receptor CXCR4 can stimulate glioma stem cells to secrete VEGF to promote glioma growth and angiogenesis [61]. CSCs can promote vasculogenesis by serving as tumor vasculogenic progenitors [62]. $CD133^{+}$ liver CSCs promote tumor angiogenesis by upregulating IL-8 and CXCL1 signaling [63]. When endothelial cells are selectively eliminated in glioblastomas, the self-renewal ability of CSCs is downregulated, suggesting that endothelial cells are also critical for the maintenance of GSCs [64]; however, anti-angiogenic therapies have the potential to trigger a more invasive and metastatic phenotype in some tumors [65]. The anti-angiogenic agent increases the population of breast CSCs by generating a hypoxic niche [66]. Hypoxia inducible factors (HIFs) contribute to angiogenesis by binding to the HIF element and activating downstream pathways. Unlike HIF-1α, which is expressed in abundant hypoxic niche cells, HIF-2α is only expressed in GSCs and regulates the self-renewal and survival of GSCs but not that of non-stem tumor cells or normal neural progenitors [67]. HIF-2α might, therefore, represent a promising target to inhibit tumor angiogenesis. Interestingly, in glioblastoma, subsets of GSCs are able to transdifferentiate into vascular endothelium cells [41, 42]; however, a new study demonstrates that GSCs preferentially transdifferentiate into vascular pericytes but not endothelial cells. The selective deletion of GSC-derived pericytes in vivo impairs glioblastoma tumor growth and progression [43, 44].

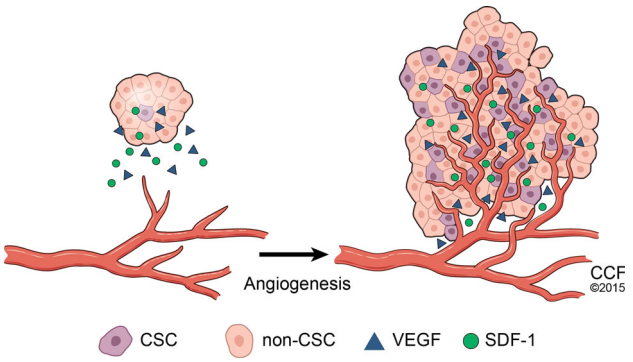

Fig. 2 Schema of tumor angiogenesis. During tumor angiogenesis, cancer stem cells release molecules that send signals to surrounding endothelial cells and encourage the growth of new blood vessels. Blood vessels are depicted as *red* tissues

Increased invasive and metastatic capabilities in CSCs

Metastasis can be divided into several steps. First, tumor cells disseminate into the surrounding tissues and enter capillaries. Second, the disseminated tumor cells are circulated in the blood and reach their target organs. Finally, tumor cells infiltrate from the blood and colonize to form metastatic tumors (Fig. 3). Recent evidence reveals that the epithelial to mesenchymal transition (EMT) is involved in cancer cell invasion and metastasis to distant organ sites [68]. Moreover, EMT contributes to the generation of CSCs with mesenchymal cell-like properties [69]. Our work reveals that Twist2 endows breast and liver cancer cells with mesenchymal phenotypes and stemness [70, 71]. Interestingly, CSCs display a combination of epithelial and mesenchymal phenotypes, indicating that cancer cells may adapt EMT programming to gain stem cell status [72]. Multiple genes contribute to regulate both self-renewal and

