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Cancer Stem Cell Characteristics, Microenvironment and Drug Resistance

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Abstract

Cancer stem cells (CSCs), also known as tumor-initiating cells (TICs), contribute to tumorigenesis, cancer progression, metastasis, and therapeutic resistance. Their self-renewal, survival, and ability to evade treatment are strongly influenced by the tumor microenvironment and its associated signaling networks. This narrative review examines the biological characteristics of CSCs, their interactions with the tumor microenvironment, and the mechanisms underlying their proliferation, invasion, and resistance to anticancer therapies. Relevant literature was identified through searches of PubMed, Scopus, Web of Science, and Google Scholar using terms related to CSCs, the tumor microenvironment, drug resistance, and major signaling pathways, including Wnt, bone morphogenetic protein (BMP), Notch, and Hedgehog. Original research articles and review papers were considered, with no restrictions on the publication period, to integrate foundational knowledge with recent advances. The review discusses the role of CSC-associated signaling pathways and epithelial-mesenchymal transition in tumor progression and treatment resistance, as well as emerging therapeutic strategies targeting CSCs and their microenvironment. Understanding these mechanisms may provide valuable insights into the development of more effective therapeutic approaches for overcoming cancer recurrence and treatment resistance.

Keywords: Cancer stem cells, Tumor microenvironment, Drug resistance, Wnt signaling pathway, Epithelial–mesenchymal transition (EMT)

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Introduction

Biology of cancer stem cells

Stem cells are characterized by their capacity for long-term self-renewal and their ability to generate differentiated cells belonging to a particular tissue. These cells are present at relatively low frequencies in most tissues. Although it may seem reasonable to assume that individual tissues originate exclusively from their corresponding tissue-specific stem cells, the relationship between stem cells and tissue development is more complex (1-3).

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Normal and Cancer Stem Cells

A clear understanding of cancer stem cell biology requires an initial consideration of the properties of normal stem cells. Normal adult stem cells are somatic cells capable of extensive proliferation while retaining the capacity to produce both new stem cells and specialized differentiated cells (4). Their fundamental biological functions depend on two defining properties: self-renewal, which maintains the stem cell population, and differentiation, through which tissue-specific mature cells are produced (5).

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Like normal SCs, CSCs can exist in a quiescent state, are long-lived, and appear to have indefinite proliferative potential (6). They can undergo symmetric division to maintain the CSC population and asymmetric division to generate both a CSC and a shorter-lived progeny cell that contributes to the tissue or tumor. Their multipotency also enables them to generate differentiated progeny. CSCs possess mesenchymal characteristics, including the ability to migrate (7), which contributes to tumor metastasis (8). Some CSCs express specific stem cell markers and regulators of stemness, including NANOG, OCT3/4, and SOX2 (2).

Since stem cells often persist longer than other cell populations within many tissues, they may have greater opportunities to acquire early genetic alterations involved in transformation. These mutations can contribute to cancer development by disrupting cellular processes that regulate cell proliferation, maintain DNA integrity, and control intracellular signaling pathways (5).

The CSC hypothesis

Whereas normal tissues maintain cellular heterogeneity through tightly regulated developmental and functional programs, malignancy disrupts these programs, giving rise to heterogeneous populations of cancer cells with distinct biological behaviors (9,10).

Two major models have been proposed to explain how tumors develop heterogeneous cell populations: the stochastic or clonal evolution model and the hierarchical model, commonly referred to as the cancer stem cell (CSC) theory. The clonal evolution concept was introduced by Peter Nowell in 1976 and proposes that cancer arises through the progressive accumulation of somatic genetic alterations (11,12). According to this model, a cellular clone carrying an oncogenic alteration that confers a survival or growth advantage can expand within the tumor. As these cells proliferate, their progeny may acquire additional somatic changes that further enhance their fitness and malignant characteristics. Clones with greater adaptive fitness can progressively expand and replace less competitive populations. Continued acquisition of genetic alterations consequently generates multiple genetically distinct subclones within the same tumor. In accordance with the Darwinian principle of selection, subclones with advantageous alterations are preferentially maintained and contribute to the genetic and cellular heterogeneity observed in the resulting tumor.

The clonal evolution model assumes that tumor cells have a comparable capacity to contribute to tumor growth and progression, with malignancy resulting from the accumulation of advantageous genetic alterations. This concept has influenced many conventional cancer treatments, which primarily aim to eliminate rapidly proliferating tumor cells in an effort to achieve complete disease control. Nevertheless, durable cures remain uncommon in several human cancers, particularly in solid tumors, where cancer-associated mortality continues to be substantial (13).

The hierarchical model of tumor development proposes that tumor-forming potential is restricted to a relatively small subset of tumor cells, referred to as CSCs. Initial evidence in support of this model was obtained mainly from studies of leukemia and multiple myeloma, which showed that only a minority of malignant cells could sustain extensive proliferation. In one study, mouse myeloma cells isolated from ascitic fluid were separated from normal hematopoietic cells and subsequently examined using in vitro clonal colony-forming assays. The results showed that the frequency of colony-forming cells ranged from approximately 1 in 10,000 to 1 in 100 cancer cells (14). Similarly, following in vivo transplantation of leukemic cells, only about 1-4% of the cells were able to produce spleen colonies (15,16). These clonogenic cells were

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subsequently characterized as leukemic stem cells (14).

These observations led to two potential explanations. One possibility was that all leukemia cells possessed a low but measurable probability of undergoing extensive proliferation and could therefore function as leukemic stem cells. The alternative explanation was that most leukemia cells lacked substantial proliferative capacity and that this property was confined to a small, defined subpopulation. The distinction between these models has important implications for tumor development: the latter suggests that, under appropriate cellular and microenvironmental conditions, a phenotypically distinct minority of cancer cells can undergo sustained expansion and initiate a new tumor (2).

