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Mini Review

Cancer stem cells as a biomarker – A mini review

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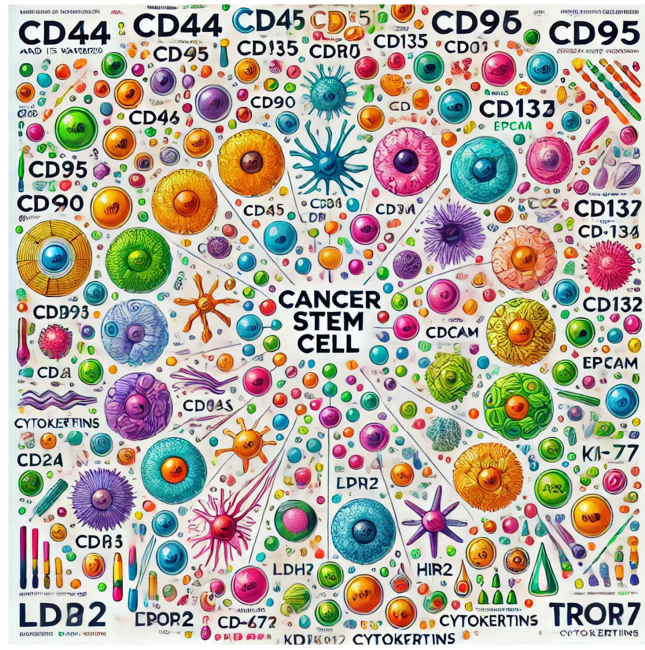
Abstract

Cancer stem cells (CSCs) also known as tumor stem cells (TSCs), are pivotal in cancer development and progression. They can be identified through specific markers and surface proteins (e.g., CD44, CD133) that differ from those on non-CSC tumor cells. As well high CSC levels often correlate with poor prognosis, aggressive disease, and resistance to conventional therapies. CSCs are more resistant to standard treatments like chemotherapy and radiation, leading to relapse and metastasis. Therapies targeting CSC-specific pathways and markers are developing to improve treatment efficacy and prevent recurrence. Understanding their role and mechanisms is essential for developing more effective and targeted cancer treatments. While significant progress has been made in developing therapies to target tumor stem cells, much work remains. Tracking CSC markers can help monitor residual disease and predict the likelihood of recurrence, allowing for more tailored treatment approaches. Research into CSC biomarkers continues to evolve, with ongoing studies aiming to refine their use for better diagnosis, prognosis, and treatment of various cancers. Overall, using CSCs as biomarkers offers a promising avenue for more personalized and effective cancer treatment strategies.



Introduction

Normal stem cells, including embryonic and adult types, are crucial for growth, development, and tissue repair, while tumor stem cells self-renew and divide into various cancer cell types [1]. Cancer stem cells (CSCs) also known as Tumor stem cells (TSCs), are a subpopulation of cells within a tumor that possess unique properties compared to the rest of the tumor cells, first found in the context of acute myeloid leukemia in 1994 [2,3], later on also confirmed in cancers of brain, breast, lung, liver, pancreas, colon, and prostate cancer [4]. CSCs exhibit self-renewal, differentiation, and tumor initiation and maintenance, generating new cells to sustain tumors, forming various types of cancer cells, and presumably initiating and maintaining tumors [5]. CSCs, unlike other cancer cells, can produce tumors upon transplantation, exhibiting resistance and metastasis, potentially contributing to cancer spread through tissue invasion and bloodstream entry [6]. CSCs often exhibit resistance to conventional therapies such as chemotherapy and radiation, which can lead to relapse and metastasis [7,8]. CSCs' regulation is less understood than normal stem cells, potentially affecting signaling pathways and tumor microenvironment interactions. Understanding the differences between normal stem cells and CSCs is crucial for developing targeted cancer therapies [9].