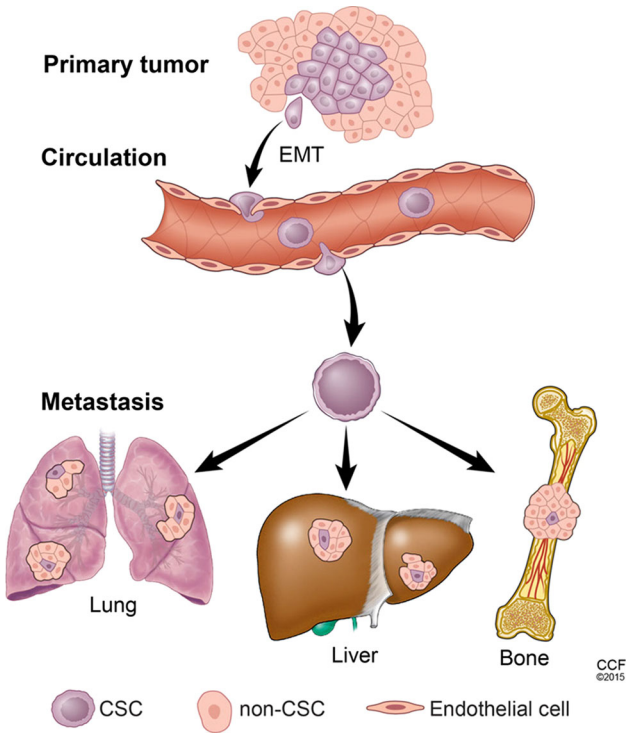

Fig. 3 Schema of metastasis. Cancer stem cells from a primary tumor disseminate to distant organs through the circulation and subsequently initiate macrometastatic deposition

EMT. The EMT activator Twist1 can interact with BRD4 to control the properties of basal breast CSCs by regulating Wnt5A [73]. YAP is important for stem cell pluripotency [74] and has also been implicated in regulating EMT [75].

Although EMT is very important for tumor dissemination, mesenchymal to epithelial transition is required for the colonization of tumor cells. Yang et al. [76] reported that the reversion of EMT is required for the disseminated tumor cells to proliferate and metastasize to distant sites. miR-200s promote the expression of E-cadherin by inhibiting ZEB but also regulate metastatic colonization by targeting metastasis-suppressing proteins [77]. Breast CSCs secrete TGF-β to stimulate stromal cells in the lungs expressing periostin, which interacts with Wnt1 and Wnt3A to augment Wnt signaling in CSCs [78]. $CD133^{+}CXCR4^{+}$ CSCs are found in the invasive front of pancreatic tumors, and deletion of this subpopulation abrogates tumor metastasis [79]. Autocrine CCL5 signaling activates the NF-κB pathway, leading to enhanced matrix metallopeptidase 9 (MMP9) secretion that promotes ovarian CSC invasion of stromal tissue [80]. $CD117^{+}Stro\text{-}1^{+}$ osteosarcoma CSCs show high invasive capacities, and CSC-derived tumors metastasize at a higher frequency [31]. CD44v6-expressing colorectal CSCs can initiate the process of tumor metastasis [11]. Therefore, CSCs are crucial for metastatic colonization [2].

CSCs and genomic instability

Genomic instability provides the engine power for the genetic mutations and epigenetic alterations that promote tumorigenesis and tumor progression. Cancer can be caused by the sequential accumulation of genetic mutations and epigenetic modifications that initiate the transformation of neoplasms. Shiras et al. [81] found that genomic instability in glioblastomas promotes the development of an immortalized clone into a CSC-like clone with the capacity of self-renewal, indicating that genomic instability contributes to the formation of CSCs.

Chromosome translocation is involved in the initiation of CSCs and tumorigenesis. The translocation of chromosomes 9 and 22 generates the new fusion protein Bcr-Ab1, and the continuously activated Bcr-Ab1 results in unregulated cell division in chronic myeloid leukemia (CML) [82]. Recently, a fused FGFR-TACC gene was found in glioblastoma. The tyrosine kinase coding domains of FGFR are translocated to the coding domains of TACC. The FGFR-TACC fusion protein exhibits tumor-initiating activity [83]. Similarly, chromosomal inversion between 3q21 and 3q26 brings the GATA2 distal hematopoietic enhancer into close proximity with the EV1 gene, leading to the hyper-activation of EV1 and the formation of AML [84, 85]. The active site mutation (R132H) of isocitrate dehydrogenase (IDH) was found in a high percentage of glioblastoma and AML patients [86, 87]. This type of mutant IDH acquires the ability to catalyze the NADPH-dependent reduction of α-ketoglutarate to R(–)-2-hydroxyglutarate but loses the ability to catalyze the conversion of isocitrate to α-ketoglutarate [88]. IDH1 (R132H) transgenic mice exhibit an increased number of early hematopoietic progenitors [89]. The IDH1 (R132H) mutation can also prevent some of the histone demethylation that is required for specific stem cell differentiation [90]. This evidence indicates that point mutations can affect stem cell maintenance and the incidence of CSC formation. Although random mutations are abundant, only one or two mutations are usually enough to drive the malignant progression of AML. Subsequent, continuous gene mutations may then contribute to cancer progression or relapse [91]. Interestingly, ultraviolet (UV) and mitomycin C, which induce DNA damage, can increase the quantity of CSCs in nasopharyngeal carcinoma [92]. DNA methylation and histone deacetylase inhibitors can induce redifferentiation in CSCs by promoting the re-expression of silenced genes [93].