Testing the latter hypothesis requires different leukemic cell populations to be isolated and compared according to their colony-forming capacity. Dick et al. provided such evidence by demonstrating that human acute myeloid leukemia (AML) stem cells are characterized by a CD34+CD38− phenotype and can be identified and isolated from patient-derived samples (3). These findings challenged the assumption that all AML cells possess comparable clonogenic potential and instead supported the existence of a distinct leukemic cell population with enhanced colony-forming capacity (2).

Similar heterogeneity has been observed in solid tumors, in which cancer cells differ phenotypically and only a limited fraction exhibits clonogenic potential under both in vitro and in vivo conditions (17). For instance, studies have reported that only approximately one cell in every 1,000 to 5,000 cells derived from lung, ovarian, or neuroblastoma tumors can generate colonies in soft agar (18). Such findings support the view that tumor-forming capacity is restricted to a limited subset of tumor cells, which may consequently be regarded as cancer stem cells (2). Figure 1a summarizes the key concepts of the stochastic (clonal evolution) model and the CSC model of tumorigenesis. Figure 1b illustrates the proposed cellular origins of CSCs, including their possible derivation from normal stem cells or progenitor cells following oncogenic transformation.

Like normal stem cells, CSCs can maintain themselves through self-renewal while generating diverse cancer cell populations through differentiation, thereby contributing to the initiation of new tumors (20-22). Unlike the clonal evolution model, the CSC model attributes tumor heterogeneity largely to the multipotent nature of CSCs and their aberrant differentiation. Cells with the greatest tumor-initiating potential occupy the apex of a hierarchical cellular organization, which reflects the normally ordered pattern of tissue development but becomes disrupted during tumorigenesis (23,24).

CSC niche microenvironments

Normal stem cells (NSCs) are maintained within specialized niches that provide the signals necessary to preserve their defining properties, including self-renewal and pluripotency. Recent evidence suggests that CSCs also depend on a similar niche, referred to as the “CSC niche,” which regulates CSC differentiation and proliferation (25-27). The CSC niche is a highly complex microenvironment comprising stromal and mesenchymal cells, immune cells, blood vessels, the extracellular matrix (ECM), and soluble molecules released by niche-associated cells (Figure 1) (27). An important question is whether all cells residing within this microenvironment can undergo reprogramming and acquire stem-like properties or whether this capacity is restricted to cells originating from stem or progenitor lineages. Recent evidence from developmental and pathological models suggests that various cell types can undergo reprogramming and acquire stem-like characteristics under appropriate signaling conditions (10).

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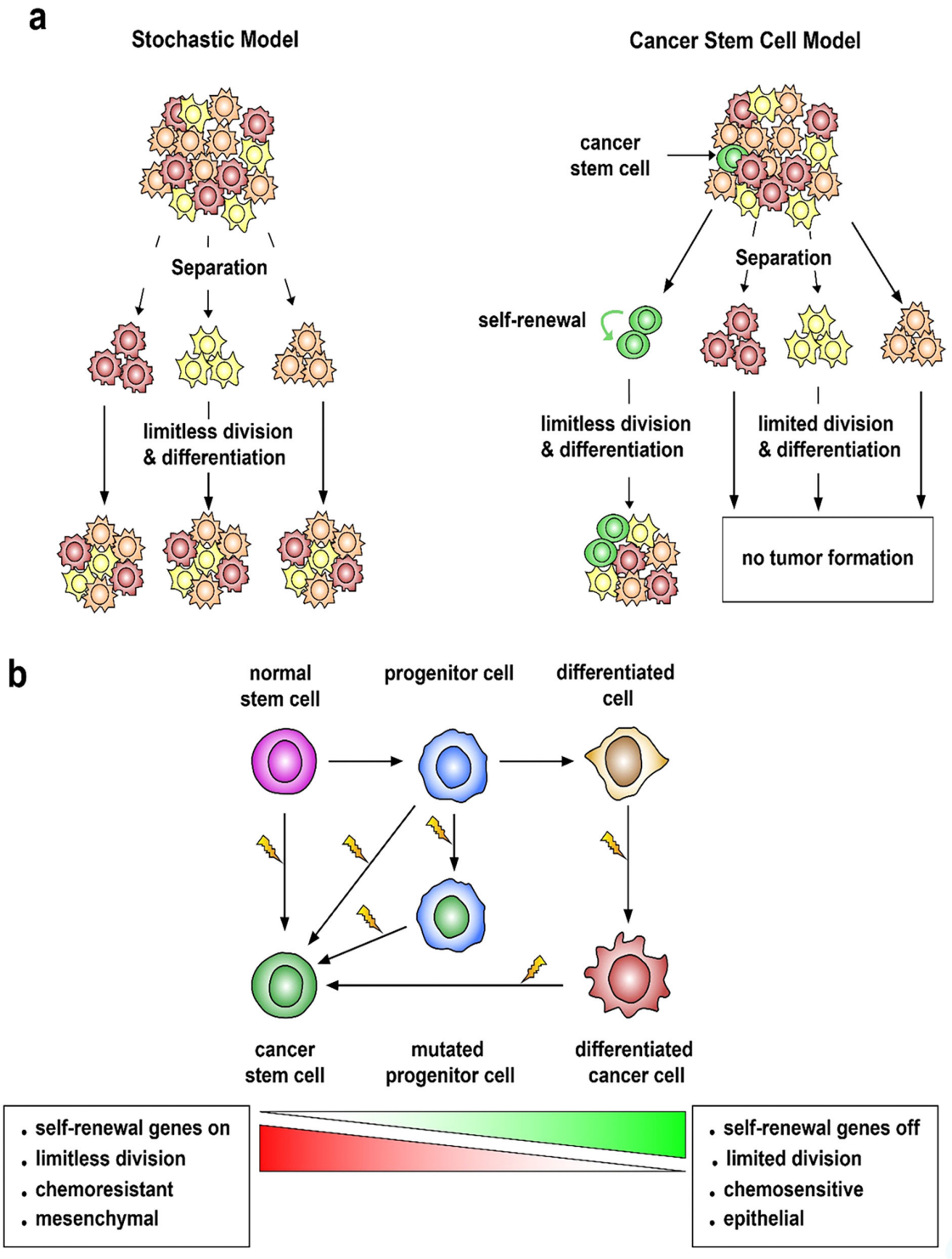