Contribution of TSCs to Cancer Development

Tumor growth and maintenance

CSCs are thought to be responsible for initiating tumors. They can form new tumors even from a small number of cells, which makes them crucial in the initial stages of cancer development [10]. CSCs can self-renew and are essential for initiating and sustaining tumor growth. Even at low cell numbers, TSCs can initiate tumors when transplanted into immunocompromised mice [11]. CSCs generate diverse cancer cell populations, maintain tumor growth, and interact with their surrounding microenvironment to maintain the tumor's diverse population, including immune cells to protect themselves from immune clearance and to provide signals that support their survival and proliferation [12].

Invasion and spread

CSCs use immune checkpoint molecules and extracellular vesicles to evade immune surveillance, enabling them to spread and establish secondary tumors, despite their crucial role in maintaining self-tolerance [13,14]. These pathways help to maintain self-tolerance, preventing the immune system from attacking normal cells indiscriminately [15]. However, some cancers exploit these checkpoints to protect themselves from immune attack. Here are some key immune checkpoint molecules including CTLA-4 (Cytotoxic T Lymphocyte Antigen-4) [16], PD-1 (Programmed Cell Death Protein 1) and PD-L1 (Programmed Death Ligand 1) [17], TIM-3 (T Cell Immunoglobulin and Mucin Domain-Containing Protein 3) [18] and CD27, CD28, CD40, and CD137, etc [19,20]. Certainly, Immune checkpoint inhibitors, which are used in cancer treatment, can have both common and rarer side effects. Natural killer (NK) cells can also recognize and kill CSCs, but CSCs often develop mechanisms to escape this targeting [21]. There are reports that exosomes from CSCs interact with immune cells, affecting signaling pathways and immune responses. CSC-derived exosomes can suppress T-cell function and induce immunosuppressive macrophages as well exosome-based drug delivery systems show promise in targeting CSCs with improved precision and reduced side effects [22].

Genetic and epigenetic alterations

CSCs' genetic and epigenetic alterations drive cancer development, modulating cell growth, survival, and differentiation, impacting tumor response and contributing to therapeutic resistance [23]. Epigenetic mechanisms impact CSC behavior in various ways as DNA methylation involves hypermethylation of tumor suppressor genes that can silence their expression, for example, genes like p16INK4a (a tumor suppressor gene) are frequently hypermethylated in CSCs [24]. Global DNA hypomethylation can activate oncogenes or repetitive elements that promote genomic instability and CSC properties. Furthermore, histones undergo modifications (acetylation, methylation, phosphorylation) that affect chromatin structure. These modifications regulate gene accessibility, impacting CSC properties [25]. CSCs often carry mutations in genes that drive cancer, such as tumor protein p53(TP53), Kirsten rat sarcoma viral oncogene homolog (KRAS), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), and breast cancer susceptibility genes (BRCA1/2) [26]. Overexpression or activation of transcription factors like Oct4, Sox2, Nanog, and KLF4 are commonly observed in CSCs. These factors influence stem-like characteristics and pluripotency of CSCs, which can be enhanced by mutations, contributing to tumor growth and therapy resistance [27,28]. Moreover, dysregulation of miRNAs can influence CSC self-renewal and differentiation [29]. Key pathways (Wnt/β-catenin, Notch, Hedgehog, TGF-β/BMP) are altered in CSCs through epigenetic changes. These alterations maintain stemness, differentiation, and drug resistance in CSCs [3].

Biomarkers

Cancer stem cells (CSCs) serve diverse roles in cancer progression, providing biomarkers for prognosis and therapy response, although their clinical application is still evolving and limited in routine practice [30]. Here are some of the clinically relevant cancer stem cell biomarkers that have been explored or approved for use in cancer diagnostics or treatment planning:

