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Cancer stem cells

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ABSTRACT

Cancer stem cells (CSCs) are at the center of processes such as tumor heterogeneity, drug resistance, metastasis, and post-treatment recurrence in tumor biology. Due to their self-renewal and differentiation capabilities, these cells play a significant role in the course of disease by exhibiting resistance to conventional therapies. In malignancies with a high risk of recurrence and metastasis, such as ovarian cancer (OC), the development of new therapeutic strategies targeting CSCs has become critically necessary. This review presents the biological characteristics of CSCs and current treatment approaches in light of the literature, offering a comprehensive perspective on the subject.

Keywords: Cancer stem cells, tumor biology, tumor metabolism

INTRODUCTION

Cancer stem cells (CSCs) represent a heterogeneous cell population positioned at the top of the hierarchical structure in tumor development, with demonstrated capacity to generate an entire tumor tissue from a single cell. Through their abilities for self-renewal and differentiation, they are distinguished from progenitor or precursor cells. CSCs have been identified in solid neoplasms such as breast, brain, bone, prostate, ovary, skin, liver, bladder, lung, colon, pancreas, and head and neck tumors, as well as in hematological malignancies.[1]

These cells retain biological characteristics specific to pluripotent stem cells and are characterized by mechanisms such as the expression of CD133, CD44, and aldehyde dehydrogenase (ALDH), along with the reactivation of developmental signaling pathways like Wnt/β-catenin, Notch, and Hedgehog. Moreover, with their enhanced adaptive capabilities under stress conditions, they exhibit resistance to conventional therapies such as chemotherapy and radiotherapy, and are associated with tumor recurrence.[2] Therefore, therapeutic approaches that directly target CSCs are considered promising strategies for enhancing the effectiveness of oncological treatments.[3]

CANCER STEM CELLS METABOLISM

CSCs are metabolically specialized to produce energy using various substrates in order to survive under diverse microenvironmental conditions. As with normal stem cells, glucose is of vital importance for CSCs, and the presence of glucose in the microenvironment has been shown to significantly increase the number of stem cell-like cancer cells. CSCs exhibit significantly higher glucose uptake, lactate production, glycolytic enzyme expression, and intracellular ATP levels compared to other cells.[4] Among stem cell markers, CD44 is known to play a critical role in glycolytic metabolism.[5] The active maintenance of glycolysis is essential for the survival of CSCs and the sustained progression of the tumor.[6] Although glycolysis stands out as the primary energy production pathway in CSCs, recent studies have demonstrated that mitochondrial oxidative metabolism is also actively utilized by these cells.[7] Some studies have shown that CSCs possess higher ATP levels despite lower glucose consumption and lactate production compared to differentiated cancer cells.[8] Moreover, CSCs have been reported to utilize not only glucose but also various amino acids, such as glutamine and lysine, as energy sources. In addition, fatty acid oxidation may serve as an alternative metabolic pathway for energy production in these cells.[9]

CANCER STEM CELLS SIGNALING PATHWAYS

The persistence of CSCs and their ability to evade therapeutic interventions depend on the active maintenance of various intracellular signaling pathways. Recent studies have revealed that therapeutic strategies targeting these signaling pathways yield successful results in both cell culture and animal models. While signaling pathways such as Sonic Hedgehog (Shh), Wnt, fibroblast growth factor (FGF), Notch, and bone morphogenetic protein (BMP) play crucial roles in normal cell development and morphogenesis, they also hold critical functions in tumor formation and progression. Targeting these pathways offers a potential approach for the elimination of CSCs and for overcoming therapy resistance mechanisms.[10]

The Notch Pathway

The Notch signaling pathway is a mechanism that operates through cell-cell interaction and plays a critical role in various fundamental biological processes such as embryonic development, tissue homeostasis, and cell differentiation. Notch receptors are key components of an extensive signaling network that regulates cellular fate determination, proliferation, apoptosis, and stem cell renewal in complex organisms. This pathway functions through four distinct membrane-bound Notch receptors (Notch1, Notch2, Notch3, Notch4) and their ligands (Jagged1, Jagged2, Delta-like 1, Delta-like 3, Delta-like 4).