Figure 1. Proposed models describing the origin of cancer stem cells (CSCs). (a) Comparison of the stochastic and cancer stem cell (CSC) models of tumorigenesis. The stochastic model assumes that tumorigenic potential is distributed among a broad population of cancer cells, whereas the CSC model proposes that this capacity is concentrated within a distinct subpopulation with long-term self-renewal and tumor-initiating properties. (b) Possible cellular origins of CSCs, including transformation of normal stem cells or acquisition of stem-like properties by progenitor cells during malignant transformation. Adapted with permission from van Vlerken et al. (2012) (19).

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Studies of normal tissue development have also shown that certain progenitor populations can revert to a stem-like state when exposed to specific signals from the niche. Such processes represent examples of cellular fate reprogramming (13). These components participate in a complex regulatory network that remains incompletely characterized and involves various transcription factors, enzymes responsible for histone modifications, and polycomb group complexes, which collectively contribute to the reprogramming of differentiated cells (28).

Recent evidence from studies supporting the dedifferentiation theory suggests that differentiated cancer cells can spontaneously or in response to therapy acquire stem-like properties under pathological conditions.

Iliopoulos et al. demonstrated that IL-6 plays a central role in promoting the transition from non-CSCs to a CSC phenotype in breast and prostate cancer (29). These studies used a model in which chemotherapy was employed to induce tumorigenesis, demonstrating that CSCs and non-CSCs can coexist in a dynamic state of equilibrium, with the relative proportions of the two populations remaining stable across successive generations. A comparable shift in cell fate has been observed in glioblastoma multiforme (GBM), in which differentiated glioma cells acquired stem-like characteristics following treatment with clinically relevant concentrations of chemotherapeutic agents (30). This chemotherapy-induced cellular plasticity has been shown to promote the emergence of glioma stem cells (GSCs) in recurrent tumors and may contribute to the development of a more aggressive tumor phenotype (31,32). During tumor progression, the tumor-specific niche contributes substantially to the maintenance of cellular plasticity and the dynamic equilibrium between CSCs and their more differentiated, lineage-committed progeny (33).

Factors that disrupt this equilibrium may be influenced by the intratumoral microenvironment and can potentially affect clinical outcomes, given that CSCs are intrinsically resistant to conventional treatment modalities. However, the molecular mechanisms through which the tumor-specific CSC niche contributes to the maintenance of this equilibrium remain poorly understood in many solid cancers. Here, we describe several aspects of the CSC niche (10).

Signaling pathways

As discussed in relation to NSCs, CSCs rely on a specialized microenvironment that provides regulatory signals controlling their self-renewal and differentiation. CSC niches contain various types of stromal cells that not only maintain and nurture CSCs in a quiescent state but also actively regulate their biological functions, including self-renewal and differentiation, through the modulation of multiple signaling pathways (34). The niche microenvironment plays a central role in determining CSC fate and plasticity through a complex network of cell-cell and cell-matrix interactions, together with paracrine and autocrine signaling mechanisms (35). Many of the molecular pathways that regulate stemness, including those involving Hox genes and Wnt, Sonic hedgehog, and Notch signaling, are shared by CSCs and normal stem cells (NSCs). Current evidence indicates that Wnt and BMP signaling contribute to the regulation of CSC fate and the maintenance of cellular equilibrium, with Wnt generally promoting these processes and BMP negatively regulating them (36,37). Disruption of these signaling pathways can impair normal stem cell differentiation and proliferation, potentially contributing to tumor development. Experimental evidence has shown that β-catenin is required for the long-term maintenance of hematopoietic stem cells (HSCs) in vivo, whereas conditional deletion of β-catenin in mice impairs the development of Bcr-Abl-induced chronic myeloid leukemia (CML) (38).

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Notch signaling also plays an important role in cellular proliferation and differentiation. Excessive Notch activation can promote tumorigenesis and enhance cell survival, and Notch signaling has also been implicated in tumor angiogenesis (39). Increasing evidence further supports a role for the Sonic hedgehog (Shh) pathway in stem cell regulation, with aberrant Shh activation frequently associated with several malignancies, including multiple myeloma (40).

Alterations in niche-derived signals, particularly those that suppress pathways involved in regulating cell proliferation, may also affect stem cell self-renewal and promote tumorigenesis (41). An altered microenvironment may therefore contribute to the development of precancerous conditions. For example, studies have shown that a retinoic acid receptor γ (RARγ)-deficient microenvironment can induce a myeloid proliferative disorder (MPD). Similarly, MPD has been observed in retinoblastoma 1 (Rb1)-deficient mouse models, which are characterized by a marked reduction in trabecular bone volume (42).

Several mechanisms involved in normal stem cell migration are also shared with cancer invasion and metastasis. The Wnt/β-catenin and Bmi-1 pathways play important roles in regulating tumor metastatic behavior (43,44). Metalloproteinases and integrins contribute to the activation and migration of bone marrow-derived stromal cells and can also facilitate cancer cell migration and metastasis. In addition, cancer cells may express CXCR4 and migrate along an SDF1 gradient, thereby resembling the migratory behavior of their normal counterparts (38,45,46).