CD44 and its variants

CD44 is a transmembrane glycoprotein, highly expressed in CSCs and involved in cell adhesion, migration, and interaction with the extracellular matrix. It influences various signaling pathways, including the Wnt, Notch, and Hedgehog pathways, essential for maintaining CSC properties [31]. CD44 has multiple isoforms, with CD44s being the most common and smallest, and CD44v being overexpressed in tumor cells [32]. CD44 is a widely used marker for cancer stem cells in various malignancies, including breast, pancreas, prostate, colorectal, ovarian, lung, liver, head/neck, blood, bladder, gastric, brain, bone, and cervical. Also, it is found in stem cells in various regions [33,34]. The CD44 expression is elevated in metastatic lymph nodes of breast cancer compared to original tumors, unlike CD44 knockdown yields contrary results [35]. CD44 overexpression increases cell invasion and migration, leading to worse prognosis and more aggressive tumor behavior. The many isoforms of CD44, a crucial component of colorectal cancer, affect the disease's onset, progression, metastasis, and therapy resistance [36]. CD44, a potential therapeutic target in leukemia treatment, has the potential to eradicate CSCs and prevent relapse

[37]. CD44-targeting strategies are being explored in clinical trials to inhibit tumor growth and metastasis, aiding in the identification of CSCs, although not directly used as a treatment target. Although, a few medications that target CD44 have been authorized for use in clinical trials [32]. Hyaluronic acid (HA) is used for CD44 targeted delivery to eradicate cancer cells and CSCs, while silibinin (SIL) and cabazitaxel (CBX) are co-loaded onto cationic liposomes for prostate cancer stem cell treatment [38,39].

CD45

It is also known as protein tyrosine phosphatase receptor type C (PTPRC). CD45 is used to identify and isolate cancer stem cells in various types of cancer, including leukemia [40, 41] and solid tumors [42]. High CD45 expression levels have been associated with better prognosis in certain cancers, such as bladder cancer [43]. Glatting *et al.*, [44] reported that when tagged with 90Y, the anti-CD45 monoclonal antibody YAML568 can deliver radiation to hematopoietic regions selectively. Targeting CD45 and its associated pathways can potentially enhance the effectiveness of cancer treatments, especially immunotherapies [45]. The bispecific Abs (target CD45 and Y-DOTA) effectively delivered radiation to leukemia cells, reducing tumor growth and improving survival rates in both murine and human leukemia models [46].

CD87

CD87, also known as the Urokinase-type plasminogen activator receptor (uPAR), is indeed used as a cancer stem cell (CSC) marker in lung cancer. It helps distinguish lung cancer stem cells from other types of cancer stem cells, such as those found in blood cancers [47]. Targeting CD87 could potentially disrupt processes such as cell adhesion, migration, and interaction with the extracellular matrix (ECM), making it a promising therapeutic target for lung cancer treatment [48]. uPAR-targeted therapeutic strategies have shown potential in animal models, but no uPAR-targeted agents have been developed or evaluated in cancer clinical trials. Although phase I clinical trials employing 64Cu-DOTA-AE105 are already in progress, humanized ATN-658 is still awaiting translation to diagnose aggressive malignancies and evaluate cancer aggressiveness [49].

CD90

CD90, also known as Thy-1, is a glycoprotein, an important biomarker for cancer stem cells in multiple cancer types, including the brain [50], liver [51], colorectal [52], and breast cancers [53]. CD90 is not exclusively expressed by cancer stem cells. It is also expressed in mesenchymal stem cells and liver stem cells [54]. CD90 expression, particularly in triple-negative breast cancer (TNBC), is an aggressive subtype associated with poor prognosis and limited treatment options [53]. According to previous studies, CD90-positive cells express more CD133 than CD90-negative tumor cells, and signaling analyses showed that CD90 induction of CD133 requires β3 integrin and adenosine monophosphate (AMP)-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) [55,56]. During *in vitro* studies, the survival and carcinogenic potential of CD90+ HCC cells are found to be controlled by CD44 [57].