CSCs, immune surveillance and inflammatory responses

Immune evasion or dysfunction may contribute to the development of tumors. Tumors transplanted in immunodeficient mice grow faster than those in normal animals. There is also a higher incidence of malignant neoplasms in organ transplant recipients and HIV-infected individuals [94]. These findings indicate that the immune system plays an important role in preventing tumorigenesis. CSCs might successfully escape immune surveillance and reconstitute a new tumor mass in new organs or recipients. GSCs contribute to the immune evasion of tumors by inhibiting T-cell proliferation and activation and by inducing regulatory T cell apoptosis [95]. CSCs in renal carcinoma escape immune surveillance by expressing low levels of Fas, natural killer receptors and complement regulatory proteins [96]. A recent study demonstrates that EMT contributes to the inhibition of cytotoxic T lymphocyte-mediated breast tumor cell lysis [97], indicating that CSCs potentially escape from immune surveillance via the EMT program. In addition, AML stem cells attenuate macrophage-mediated phagocytosis through SIRPα/CD47 signaling [98].

To some extent, tumors can be regarded as unhealed chronic inflammatory diseases. Chronic inflammation also contributes to the development of cancer. Hepatitis B infection is the main risk factor for hepatocellular carcinoma (HCC) in Asia. *Helicobacter pylori* is the most common bacteria found in the human stomach and is a high risk

factor for gastric cancer [99]. Inflammation can lead to aberrant DNA methylation in PcG target genes, which promotes the malignant transformation of intestinal tissues [100]. IL-6 is the most common inflammatory cytokine secreted by T cells and macrophages to stimulate immune responses [101]. The cytokine IL-6, which is generated by inflammatory cells, transforms prostate stem cells to prostate CSCs [102]. IL-6 cooperates with tumor-associated macrophage-derived MFG-E8 to promote CSC self-renewal and anticancer drug resistance by activating STAT3 and Sonic Hedgehog pathways [103]. Let-7 inhibition promotes IL-6-mediated activation of the STAT3 signal, which is necessary for the transformation of breast cells to CSCs [104]. Interferon regulatory factor 7 promotes the maintenance of glioma stem cells by activating IL-6 and Notch signaling [105]. Both GSCs and tumor-associated macrophages are enriched in the perivascular niche. Recently, GSCs have been found to secrete periostin to recruit monocyte-derived macrophages from the peripheral blood to support tumor growth [106]. Other immune and inflammatory cells and their secreted factors also play important roles in regulating CSCs. Therefore, CSCs may not only escape immune destruction but they may also hijack and adapt the reprogrammed immune responses and inflammatory cells and cytokines to promote self-maintenance and proliferation.

CSCs and dysregulated metabolism

In contrast to normal cells, which rely on mitochondrial oxidative phosphorylation to produce energy, cancer cells employ glycolysis, even in the presence of oxygen. This phenomenon is termed the "Warburg effect" [107]. This aerobic glycolysis metabolism provides cancer cells with an acidic environment that promotes cancer cell invasion into normal stromal tissue. Moreover, the metabolites generated by glycolysis can be used as intermediate materials to support the rapidly proliferating cells. The embryonic M2 isoform of pyruvate kinase (PKM2) is exclusively expressed in cancer cells and contributes to the Warburg effect. Aerobic glycolysis can be switched off by expressing PKM1 instead of PKM2, leading to reduced lactate production, increased oxygen consumption and a reduced ability to form tumors [108]. When cancer cells are stimulated by certain growth factors, phosphotyrosine signaling can regulate PKM2 to divert glucose metabolites toward anabolic processes instead of energy production [109]. Thus, it has been proposed that only cells experiencing the Warburg effect undergo the genetic aberrations that transform cells into CSCs [110].