The CSC niche is also closely associated with the tumor microvasculature, which can provide regulatory signals that influence the fate of primitive cell populations. Components of the perivascular environment, including the basement membrane, endothelial cells, pericytes, and vascular smooth muscle cells, are considered potential regulators of the normal stem cell niche. These components may similarly contribute to CSC niches and may be involved in processes associated with blood-borne metastasis (44).

Extracellular matrix (ECM)

The ECM is a key component of the CSC niche, providing structural support that helps retain CSCs within their niche while also potentially influencing their biological functions (47).

CSCs can actively remodel the surrounding stroma through the secretion of matrix components and interactions with ECM proteins produced by neighboring stromal cells, thereby establishing conditions that favor their proliferation, survival, and invasive behavior (38). The regulatory effects of the ECM on stem cells have been extensively documented, with at least three well-characterized examples described in mammalian stem cell systems. One such example is found in the skin, where the positioning of stem cell populations is thought to depend on interactions between matrix glycoprotein ligands and β1 integrins, which are differentially expressed by primitive cells (48,49). A second example comes from the nervous system, where loss of tenascin C has been associated with changes in the number and functional properties of NSCs. Tenascin C appears to regulate stem cell sensitivity to agents such as fibroblast growth factor 2 (FGF2) and bone morphogenetic protein 4 (BMP4), thereby promoting the differentiation of stem cells into glial progeny (38). In the hematopoietic system, depletion of tenascin C has also been shown to alter primitive cell populations, suggesting that this matrix component may play a role in multiple stem cell niches (48). A third example involves osteopontin (OPN), an Arg-Gly-Asp (RGD)-containing sialoprotein that has been shown to contribute to the regulation of hematopoietic stem cells (HSCs) (50,51).

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Collectively, these examples indicate that ECM components can serve as localizing elements within the stem cell niche and modulate the size and behavior of stem cell populations through either stimulatory or inhibitory effects (48,49).

Vascular microenvironment

Accumulating evidence indicates that CSCs can reside within vascular microenvironments that support their long-term maintenance and self-renewal (34,52). Vascular endothelial cells have been identified as fundamental components of the CSC-specific niche (52). Calabrese and colleagues demonstrated that soluble mediators released by vascular endothelial cells can promote CSC self-renewal while suppressing differentiation in brain tumors (52). Moreover, recent experimental studies have indicated that proangiogenic mediators, including basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), and platelet-derived growth factor, may accumulate around blood vessels and support the maintenance and expansion of glioma stem-like cells in culture (52,53). Nitric oxide secreted by endothelial cells mediates this interaction and induces CSC self-renewal by activating the Notch pathway in brain CSCs. However, the interaction between the vascular niche and CSCs is likely to be more complex and bidirectional. Antiangiogenic treatment has been reported to reduce the CSC population while simultaneously altering the characteristics of the associated vascular niche. CSCs help protect their niche, while the vascular niche, in turn, promotes therapeutic resistance in brain CSCs. Thus, treatments targeting the vasculature could disrupt the CSC niche microenvironment and potentially lead to tumor eradication (35,38).

CSC niche microenvironment and EMT

One mechanism proposed to contribute to CSC maintenance involves epithelial-to-mesenchymal transition (EMT) (54). Although EMT is a key stage in metastatic progression, it also plays an important physiological role in tissue formation during embryogenesis (55). Recent data have demonstrated that EMT plays a crucial role in carcinogenesis, tumor progression, and metastasis (56,57). Embryonic transcription factors have recently been shown to drive classic cancer-associated characteristics, including resistance to apoptosis (58), invasiveness (59), and motility (60). Basal-like mammary cells in breast cancer may be capable of spontaneously dedifferentiating into a stem-like state following oncogenic transformation through EMT (61). In GBM, CD95 has been implicated in sustaining EMT-related programs and promoting the acquisition of stem-like characteristics by glioma cells (62,63). In two glioma patient-derived xenograft (PDX) models, increased expression of the EMT-associated transcription factor Twist was accompanied by enhanced invasive capacity and reduced responsiveness to treatment (64). During EMT, epithelial tumor cells lose their cell-cell adhesion properties and polarity while acquiring mesenchymal characteristics, including invasiveness, motility, and increased resistance to apoptosis (38).

Tumors may outgrow their oxygen supply and consequently develop greater hypoxia than the surrounding intact tissues (10,23). Recent studies suggest that hypoxia can increase the expression of stemness-associated factors, including c-MYC, OCT4, and NANOG, in previously non-stem tumor cell populations (44,56,57). The cellular response to hypoxia is generally regulated by hypoxia-inducible factors (HIFs), which are key transcription factors upregulated under low-oxygen conditions (65). Hypoxic conditions also stimulate angiogenesis by inducing the production of angiogenic factors, including vascular endothelial growth factor (VEGF). Although HIF1α is generally considered the main regulator of angiogenesis under hypoxic conditions, HIF2α also promotes angiogenesis by regulating VEGF expression. VEGF is one

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of the best-characterized endothelial cytokines regulated by hypoxia, and its effects on angiogenesis and tumor malignancy have been investigated in various tumor models (66-68). The perivascular niche also induces VEGF expression, and a recent study has shown that autocrine VEGF-VEGFR2 signaling can promote GSC viability and tumor development (69). In a mouse model of skin cancer, effective blockade of VEGFR2-neuropilin signaling was shown to eliminate the CSC population (70). Overall, these studies suggest that blocking the VEGF-VEGFR2 signaling pathway to target the perivascular CSC niche may represent an effective therapeutic strategy. Inhibition of VEGF activity using bevacizumab, a humanized monoclonal antibody directed against VEGFA, has been approved as a strategy for targeting tumor angiogenesis in glioma (71).