CD133 (Prominin-1)

CD133 is another stem cell marker that has been used to identify cancer stem cells in several cancers, including glioblastoma, colon cancer, pancreatic cancer, and breast cancer [58]. CD133+ cells are enriched in the CSC population and are associated with increased tumorigenicity and resistance to chemotherapy. Research is ongoing to assess the therapeutic targeting of CD133, particularly in combination with other CSC markers [59]. Currently authorized treatments do not specifically target CD133, it is utilized in experimental treatments and clinical studies to detect the existence of cancer stem cells [60,61]. Several approaches, such as Sorafenib, a multi-kinase inhibitor, are being explored, which diminishes CD133 expression and suppresses tumor growth in vivo. Additionally, Nifuroxazide, a STAT3 inhibitor, diminishes CD133 expression and suppresses tumor growth *in vivo* [62]. Trifluridine (FTD)/tipiracil (TPI) is an oral combination medication that may be efficacious against colorectal cancer cells with high levels of CD44 and CD133 expression [63].

Leucine-rich repeat-containing G protein-coupled receptor 5 (Lgr5)

Lgr5 is a promising biomarker for cancer stem cells (CSCs) [64]. Aberrant overexpression of Lgr5 is common in some human cancers, leading to the potentiation of canonical Wnt/β-catenin signaling [65]. Lgr5 is used to identify and isolate CSCs in various types of cancers, including colorectal, gastric, and esophageal cancers [66].

Epithelial cell adhesion molecule (EpCAM)

EpCAM is a cell surface glycoprotein overexpressed in many epithelial cancers, including breast, colorectal, and lung cancers [67]. It is involved in the regulation of cell cycle progression and can act as a transcription factor by activating genes like c-myc, cyclin A, and cyclin. EpCAM has oncogenic potential and can contribute to cancer progression by interacting with various signaling pathways, such as Wnt/β-catenin, TGF-β/SMAD, and PI3K/AKT/mTOR [68]. It is used in liquid biopsy techniques, such as the detection of circulating tumor cells (CTCs), which are thought to originate from cancer stem cells. Targeting EpCAM is being explored as a strategy to eliminate cancer stem cells in solid tumors [69]. Moreover, bispecific antibodies and CAR T-cell therapy have shown promise in eliminating CSCs and improving treatment outcomes. While not yet FDA-approved as a direct CSC target, EpCAM is being explored as part of clinical trials targeting CTCs in cancers [70].

Aldehyde dehydrogenase 1 (ALDH1)

In breast cancer, high populations of ALDH1 are associated with triple-negative breast cancer (TNBC), a subtype that is particularly aggressive and difficult to treat [71] ALDH1 is an enzyme that detoxifies aldehydes and is a key marker for cancer stem cells in various cancers, including breast, liver, and lung cancers [72]. Elevated ALDH1 expression is linked to poor prognosis, chemoresistance, and aggressive tumor behavior. Clinical trials are investigating ALDH1 as a target for therapy, as well as its use as a biomarker to assess the stem cell population in tumors. ALDH1A3 with the other two markers CD24-/CD44 + and CD24 + /CD44 + was found to be associated with poor prognosis, limited response to chemotherapy, higher chances of metastasis, and aggressive tumor formation in breast cancers [73]. However, direct FDA approval for therapeutic targeting of ALDH1 in CSCs is not yet available.

Human epidermal growth factor receptor 2 (HER2)

HER2 is an important biomarker and therapeutic target in breast cancer, particularly in breast cancer stem cells (BCSCs) [74].

It was found to be overexpressed in approximately 15-20% of breast cancers (oncologypro.esmo.org). While not strictly a cancer stem cell marker, HER2 overexpression is associated with aggressive breast cancers, particularly HER2-positive breast cancer. HER2 signaling has bidirectional communication with stemness-related pathways, influencing both the maintenance of BCSCs and the response to targeted therapies. It interacts with stemness-related pathways, such as Notch and Wnt/β-catenin, contributing to the self-renewal and differentiation properties of BCSCs [74]. A splice variant of full-length HER2 mRNA, d16HER2, has been identified as one of the most oncogenic isoforms, significantly implicated in tumorigenesis and epithelial-mesenchymal transition (EMT) [75]. HER2-targeted therapies, such as trastuzumab (Herceptin), Pertuzumab (Perjeta), Ado-Trastuzumab Emtansine (T-DM1, Kadcyla), Lapatinib (Tykerb), Neratinib (Nerlynx), Tucatinib (Tukysa) are used to treat HER2-positive breast cancer [76]. HER2-positive cancer stem cells are often more resistant to conventional therapies, making HER2-targeted therapy an important approach. These treatments aim at eradicating both differentiated cancer cells and cancer stem cells that express HER2 [77].