In particular, the Notch3 receptor has been reported to be overexpressed in high-grade serous OC. The overexpression of Notch3 leads to upregulation of pathways necessary for the development of CSCs in serous OC cell lines (**Figure 1**).[11] Administration of Notch pathway inhibitors combined with cisplatin resulted in significant reductions in both cancer stem cell population and tumor cell number.[12] The Notch signaling pathway is also associated with cervical cancer. Numerous studies have demonstrated increased Notch expression in cervical carcinoma cells. However, there is also evidence suggesting that in advanced-stage HPV-infected tumors, the expression level of Notch1 is decreased, and Notch signaling may suppress HPV-mediated transformation. These data indicate that the role of the Notch pathway in cervical carcinogenesis is complex and context-dependent.[13]

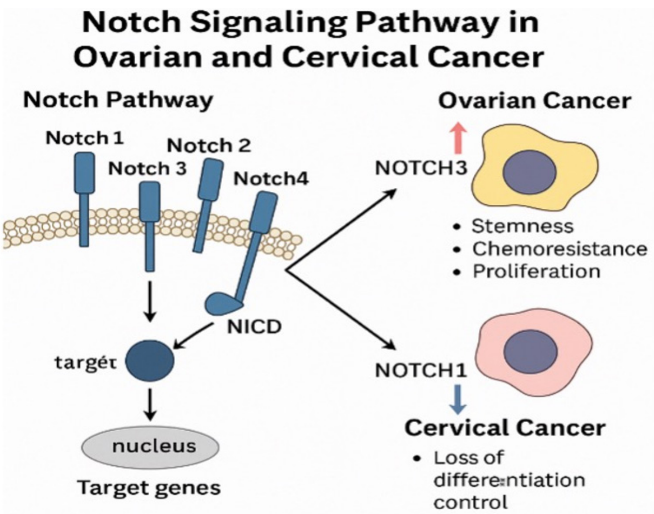

Figure 1. Differential activation of the Notch signaling pathway contributes to tumor progression in ovarian cancer and may play a suppressive role in HPV-related cervical cancer

The Wnt Pathway

The Wnt signaling pathway is one of the fundamental cellular signaling mechanisms involved in various developmental processes, including embryonic development, cell proliferation, and differentiation.[14] This pathway plays a critical role in the formation and maintenance of CSCs. Particularly, disruptions in Wnt signaling are thought to mediate the transformation of somatic stem cells into a CSC phenotype by conferring regenerative capacity.[15] Irregularities in the Wnt pathway have been associated with the emergence and persistence of leukemic stem cells as well as the development of various solid and hematologic malignancies.[16] Moreover, CSCs are believed to develop resistance to conventional chemotherapy agents through this pathway, which may adversely affect therapeutic outcomes (**Figure 2**).

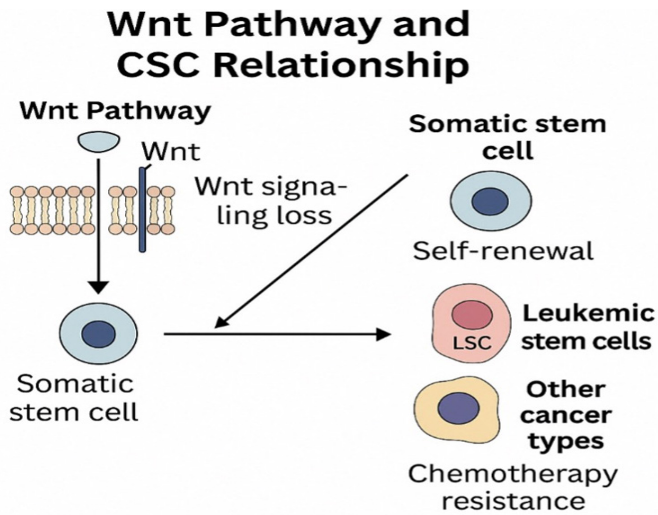

Figure 2. Wnt pathway alteration supports CSC self-renewal, survival, and resistance to therapy

Sonic Hedgehog (Shh)

The Hedgehog (Hh) signaling pathway plays a vital role in regulating cellular proliferation, differentiation, and tissue organization during vertebrate embryonic development. Recent studies have revealed striking similarities between embryogenesis and tumor formation.[17] In particular, there are significant overlaps between the two processes in terms of the acquisition of invasive cell properties, epigenetic regulations, gene expression profiles, the presence of oncofetal proteins and metabolic properties (e.g. high proliferative capacity, suppression of immune response). These similarities indicate that the Hedgehog signaling pathway is a determining element not only in developmental processes but also in malignant transformation and tumor progression.