Crosstalk between tumor cells and their surrounding niche may promote EMT through autocrine and paracrine signaling involving multiple cytokines and growth factors (53,57). For example, squamous carcinoma cells may induce myofibroblast-like differentiation in neighboring cells through the secretion of TGF-β. This process may stimulate proliferation and expansion of the pre-existing CSC pool. Moreover, YB-1 is a protein associated with aggressive breast cancer (38,56). YB-1 promotes the translation of mRNAs encoding ZEB1, Twist, Snail, and other transcription factors that coordinate EMT. Increasing evidence suggests that ZEB1 not only promotes EMT but also maintains stemness. Therefore, targeting EMT-related pathways may represent a promising therapeutic strategy (38).

CSCs and drug resistance

Cancer represents a substantial global health burden and contributes to approximately one-fifth of all deaths in developed countries (72). Extensive cancer research has led to new approaches to cancer diagnosis and treatment, resulting in considerable advances in prevention, prognostication, and patient management (73). Tumor heterogeneity is one of the major causes of therapeutic failure and subsequent disease progression. Among the most common cancer treatment modalities are surgery, radiotherapy, and chemotherapy, which are frequently used in combination. Surgical intervention may provide effective control of localized tumors, whereas combining chemotherapy with radiotherapy can improve treatment outcomes in several malignancies (74). Chemotherapeutic approaches are also used to target primary tumor sites and residual disease that persists following surgery or radiotherapy (75). Nevertheless, exposure to anticancer treatments may promote the emergence of diverse tumor cell populations. This intratumoral heterogeneity can subsequently reduce therapeutic effectiveness and ultimately contribute to treatment resistance and continued tumor progression (76,77). Chemotherapy resistance, defined as a reduction in the responsiveness of cancer cells to anticancer agents, represents a major challenge in cancer management (78). It is also frequently associated with tumor recurrence, which may be characterized by more aggressive behavior and the development of metastatic disease (79,80). Existing evidence supports the role of CSCs in chemoresistance and cancer relapse, given their capacity for self-renewal and differentiation into diverse cancer cell phenotypes following exposure to chemotherapeutic agents (72,81). CSCs can also enter a quiescent state characterized by temporary cell cycle arrest, which may enhance their resistance to chemotherapy and radiotherapy (72,82-84).

Chemotherapy resistance and subsequent tumor recurrence

Recent studies suggest that treatment may selectively favor the persistence and expansion of CSCs. Many cytotoxic agents eliminate a large proportion of the tumor mass, whereas a relatively small CSC population can withstand

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treatment and subsequently survive and proliferate within the tumor microenvironment (26,85). Elucidating the molecular mechanisms and oncogenic factors that enable CSCs to evade the effects of chemotherapy and radiotherapy may facilitate the development of more effective treatments. In this context, we discuss how CSCs contribute to chemotherapy resistance and the cellular processes underlying this phenomenon (72).

Elevated detoxification capacity and multidrug resistance (MDR)

Side-population (SP) cells exhibiting stem-like features have been identified in various solid malignancies, including lung cancer, retinoblastoma, breast cancer, neuroblastoma, gastrointestinal cancer, and glioblastoma. These cells express elevated levels of drug efflux transporters, including MDR1, ABCG2, and ABCB1, which facilitate the efflux of Hoechst dye and cytotoxic drugs, thereby conferring substantial resistance to chemotherapeutic agents and potentially contributing to disease relapse (86,87). As suggested by Alisi et al., the overexpression of ABC proteins may represent a major defense mechanism that protects CSCs from the cytotoxic effects of chemotherapeutic drugs (88). Notably, the PI3K/Akt signaling cascade has been implicated in the regulation of ABCG2 function by influencing its trafficking and retention at the plasma membrane. In addition, PTEN loss has been associated with the emergence of an SP phenotype in human glioma stem-like cells (89). Another mechanism implicated in chemoresistance involves aldehyde dehydrogenase (ALDH), whose activity has been reported to be elevated in both normal and patient-derived $CD34^{+}/CD38^{-}$ leukemic stem cells. As a cytosolic enzyme, ALDH catalyzes the oxidation of intracellular aldehydes and may thereby protect cells against the damaging effects of reactive oxygen species (ROS), contributing to resistance to anticancer treatment (90). Elevated ALDH activity has also been proposed as a useful marker for identifying CSCs across several malignancies, including breast cancer (91), bladder cancer (92), head and neck squamous cell carcinoma (93), lung cancer (94), and embryonal rhabdomyosarcoma (95). In lung cancer cell culture models, ALDH1A1-positive CSCs have demonstrated greater resistance than ALDH1A1-negative cells to several chemotherapeutic agents, including gefitinib, cisplatin, etoposide, and fluorouracil (96).

EMT effect on drug resistance

In patients with metastatic cancer, circulating tumor cells can simultaneously exhibit molecular signatures characteristic of epithelial-mesenchymal transition (EMT) and stem-like properties (97). The induction of EMT or the activation of EMT-associated transcription factors (TFs) can confer stem-like characteristics on cancer cells (98). In human breast cancer, normal mammary stem cells and neoplastic stem-like cells exhibit molecular markers that overlap with those observed in cells undergoing EMT. EMT may also promote the acquisition of stem cell properties by more differentiated tumor cells, thereby contributing to the expansion of the CSC population (54). Its activation has further been associated with the development of resistance to therapeutic agents (99). This association has been demonstrated in gefitinib-resistant lung cancer cells, which acquire EMT-associated characteristics alongside the activation of Notch-1 signaling (100,101). The phenotypic changes associated with EMT may also confer stem-like properties on malignant cells, facilitating their invasion of other tissues and enabling them to withstand therapeutic treatment (102). ZEB1 is an important regulator of this process and has been implicated in maintaining CSC characteristics, including stemness and chemoresistance. In malignant glioma, ZEB1 regulates these properties by modulating the transcription of O-6-methylguanine-DNA methyltransferase

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(MGMT) through mechanisms involving miR-200c and c-MYB (103).