CSCs are also maintained by the metabolic switch that is caused by gene dysfunction-mediated decreased oxygen consumption and low levels of reactive oxygen species [111]. Compared with non-CSCs, CSCs preferentially perform glycolysis over oxidative phosphorylation. Forced activation of pyruvate dehydrogenase, a key regulator of oxidative phosphorylation, inhibits CSC self-renewal in vitro and in vivo [112]. AMPK activation establishes a metabolic barrier to reprogramming and imposes a normalized metabolic flow away from glycolysis, the process required to promote stemness and pluripotency [113]. Glycolytic and aldehyde dehydrogenase (ALDH) activities are elevated in mesenchymal GSCs. Inhibition of ALDH1A3 sensitizes mesenchymal GSCs to irradiation [114]. Dichloroacetate inhibits pyruvate dehydrogenase kinase and shifts the metabolism from glycolysis to glucose oxidation, but it cannot promote the production of reactive oxygen species. In conjunction with irradiation, dichloroacetate induces Bax-dependent apoptosis [115]. VHL loss of function in renal carcinoma cells significantly increases HIF-1 activity and the switch from oxidative phosphorylation to glycolysis. Inhibition of HIF-1 can make cancer cells more sensitive to chemotherapy [116]; however, one study showed that GSCs are less glycolytic than differentiated glioma cells. CSCs rely on oxidative phosphorylation to produce more energy that correlates with radioresistance [117]. Most studies support the role of glycolysis in maintaining the stemness of CSCs. Therefore, metabolic therapy is a potential avenue for human cancer treatment.

CSCs and therapeutic resistance

Currently, therapeutic resistance is a fundamental obstacle to human cancer radiotherapy and chemotherapy. CSCs have been shown to contribute to therapeutic resistance and cancer treatment failure [118]. CSCs have channel proteins to efflux chemical compounds. Moreover, compared with non-CSCs, CSCs activate higher levels of survival signal pathways, which make them difficult to be eradicated.

The ABC super-family of transporters is a class of transmembrane proteins that induce multidrug resistance by effluxing drugs out of cells, thus reducing their toxicity [119]. Stem cells are able to pump out Hoechst 33342, so stem cells capable of exporting this dye are known as side population cells [120]. Side population cells express high levels of the transporter genes, ABCA3 and ABCG2, and exhibit a greater ability to expel cytotoxic drugs, leading to an enhanced survival of CSCs [121]. LSCs display a higher drug efflux than non-CSCs and contribute to leukemia relapse [122]. Therefore, ABC transporters in CSCs are potential targets for cancer treatment.

$CD133^{+}$ GSCs contribute to radioresistance by preferentially activating DNA damage repair pathways in these cells compared with non-CSCs [123]; however, the detailed

mechanism of radioresistance in CSCs is not well defined. c-Myc is involved in radioresistance by activating CHK1 and CHK2 in nasopharyngeal CSCs [124]. $CD133^+$ HCC cells promote chemoresistance through the preferential activation of the Akt and Bcl-2 survival signaling pathways [125]. TGF-β is induced as a negative feedback mechanism in breast cancer after chemotherapy treatment. The increased TGF-β signal contributes to breast cancer recurrence through the IL-8-mediated expansion of CSCs, and inhibition of the TGF-β pathway prevents the development of drug-resistant CSCs [126]. Temozolomide is one of the common chemical drugs used in treating GBM patients; however, subsets of quiescent GSCs escape the drug's effects and are responsible for tumor relapse after treatment [127]. The quiescent bladder CSCs can be activated into proliferative cycles when tumors are exposed to chemotherapy. Blocking this PGE-induced CSC repopulation by a PGE-neutralizing antibody significantly attenuates chemoresistance in bladder tumors [128]. Receptor kinase inhibitor is a common cancer treatment with fewer side effects. A recent report reveals that treatment with high concentrations of an EGFR inhibitor in lung cancer patients results in not only EMT features but also stem cell-like properties [129]. In addition to involvement in the metastatic cascade and acquirement of stemness of cancer cells, the EMT program contributes to radioresistance and chemoresistance. The EMT inducer ZEB1 is found to be stabilized by ATM and to interact with USP7 to stabilize CHK1, which promotes the DNA damage repair response in breast CSCs [130]. miR-30c sensitizes breast cancer cells to paclitaxel and doxorubicin by regulating TWF1 that promotes EMT [131]. Moreover, some cancers evade drugs through a loss of the expression of key proteins. For example, prostate CSCs that fail to express the androgen receptor do not respond to hormonal treatment, leading to the failure of hormone-based therapies [132]. Overall, CSCs can employ diverse mechanisms to acquire therapeutic resistance, and thus, targeting CSCs directly may be more effective than current treatment regimes and may improve the overall survival of cancer patients.