TGF-β

Transforming growth factor-β (TGF-β) is a multifunctional cytokine involved in numerous biological processes, including early embryonic development, organogenesis, immune responses, tissue repair, and homeostasis. The effects of TGF-β on fibrosis and cancer are highly complex and context-dependent, varying with stage of the disease and cellular environment. While it acts as a tumor suppressor in early stages, it may promote tumor progression in advanced stages.[18] Its pathological overexpression contributes to the development of fibrotic diseases and various cancer types by inducing epithelial-mesenchymal transition (EMT), extracellular matrix (ECM) accumulation, and the formation of cancer-associated fibroblasts (CAFs). Therapeutic approaches targeting the TGF-β signaling pathway are considered promising strategies, particularly for reshaping the tumor microenvironment (TME) and preventing metastasis. However, due to its potential for systemic cytotoxicity, the clinical application of TGF-β-focused therapeutics remains limited.

IL-6/JAK/STAT3

The IL-6/JAK/STAT3 signaling pathway is hyperactivated in many types of cancer and is often associated with poor prognosis. JAK/STAT3 signaling, activated via IL-6 within the TME, increases the proliferation, survival, invasive capacity and metastatic potential of tumor cells, while also allowing immune escape by suppressing the antitumor immune response (**Figure 3**). Therefore, therapeutic strategies targeting the IL-6/JAK/STAT3 pathway are considered an effective therapeutic approach due to their potential of both directly inhibiting tumor cell growth and enhancing the antitumor capacity of the immune system.[19]

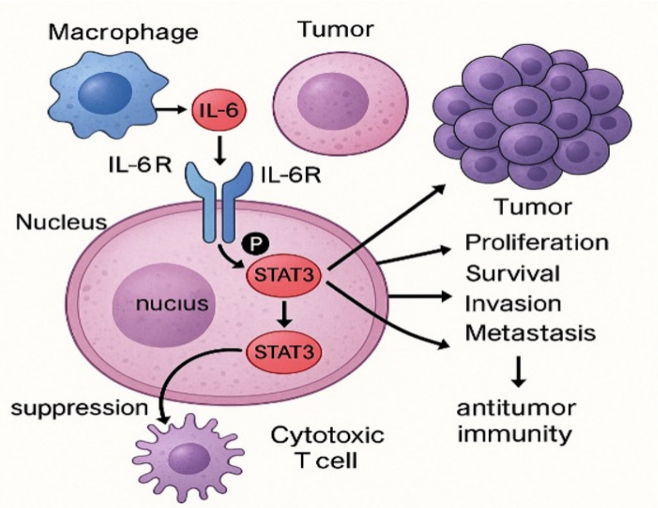

Figure 3. The IL-6/JAK/STAT3 pathway supports cancer progression and immune evasion through persistent signaling activation

NF-κB Pathway

In OC, BRCA1 mutation is constitutively associated with the activation of the p65 subunit of NF-κB;20, 21 in OC cases treated with DNA damage repair inhibitors, activation of the p50 subunit of NF-κB has been observed. This reciprocal dependence between NF-κB and BRCA1 is considered responsible for chemotherapy resistance in OC. Inhibition of the NF-κB signaling pathway induces apoptosis in cisplatin-resistant OC cell lines and reduces the number of $CD44^+$ ovarian cancer stem cells (OCSCs).[22]

CAFs, which are one of the main components of the TME, stimulate the overexpression of the ECM proteoglycan versican, which binds to the CD44 molecule on OCSCs and activates NF-κB and c-Jun N-terminal kinase (JNK) signaling.[23,24]