Cytokeratins (e.g., CK5, CK14, CK19)

Cytokeratins are proteins found in the cytoskeleton of epithelial cells and are used as biomarkers for certain types of cancer stem cells [78]. In cancers like breast cancer, certain cytokeratins (e.g., CK5 and CK14) are expressed in basal-like breast cancer subtypes, which are often triple-negative (lacking estrogen receptor, progesterone receptor, and HER2), often harbor cancer stem cells [79,80]. There is a strong association between CK5/14-positive tumors and BRCA1 mutations. These tumors are often found in patients with hereditary breast cancer [79]. CK19, an upregulated gene in ovarian cancer tissue, promotes cell invasion, proliferation, and migration, activating the Wnt/β-catenin signaling pathway through β-catenin, TCF7, LEF1, c-MYC, and cyclin D1 [81]. A novel CSC marker, CK19 is linked to TGFb/Smad signaling and EMT in hepatocellular carcinoma (HCC) [82]. CK expression patterns help identify stem-like cells and predict the aggressiveness of tumors. Cytokeratin-based markers are used for diagnostic purposes, particularly in pathology to distinguish different subtypes of cancer. However, direct therapeutic targeting of these markers is still under investigation [83].

Trophoblast antigen 2 (Trop2)

Trop2 is a transmembrane protein involved in cell proliferation and survival and is expressed in many cancer stem cells [84]. Trop2 is overexpressed in various cancers, including breast cancer, and is associated with tumor progression and stem-like properties. The FDA approved sacituzumab govitecan in 2020 for treating metastatic triple-negative breast cancer, and in 2021 for hormone receptor-positive, HER2-negative breast cancer. This therapy is particularly beneficial for treating cancers that express high levels of Trop2, which are often resistant to standard treatments [85]. This FDA-approved antibody-drug conjugate targets Trop2 for treating metastatic triple-negative breast cancer (TNBC) [86].

Ki-67 (Proliferation marker)

Ki-67 is expressed in all active phases of the cell cycle (G1, S, G2, and M) but is absent in resting (G0) cells. It is widely used to assess the proliferation rate of tumor cells [87]. However, its role in CSCs extends beyond mere proliferation, as it is also involved in maintaining the stem cell phenotype. Genetic disruption of Ki-67 in human epithelial breast and colon cancer cells deplete the cancer stem cell niche [88]. It is widely used in clinical settings to predict outcomes in various cancers, including breast [89], prostate [90], and colon cancers [91]. Ki-67 is routinely used in clinical diagnostics to guide treatment decisions, especially in breast cancer, where it helps to classify tumors as high or low grade based on proliferation [92]. Future studies should focus on standardizing Ki67 measurement and exploring its combination with other biomarkers to improve its predictive value.

P-glycoprotein (MDR1)

P-glycoprotein, a membrane-bound transporter, is involved in multidrug resistance by pumping out drugs from cells. It is often overexpressed in cancer stem cells, contributing to their resistance to chemotherapy [93]. P-glycoprotein in CSCs can be used to predict drug resistance and guide treatment strategies [94]. In clinical practice, P-glycoprotein inhibitors (e.g., verapamil) are sometimes used in combination with chemotherapy to overcome resistance, though the direct targeting of P-glycoprotein in CSCs is not yet FDA-approved [95]. Here's an overview of how CSCs are utilized as biomarkers in different cancers, discussed in **Table 1**.