CSCs as therapeutic targets in cancer

Currently, drug candidates that target CSCs are being screened (Table 2). Salinomycin can specifically induce the loss of expression of breast CSC genes and reduce the proportion of CSCs in breast cancers [150]. Another drug, thioridazine, antagonizes dopamine receptors to selectively impair leukemic CSCs without affecting normal blood stem cells [151]. Finally, DECA-14 was identified to specifically target neuroblastoma CSCs without affecting normal pediatric stem cells [152].

The Bcl-2 family proteins are important anti-apoptotic proteins. The inactivation of Bcl-2, Bcl-xl, and Mcl-1 induced by an EGFR inhibitor, lapatinib, significantly promotes breast CSC apoptosis, suggesting that the Bcl-2 family proteins can be used as therapeutic targets in breast

Table 2 Drugs that target cancer stem cells

Drugs	Targets	CSC types	Mechanisms	References
WZB117	GLUT1	Pancreatic, ovarian, glioblastoma	Regulating metabolism	[133]
PTC-209	BMI-1	Colorectal	Inhibiting self-renewal	[134]
PF-2341066	c-Met	Head and neck squamous carcinomas	Eliminating CSC, inhibiting metastasis	[135]
ABT-737	BAD	Breast	Inducing CSC apoptosis	[136]
SP600125	JNK	Pancreatic	Inhibiting self-renewal	[137]
AD-01	CD44	Breast	Inhibiting self-renewal, inducing differentiation	[138]
All-trans retinoic acid	Nuclear receptor	Breast	Inhibiting self-renewal	[139]
IIIA4	EphA3	Glioblastoma	Inducing apoptosis	[140]
1B50-1	Calcium channel	Liver	Inhibiting self-renewal	[141]
Rituximab	CD20	Melanoma	Inhibiting metastasis	[142]
GSI	γ-Secretase	Ovarian	Inhibiting self-renewal	[143]
C3B3	HLA class I	Myeloma	Inhibiting self-renewal	[144]
Echinomycin	HIF1α	Leukemia	Inhibiting self-renewal	[145]
GLPG0187	α(v)-Integrins	Prostate	Inhibiting metastasis	[146]
Transtuzumab	HER2	Breast	Inhibiting self-renewal	[147]
7G3	CD123	Acute myeloid leukemia	Impairing homing to bone marrow	[148]
21M18	DLL4	Colon	Inhibiting self-renewal	[149]

cancer [153]. ABT-737, a Bcl-2 inhibitor, can specifically kill AML stem cells without affecting normal hematopoietic cells by inducing the disruption of the BCL-2/BAX complex and the BAK-dependent activation of the apoptotic pathway [154]. Docetaxel exposure can target the Notch and Hedgehog pathways to deplete CSCs by inhibiting Akt and Bcl-2 activities in prostate cancer [155]. The inhibition of TGF-β signaling by a compound was also identified to dramatically decrease the tumorigenicity of glioma stem cells by inducing cell differentiation [156].

A prostate stem cell antigen-based vaccine could affect long-term protection against prostate cancer progression in transgenic mice [157]. In addition, vaccination using dendritic cells that present CSC-associated antigen to stimulate cytotoxic T lymphocytes against CSCs prolongs the survival of animals bearing CSC-derived glioblastoma [158]. The monoclonal antibody against the epitope of CSCs exhibits an anti-cancer effect by suppressing the invasion of cancers or the expansion of CSCs [159, 160].

siRNA also exhibits therapeutic potential in targeting CSCs. A recent study has shown that the targeting of thymosin β4 by siRNA leads to the loss of chemoresistance in breast CSCs [161]. Inhibiting c-Myc expression by siRNA significantly suppresses CSC maintenance [162]. Recently, we reported that the transcription factor, ZFX, could regulate c-Myc to maintain the tumorigenic potential of GSCs [163]. Therefore, using siRNA to target CSC transcription factors represents an additional cancer treatment strategy.