Furthermore, interleukin-17 (IL-17), which enhances the formation of $CD133^+$ cell spheroids and the self-renewal capacity of OCSCs, exerts these effects through the NF-κB and p38 mitogen-activated protein kinase (p38 MAPK) pathways.[25] OCSCs are capable of autocrine stimulation via cytokines that activate inflammatory signaling pathways, thereby contributing to tumor progression.[26,27]

$CD133^+$ OCSCs stimulated by IL-23 enhance their self-renewal capacity through the activation of the NF-κB and STAT3 pathways.[28] Activation induced by chemokine ligand-5 (CCL5) and its receptors promotes the migration of $CD133^+$ OCSCs and their differentiation into endothelial cells via NF-κB and matrix metalloproteinase-9 (MMP-9).[29]

Constitutive NF-κB activity has been attributed to $CD44^+MyD88^+$ OCSCs, and activation of the TLR/MyD88/NF-κB pathway has been associated with an increase in the number of OCSCs.[30]

CANCER STEM CELL HETEROGENEITY

Intratumoral heterogeneity is defined as the ability of cancer cells to exhibit genetic, epigenetic, and phenotypic differences even within the same tumor tissue. In a study conducted by Gerlinger and colleagues,[31] primary renal carcinomas and their metastatic lesions were examined, revealing that only 31–37% of somatic mutations were shared between intratumoral regions, with the remainder showing regional differences.

It was also determined that this heterogeneity occurs through the loss of function of multiple tumor suppressor genes and that gene expression profiles indicative of both good and poor prognosis exist in different regions. Recent analyses have shown that epigenetic variations such as allelic composition, ploidy, and promoter hypermethylation differences also contribute to intratumoral diversity.[32]

This diversity is a significant factor complicating the targeting and treatment of CSCs. The fact that CSC-specific markers do not show a consistent (uniform) expression pattern across different cancer types hinders the development of a universal marker set. For example, although markers such as CD133, CD44, CD166, CD24, and ALDH1 have been used in CSC isolation in many solid tumors, their expression varies significantly among tumor types.[33] While CD133 is identified as an effective CSC marker in glioblastoma, the $CD44^+/CD24^-$ phenotype is considered a more meaningful isolation criterion in breast cancer.[34,35] Differences in marker expression profiles among different subtypes of the same cancer or among similar subtypes in different patients significantly complicate the development of targeted therapeutic approaches specific to CSCs.

TREATMENTS TARGETING CANCER STEM CELLS

Due to their role as the source of therapy-resistant cells, CSCs are currently receiving increasing attention as therapeutic targets. Current evidence indicates that specific biomarkers, abnormally activated cellular signaling pathways, the immunosuppressive TME, and immune escape mechanisms play significant roles in the formation and maintenance of CSCs. Targeting these components may facilitate the elimination of CSCs by inducing their differentiation, thereby increasing the efficacy of cancer treatment. Various CSC biomarkers have been identified in different types of cancer. Among the most extensively studied are CD44, CD133, ALDH, and epithelial cell adhesion molecule (EpCAM). CD44 is a surface glycoprotein widely expressed in CSCs and generally associated with poor prognosis. In a phase I clinical trial targeting CD44, the monoclonal antibody RG7356 was shown to inhibit tumor growth by blocking CD44's binding to hyaluronan (HA).[36] In another study conducted in small cell lung cancer (SCLC) patients, HA-irinotecan complex therapy targeting CD44 was reported to yield favorable clinical outcomes. CD133 is another biomarker that plays a particularly significant role in tumor dissemination. A clinical study conducted in patients with hepatocellular carcinoma (HCC) demonstrated that CART-133 cell therapy targeting CD133 exhibited significant antitumor efficacy. EpCAM is a prominent biomarker highly expressed in CSCs and evaluated as a therapeutic target. In a study conducted in bladder cancer patients, the therapeutic agent VB4-845 targeting EpCAM successfully inhibited tumor growth in patients resistant to or intolerant of Bacillus Calmette-Guerin (BCG) therapy.[37] ALDH enzymes are among the biomarkers that play a crucial role in determining the biological activity of CSCs and tumor progression. Studies conducted in patients with colorectal liver metastases (CRLM) have shown that curcumin significantly reduced CSC proliferation by specifically targeting both ALDH and CD133 biomarkers.[38] Moreover, the combination of curcumin with 5-fluorouracil and oxaliplatin enhanced chemotherapeutic efficacy, more effectively inhibiting cancer cell growth. In light of these findings, treatment strategies targeting CSC biomarkers show promise in slowing cancer progression and reducing the risk of therapy-related recurrence.[39]