Resistance to DNA Damage-Dependent Cell Killing

CSCs possess several protective mechanisms that enable them to survive the cytotoxic effects of DNA damage. These mechanisms include (1) strengthening antioxidant defenses and ROS detoxification, thereby limiting oxidative DNA damage; (2) enhancing DNA damage repair through the phosphorylation and activation of ATM, CHK1, and CHK2; and (3) stimulating intracellular survival pathways with antiapoptotic effects, particularly the PI3K/Akt, Wnt/β-catenin, and Notch signaling cascades (104).

CD44, a cell adhesion molecule commonly expressed by CSCs, can interact with the glutamate-cystine exchange transporter and thereby influence the intracellular availability of reduced glutathione (GSH). Accordingly, increased CD44 expression may enhance the cellular capacity to synthesize GSH, thereby strengthening antioxidant defenses and improving protection against ROS (105).

Interestingly, like NSCs, CSCs exhibit relatively low ROS levels, which are associated with increased expression of antioxidant scavenging systems, enhanced protection against oxidative stress, and greater resistance to radiotherapy (106). In addition, in breast cancer, the CD44+/CD24-/low CSC subset develops radioresistance through the activation of ATM signaling without alterations in the nonhomologous end joining (NHEJ) DNA repair system (107).

Inflammation

Prolonged exposure of breast cancer cells to trastuzumab has been reported to preferentially select for a CSC population characterized by EMT-related features and increased cytokine production, particularly IL-6, relative to the corresponding parental cells. This IL-6-dependent inflammatory feedback mechanism may subsequently contribute to the development of trastuzumab resistance in these cells (108).

Similarly, increased autocrine TGF-β signaling is accompanied by elevated IL-8 expression following paclitaxel treatment in triple-negative breast cancer. These signaling mediators may promote the expansion of the CSC population and contribute to subsequent tumor recurrence (109). Another example involves the stromal chemokine stromal cell-derived factor 1α (SDF-1α) and its cognate receptor CXCR4. The SDF-1α/CXCR4 signaling axis contributes to the homing of hematopoietic cells to the bone marrow niche and is also implicated in the ability of leukemia cells to resist apoptosis induced by chemotherapeutic agents (110-112). In addition, CSCs in chemoresistant tumors can produce a range of proinflammatory signals, including interferon regulatory factor 5 (IRF5). IRF5 functions as a transcriptional regulator in chemoresistant tumors and promotes the expression of macrophage colony-stimulating factor (M-CSF), which contributes to the conversion of CD14+ monocytes into M2-like immunoregulatory myeloid cells (113).

Immune cells

Previous studies have demonstrated that tumor-associated macrophages (TAMs) enhance chemotherapy resistance in both myeloma-derived cell lines and primary myeloma cells by protecting them against spontaneous or chemotherapy-induced apoptosis. This effect appears to involve direct interactions between TAMs and malignant cells within the tumor niche, resulting in the suppression of caspase activation and the cleavage of key components of apoptotic signaling pathways (114). TAMs can also induce CSC-like properties in pancreatic cancer cells through the activation of signal transducer and activator of transcription 3 (STAT3), while simultaneously suppressing antitumor CD8+ T-cell activity during chemotherapy (115). In pancreatic ductal adenocarcinoma, cancer cells

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secrete colony-stimulating factor 1 (CSF1), which promotes the recruitment and activation of CSF1 receptor (CSF1R)-expressing TAMs. This interaction increases the expression of cytidine deaminase (CDA), an intracellular enzyme that metabolizes the active form of gemcitabine, thereby protecting cancer cells from chemotherapy and contributing to treatment resistance (116).

Cancer-associated fibroblasts (CAFs)

Evidence suggests that chemotherapy preferentially targets non-CSCs while stimulating cancer-associated fibroblasts (CAFs). CAFs may establish a niche that promotes chemoresistance by enhancing the production of various cytokines and chemokines, including interleukin-17A (IL-17A). This cytokine may contribute to CSC maintenance by promoting self-renewal and invasion (117). Previous studies have also demonstrated that CSCs can differentiate into CAF-like cells (CAFLCs) and may therefore represent an important source of CAFs that support tumor survival within the tumor microenvironment (118).

Several studies have shown that CAFs produce various growth factors, cytokines, and chemokines, including hepatocyte growth factor (HGF), which may stimulate MET receptor expression in metastatic colorectal cancer cells, thereby protecting CSCs against apoptosis in response to cetuximab monotherapy (119).

Hypoxia

In pancreatic cancer, hypoxia and hypoxia-inducible factor (HIF) signaling have been implicated in the maintenance and regulation of CSCs and the EMT phenotype, including processes such as cell migration, invasion, and angiogenesis (120). These effects are associated with elevated levels of VEGF and IL-6, together with increased expression of CSC-associated markers, including Nanog, Oct4, and EZH2 (121). Accordingly, hypoxia and HIF signaling may also contribute to CSC resistance to anticancer therapies. Under hypoxic conditions, the population of gefitinib-resistant lung CSCs in epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC) may increase through HIF1α-mediated upregulation of insulin-like growth factor 1 (IGF1) and subsequent activation of the IGF1 receptor (IGF1R) (122).

Epigenetics

CSC-associated drug resistance is also influenced by epigenetic mechanisms, including DNA methylation and histone modifications. Although DNA methylation patterns remain largely unchanged during TGF-β-induced EMT, several other epigenetic alterations have been reported (123). These include (1) an LSD1-dependent global reduction in the heterochromatin-associated mark H3K9 dimethylation (H3K9Me2); (2) increased levels of the euchromatin-associated mark H3K4 trimethylation (H3K4Me3); and (3) changes in the transcription-associated mark H3K36 trimethylation (H3K36Me3). In particular, H3K4Me3 may contribute to LSD1-mediated chemoresistance (123).