CSCs show high glycolytic activity and low mitochondrial respiration, indicating that CSCs are more resistant to metabolic drugs [164]. In view of the phenomenon that CSCs display deregulated characteristics and drug resistance, combination therapy may be a better option for targeting CSCs. Sorafenib has been used to treat prostate cancer by inhibiting tyrosine protein kinases (VEGFR and PDGFR) and Raf kinases; however, sorafenib treatment can result in NF-κB activation, which promotes the survival of cancer cells. Treatment in combination with sulforaphane can completely suppress sorafenib-induced NF-κB activity and decrease ALDH1 activity in pancreatic CSCs [165]. Synergistic treatment with TRAIL and PI3K inhibitor-perifosine leads to the decrease of $CD34^+$ cells in AML patients [166]. Blockade of Akt/HIF-1α signaling with inhibitors can suppress tumor growth and prolong the survival of animals by eliminating liver CSCs [167]. In addition, inducing differentiation by arsenic trioxide has been identified as an effective strategy to treat acute promyelocytic leukemia [168, 169], but treatment that induces differentiation has a limited effect on solid tumors.

Recently, the CSC conference held in Cleveland led to more knowledge regarding CSC-targeting therapy [170]. Because CSCs exhibit preferentially active signaling pathways than non-stem cancer cells or normal cells, targeting signaling pathways is paid particular attention in clinical trials. For example, OMP-18R5, a monoclonal antibody targeting the Wnt receptor FZD7, inhibits the growth of breast, pancreatic, and colon cancer and is currently in clinical trial phase 1 [171]. Tarextumab (anti-Notch2/3) inhibits CSC self-renewal, induces cell differentiation and displays broad-spectrum anti-tumor ability. Clinical results demonstrate that the diabetic drug metformin has an antineoplastic effect by inhibiting CSC self-renewal and tumor metastasis [172]. More clinical evaluations of metformin on other solid tumors are ongoing.

Concluding remarks

Targeting CSCs provides a promising prospect for cancer treatment with few side effects and a better prognosis; however, the ratios of CSCs vary greatly in different patients. Moreover, CSCs themselves are heterogeneous and evolve continuously within a patient [173], and the different properties and phenotypes of CSCs do not necessarily coexist in the same subpopulation of CSCs. CSCs are heterogeneous among the different types of tumors. The strategy targeting CSCs in one specific tumor may not be effective in other types of tumors. Furthermore, non-tumorigenic cells might be transformed to tumorigenic cells in the presence of the appropriate microenvironmental cues [174–176]. Currently, whether the reversion of non-CSCs to CSCs is a universal phenomenon among all types of tumors remains unknown. Most importantly, both CSCs and non-stem cancer cells have to adapt multiple strategies to overcome various specific microenvironmental growth barriers [177]. Therefore, synergistically targeting CSCs and non-CSCs, together with targeting the tumor microenvironment, should be considered to achieve better therapeutic effects and less adverse reactions.

As shown in Table 1, most types of CSCs share the same cell surface protein as the CSC marker. Moreover, normal stem cells have the same antigen markers and properties with CSCs. For example, CD133 is the marker for neural stem cells and GSCs. Therefore, the drug used for targeting CSCs may inevitably attack normal stem cells. Due to the short lifespan and the severe symptoms of patients with malignant tumors, the negative effects of CSC-targeting therapy are difficult to be detected or are often neglected. Therefore, much research remains to identify the specific markers that only exist in the CSCs and not in normal stem cells.

The drug or antibody delivery efficiency is also a limitation of targeting CSCs. CSCs are only a small population of tumor cells. Some CSCs are located in the

hypoxic niche where there are fewer blood vessels. Therefore, whether the compound drug and antibody are able to target CSCs in hypoxic regions is still unknown. Furthermore, the blood–prostate barrier and blood–brain barrier are other concerns that need to be resolved. These types of barriers lead to drug delivery failure, which results in primary or metastatic tumors that cannot be effectively regressed. Therefore, developing notable drugs that effectively target CSCs will also be a major project in the next generation. Taken together, we still need to explore the characteristics of CSCs, which will lead to a better understanding of tumorigenesis and metastasis and will lay a solid foundation for cancer treatment in the future.

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Conflict of interest The authors declare no conflict of interest.

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