Targeting CSC Signaling Pathways

Various signaling pathways, such as Wnt/β-catenin, Hedgehog, Notch, and epidermal growth factor receptor (EGFR), play critical roles in the immortalization, reprogramming, and development of chemoresistance in CSCs. Therapeutic targeting of these pathways is among the promising strategies for CSC elimination. For example, Porcupine inhibitors have the potential to eliminate both proliferative CSCs activated via canonical Wnt pathways and dormant CSCs stimulated by non-canonical Wnt pathways by inhibiting the release of Wnt ligands. In Notch pathways, targeting ligands or receptors can exert therapeutic effects by suppressing aberrant signaling. In this context, delta-like ligand 4 (Dll4), a key component of the Notch pathway, plays a pivotal role particularly in angiogenesis processes. Phase I clinical trials have demonstrated that therapeutic agents such as demcizumab and enoticumab, which target Dll4, exhibit antitumor activity both as monotherapies and in combination treatment forms. In addition, oncogenic signaling pathways such as NF-κB, STAT3, and PI3K/Akt also play roles in the regulation of CSC self-renewal, survival, and differentiation capacities. These pathways contribute to the maintenance of the stem cell-like phenotype by controlling the expression of numerous target genes, including cytokines, growth factors, and genes associated with apoptosis.[40]

Targeting the Tumor Microenvironment and Immune Response

The TME represents the chronic inflammatory and immunosuppressive milieu necessary for the sustainability of CSCs. This inflammatory environment disrupts the normal functions of various stromal cells, leading to the secretion of biological agents that contribute to drug resistance and the establishment of immunosuppressive conditions. Therefore, a properly functioning host immune system is critically important in preventing inflammation-induced disruptions in TME homeostasis. In this context, various therapeutic strategies aimed at disrupting the TME are considered effective approaches for the elimination of CSCs. One of the key components of the TME, CAFs, plays a central role in the maintenance of CSCs and the development of drug resistance. Studies involving therapeutic agents developed against the surface markers of these cells have shown that tumor growth can be suppressed.[41] Transforming growth factor-beta (TGF-β) is one of the most studied cytokines derived from the TME. TGF-β supports tumor development by suppressing T lymphocyte-mediated immune responses through signaling pathways activated in stromal cells.[42] Clinical studies have reported therapeutic efficacy of agents such as M7824 and galunisertib that target TGF-β.[43] Interleukin-6 (IL-6) plays a central role in both inflammation and tumor development. Research has shown that high IL-6 levels contribute to cisplatin resistance in non-small cell lung cancer (NSCLC) patients. However, the monoclonal antibody siltuximab, which targets IL-6, has demonstrated limited clinical efficacy in advanced-stage solid tumors.[44] $CD8^+$ T lymphocytes play a fundamental role in regulating adaptive immune responses. These cells eliminate abnormal cells with high specificity by recognizing antigenic peptides presented via major histocompatibility complex class I (MHC-I). Upon stimulation with interferon-gamma (IFN-γ), the expression of molecules such as TAP (Transporter associated with Antigen Processing), ERAP (endoplasmic reticulum-associated aminopeptidases), and IFN-γ, which contribute to MHC-I antigen presentation, is increased. Although these components are not strictly essential for cellular proliferation, their deficiencies can lead to reduced MHC-I levels and impaired antigen presentation capacity.[45] Antigen presentation via MHC-I is a critical step for effective responses by $CD8^+$ T cells.[46] Nevertheless, CSCs have developed various mechanisms to escape immune surveillance. These mechanisms include suppression of dendritic cell (DC) function and downregulation of MHC-I expression.[47] It has been shown that CSCs can alter DC phenotypes, thereby limiting their accumulation in the microenvironment in ways that hinder T lymphocyte activation.[48] In the TME, activation of immune checkpoint molecules such as CTLA-4 (cytotoxic T-lymphocyte antigen 4) and the PD-1/PD-L1 (programmed death-1/programmed death-ligand 1) axis reorganizes immune homeostasis and allows tumor cells to evade immune responses. Immune checkpoint inhibitors (ICIs) targeting these pathways have demonstrated promising antitumor effects in various human cancers.[48] However, the efficacy of these agents often depends on IL-12 secretion derived from DCs.[49] Moreover, in tumors with low MHC-I expression, ICIs may exacerbate T cell dysfunction rather than correct it.[50] Accordingly, supporting antigen processing and presentation pathways, along with the development of combination therapies with ICIs, are among the promising strategies for effectively targeting CSCs.