B-cell-specific Moloney murine leukemia virus integration site 1 (BMI1), a member of the Polycomb group (PcG) of epigenetic silencer proteins, is another important regulator of stem cell maintenance. BMI1 supports self-renewal in both adult stem cells and various CSC populations through several pathways, including Notch, Wnt, and anchorage-independent growth signaling (124). Its involvement in protection against apoptosis and the development of drug resistance has been reported in several malignancies, including nasopharyngeal carcinoma (125), melanoma (126), pancreatic adenocarcinoma (127), ovarian cancer (128), and hepatocellular carcinoma (129). Another PcG protein, enhancer of zeste homolog 2 (EZH2), has also been implicated in the response of glioma stem cells (GSCs) to radiotherapy. Through its association

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with the upstream mitotic kinase maternal embryonic leucine zipper kinase (MELK), EZH2 can attenuate radiation-induced effects and consequently promote GSC survival and radioresistance (130). Interestingly, EZH2 and BMI1 have been reported to exhibit an inverse relationship with TP53 mutation status and prognostic signatures in breast cancer (131).

Histone acetylation represents another epigenetic mechanism involved in transcriptional regulation and CSC chemoresistance (132). The histone deacetylase (HDAC) inhibitor vorinostat, for example, reduces the expression and activity of EGFR, ErbB2, and ErbB3 by promoting their ubiquitination and lysosomal degradation. Combined with its ability to reverse EMT in gefitinib-resistant cells, these effects may enhance the antitumor activity of gefitinib in head and neck squamous cell carcinoma (133). In addition, DNA methylation of CpG islands within promoter regions can epigenetically silence numerous tumor suppressor genes in chemoresistant cancers. One example is insulin-like growth factor-binding protein 3 (IGFBP-3), which regulates cell growth, transformation, and survival. Hypermethylation of its promoter has been associated with reduced IGFBP-3 expression and the development of acquired chemoresistance across several cancer types (134).

CSC-Based Therapy

Because CSCs contribute to chemoresistance and radioresistance, which are major factors in malignant progression, invasion, and tumor recurrence, CSC-targeted approaches have emerged as potential strategies for improving treatment outcomes and patient survival (34,82). Targeting the signaling networks that regulate CSC self-renewal, proliferation, and differentiation therefore represents an important area of investigation in cancer therapy (135,136). Over the past several decades, combining conventional treatments with agents targeting CSC-associated pathways, including Notch, Wnt, and Hedgehog (HH), has been proposed as a means of achieving greater therapeutic efficacy than targeting the bulk tumor or CSC population alone (135).

Several classes of drugs that directly interfere with Notch signaling have subsequently entered clinical investigation, differing in their molecular targets, mechanisms of action, and pharmacological classifications (135,137). Among these, γ-secretase inhibitors (GSIs) constitute the major class of Notch inhibitors. By blocking the terminal proteolytic processing of Notch receptors, GSIs prevent the release of the functional intracellular Notch domain. They were the first class of Notch-targeting agents to enter oncology clinical trials (39,138).

Similarly, the HH pathway inhibitor vismodegib was approved by the US Food and Drug Administration (FDA) in 2012 and by the European Medicines Agency (EMA) in 2013 for patients with metastatic or locally advanced basal cell carcinoma (BCC) who are ineligible for surgical or radiation-based treatment (139,140).

Therapeutic targeting of Wnt signaling has also yielded promising findings regarding its potential to inhibit carcinogenesis, tumor invasion, and metastasis (138). In a mouse model of prostate cancer, a Wnt3A-neutralizing monoclonal antibody (mAb) was shown to inhibit proliferation and promote apoptosis. Other Wnt-targeted agents have been evaluated in phase I clinical trials involving patients with advanced solid tumors. These include vantictumab (OMP-18R5), an mAb targeting five Frizzled (Fz) receptors (Fz1, Fz2, Fz5, Fz7, and Fz8) (141,142), and OMP-54F28, an agent that targets Wnt signaling through a decoy receptor consisting of a truncated Fz8 fusion protein (143).

The EMT pathway has also emerged as a potential therapeutic target for limiting CSC aggressiveness and acquired resistance to anticancer drugs (144,145). In general, EMT-

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targeted agents can be classified into three categories: (1) regulators of extracellular EMT-inducing signals, including TGF-β, EGF, Axl-Gas6 signaling, hypoxia, and extracellular matrix components; (2) transcription factors, such as Twist1, Snail1, ZEB1/2, and T-box factors, that regulate EMT-associated transcriptional programs involving Brachyury and downstream markers, including E-cadherin, N-cadherin, vimentin, and HoxA9; and (3) regulators of EMT-related transcription factors and epigenetic mechanisms, including microRNAs (144,146,147).

Accumulating evidence also indicates that microRNAs (miRNAs) and other noncoding RNAs, particularly long noncoding RNAs (lncRNAs), are important regulators of CSC properties, including self-renewal, asymmetric division, drug resistance, and tumor recurrence (148,149). Consequently, several miRNAs have been investigated as potential therapeutic targets for CSC-directed interventions. Examples include miR-22, which targets TET2 in leukemia, including acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), as well as in breast cancer (150); let-7, which targets RAS and HMGA2 in breast cancer (151); miR-128, which targets BMI-1 in brain cancer (148); and miR-200, which regulates ZEB1/ZEB2, BMI-1, and SUZ12 in breast cancer (152,153). Other miRNAs have also been investigated in colorectal and prostate cancers, with reported effects on malignant behavior (154,155).

Finally, immunotherapeutic approaches specifically directed against CSCs may provide an additional avenue for improving cancer treatment. Various immune effectors capable of recognizing and eliminating CSCs have been investigated, including natural killer (NK) cells and γδ T cells as components of innate immunity, antibodies involved in humoral immunity, CSC-based dendritic cell approaches, and CSC-primed cytotoxic T lymphocytes (CTLs) involved in adaptive cellular immunity (156,157).

Conclusion

Cancer development is associated with the dysregulated and uncontrolled expansion of self-renewing CSC populations. Although self-renewal is a shared characteristic of normal stem cells and CSCs, the regulatory mechanisms governing this process differ substantially between the two cell types. In CSCs, dysregulation of signaling pathways such as Wnt and BMP within the niche disrupts the physiological balance between self-renewal and differentiation, thereby contributing to tumor formation and treatment failure. Characterizing the distinct mechanisms that regulate self-renewal in normal stem cells and CSCs requires the isolation and comparative analysis of these cell populations. Such approaches may help identify vulnerabilities that can be exploited to selectively target CSCs while preserving normal stem cells. In particular, therapies targeting pathways such as Wnt, BMP, Notch, and Hedgehog may offer greater selectivity and potentially lower toxicity than conventional treatment modalities.

A major finding of this review is that CSCs exhibit stem cell-like characteristics that contribute substantially to their resistance to chemotherapy and radiotherapy relative to bulk tumor cells. This resistance is mediated by multiple interconnected mechanisms, including the elevated expression of ABC drug transporters (MDR1 and ABCG2), increased ALDH activity, activation of EMT programs involving factors such as ZEB1 and Twist, efficient DNA damage repair through ATM signaling, low intracellular ROS levels, the production of inflammatory cytokines such as IL-6 and TGF-β, and supportive interactions with CSC niche components, including CAFs, TAMs, and hypoxic vascular niches. Consequently, CSCs have been implicated

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in tumor recurrence following anticancer treatment, a concept that remains subject to debate but is increasingly supported by experimental evidence.

Recent studies have further elucidated the complex mechanisms underlying CSC-driven drug resistance across different cancer types. In colorectal carcinoma, for example, CSCs can sustain drug tolerance through the activation of major signaling pathways, including Wnt/β-catenin, Notch, Hedgehog, PI3K/Akt, and MAPK/ERK, alongside mechanisms such as EMT, enhanced DNA repair, and PD-1/PD-L1-mediated immune evasion (158). In prostate cancer, lineage plasticity among prostate stem cells has similarly been identified as a key mechanism of therapeutic evasion, contributing to the development of treatment resistance (159).

Moreover, metabolic reprogramming has emerged as a critical driver of CSC-mediated therapy resistance. In ovarian cancer, CSCs exhibit considerable metabolic plasticity, switching between glycolysis and oxidative phosphorylation (OXPHOS) to survive chemotherapy-induced stress (160). Similarly, mitochondrial metabolism, regulated by PGC-1α and ERRα, plays a central role in maintaining CSC stemness and chemoresistance across multiple tumor types (161).

The tumor microenvironment (TME) is increasingly recognized as a major determinant of CSC survival. In lung cancer, bidirectional regulatory interactions between the TME and lung cancer stem cells (LCSCs), involving hypoxic conditions, extracellular matrix components, and various signaling pathways, promote self-renewal and drug resistance (162).

Furthermore, crosstalk between CSCs and cancer-associated fibroblasts (CAFs) establishes a reciprocal feedback loop that promotes therapeutic resistance, with CAFs providing a protective microenvironment that supports CSC survival and expansion (89).

Emerging therapeutic strategies increasingly focus on exploiting CSC-specific vulnerabilities. Targeting the Wnt/β-catenin pathway has shown promise in overcoming resistance to tyrosine kinase inhibitors and immune checkpoint inhibitors in hepatocellular carcinoma, particularly by reprogramming the immunosuppressive, or "cold," TME into an immunologically active, or "hot," microenvironment (163). Additionally, targeting cell surface GRP78 on brain tumor stem cells has been shown to reverse drug resistance and inhibit CSC expansion (164). Novel approaches, such as biomembrane-coated nanoparticles targeting circHIF1α, have successfully induced ferroptosis in ovarian CSCs, thereby overcoming cisplatin resistance (165).

Moreover, the CSC niche microenvironment, comprising the extracellular matrix (ECM), stromal cells, immune cells, and soluble factors, actively maintains CSC stemness and drug resistance through paracrine and autocrine signaling. Targeting this niche, for example, by blocking VEGF-VEGFR2 signaling or disrupting the perivascular niche, represents a promising adjuvant strategy for sensitizing CSCs to conventional therapies.

Finally, bibliometric analysis indicates that CSC research expanded substantially between 2001 and 2024, with major thematic clusters focusing on CSC biomarkers, drug resistance, metabolism, self-renewal, differentiation, tumor metastasis, immunotherapy, and the tumor microenvironment (166). These findings highlight the growing recognition of CSCs as important contributors to cancer progression and therapeutic failure.

In conclusion, effective cancer management requires a dual approach that directly targets CSC-specific signaling pathways, including Wnt, BMP, Notch, and Hedgehog, while simultaneously disrupting the protective CSC niche microenvironment. Future research should emphasize the application of integrated

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multiomics strategies to identify CSC-specific vulnerabilities, the development of rational combination therapies incorporating CSC inhibitors, epigenetic modulators, immunotherapies, and nanoparticle-based delivery systems, and the translation of CSC-targeted approaches into clinical practice (158,167). These advances may help overcome therapeutic resistance and improve clinical outcomes for patients with cancer.

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Code of Ethics

Not applicable. This article is a narrative review based on previously published literature and was not derived from a thesis, dissertation, or separately registered research project.

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