Targeting Differentiation

Poorly differentiated tumors derived from CSCs typically exhibit more aggressive and malignant characteristics. Differentiation-based therapeutic approaches developed in this context aim to inhibit tumor progression by promoting the maturation of undifferentiated tumor cells into more mature and well-differentiated cell phenotypes. Differentiation-inducing agents such as retinoic acid (RA), cyclic adenosine monophosphate (cAMP), sodium butyrate, and various cytokines have been shown to be effective in certain cancer types. Among these agents, all-trans retinoic acid (ATRA) has demonstrated significant anticancer activity by inducing terminal differentiation in patients with acute myeloid leukemia (AML) and acute promyelocytic leukemia (APL).[51] In recent years, next-generation differentiation-inducing agents targeting mutant isocitrate dehydrogenase (IDH) 1 and IDH2 enzymes have achieved clinical success in AML treatment and received regulatory approval in this field. IDH1 and IDH2 mutations epigenetically affect the cellular differentiation process by increasing histone and DNA methylation, leading to the suppression of differentiation. Additionally, epigenetic modulators such as DNA methyltransferase inhibitors (DNMTis) and histone deacetylase inhibitors (HDACis), which increase MHC-I expression, have also been shown to have a role in differentiation processes.[52] IDH1/2 mutations have been observed not only in hematologic malignancies but also in solid tumors. The differentiation-inducing effects of inhibitors developed against these mutations are currently being investigated in various clinical trials. Vaccines targeting IDH1 and agents such as ivosidenib and olutasidenib, have shown potential in reducing tumor burden and improving progression-free survival.[53] The dual inhibitor vorasidenib, which targets both IDH isoforms (IDH1 and IDH2), has demonstrated promising antitumor activity particularly in recurrent or progressive, contrast-enhancing-negative IDH-mutant low-grade gliomas.[54] Neomorphic mutations in the IDH1/2 genes impair the homologous recombination (HR) repair mechanism, which renders these tumors sensitive to poly (ADP-ribose) polymerase (PARP) inhibitors. Based on this rationale, the Olaparib combination study represents a phase II trial in which patients with solid tumors harboring IDH1/2 mutations were treated with olaparib as monotherapy. Both in this study and in similar research, PARP inhibitors have been reported to exhibit clinical efficacy either as monotherapy or in combination regimens.[55]

CONCLUSION

CSCs play a central role in the processes of treatment resistance, relapse, and metastasis in many solid and hematologic malignancies. The self-renewal and differentiation capabilities of CSCs render conventional treatment strategies largely ineffective, positioning CSC-targeted therapies as a priority in modern oncology practice. The data presented in this review highlight the breakthrough potential of treatment strategies targeting CSC biomarkers, signaling pathways, the TME, and immune evasion mechanisms. However, the high degree of heterogeneity and plasticity displayed by CSCs complicates the prediction of treatment responses, underscoring the importance of personalized and targeted therapeutic approaches. In the future, it is expected that clinically effective, multi-component, and combination-based treatment strategies that specifically target CSCs while minimizing systemic toxicity will occupy a broader place in clinical practice.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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