Table 1. Cancer stem cells are biomarkers in various cancers.

Types of Cancer	Markers	References
Breast Cancer	CD29+, CD49f+, CD90+, CD 133, $CD44^{+}/CD24^{-}$, ALDH1, HER2, and EpCAM.	[30, 96-101]
Colorectal Cancer	CD133, CD44, CD24, CD29, CD166, EpCAM, CXCR4 ALDH1, Oct4, Sox2, Nanog and Lgr5	[102-105]
Lung Cancer	CD44+, CD133, CD166+, CD90+ CD133, CD87+, ALDH1, and Sox2	[106-111]
Ovarian Cancer	CD133, CD44, CD24, CD117 or ALDH1, PDL-1, CD105, CD106, SOX2, EpCAM, Nestin and SSEA1	[112-121]
Glioblastoma	CD49f+ CD90+ CD44+, CD36+ CD133, Nestin, and Sox2, EGFR+A2B5+, L1CAM+, CD133+	[122-125]
Prostate Cancer	EpCAM+, CD117+, α2β1+, ALDH+, CD44+, EZH2+, CXCR4+, E-cadherin+ CD133+, CD44, ALDH1, and AR variants	[126-131]
Pancreatic Cancer	CD24, CD44, CD133, ESA, ALDH1, Nanog, EpCAM, CXCR4, DCLK1, c-MET, ABCG2 and Lgr5	[132-135]
Hematologic Malignancies (e.g.,Leukemias, Lymphomas)	CD45, CD38, CD19, CD22, CD34, CD123, Lgr5, Oct4, Sox2, Nanog, c-kit, ABCG2, ALDH, CLL-1 and her lineage-specific markers.	[136,137]
Cervical Cancer	CD44, CD133 (Promin), CD111 (c-Kit), CD24, CD117, OCT4, ALDH1, LGR5	[138-143]
Liver Cancer	CD133, CD90, CD44, CD24, CD13, EpCAM, and cytokeratin 19 (CK19),	[144,145]

Hence, CD133, CD44, and EpCAM have been recognized as prospective cancer stem cell markers in various solid and non-solid tumors.

Therapeutic Strategies

Cancer treatment researchers are exploring strategies to target specific markers or pathways associated with CSCs to achieve long-term remission and prevent relapse [146]. CSCs are often more resistant to conventional treatments such as chemotherapy and radiation. This resistance is due to various factors, including enhanced DNA repair, drug efflux pumps (ATP-binding cassette (ABC), and some enzymes such as aldehyde dehydrogenase (ALDH)) that can expel therapeutic agents from the cells. Also, the state of quiescence results in the maintenance of cells in a latent or quiescent condition, hence reducing their vulnerability to therapeutic interventions that specifically target actively dividing cells. Additionally, in relapse and recurrence, where conventional therapies may not effectively eliminate CSCs, these cells can survive and lead to relapse or recurrence of the tumor after initial treatment [147].

CSCs express specific surface markers that differentiate them from other tumor cells. Targeting these markers can help selectively eradicate TSCs. Monoclonal Antibodies targeting specific CSC markers like CD44, CD133, ALDH1, or ESA (epithelial-specific antigen) are being developed. For example, catumaxomab, an antibody targeting EpCAM and receptor of T cells-CD3, has been investigated for CSC targeting [148,149]. Chimeric antigen receptor T-cell (CAR-T) therapy can be engineered to recognize and kill CSCs by targeting surface antigens such as CD133 and CD44 [150]. Whereas, targeting signaling pathways (Wnt/β-catenin pathway, Notch pathway, Hedgehog pathway, PI3K/Akt/mTOR pathway) can inhibit CSC function and reduce tumor recurrence [3]. Agents like decitabine and azacitidine, which inhibit DNA methyltransferases, can reverse the silencing of tumor suppressor genes in CSCs. Drugs like vorinostat, panobinostat, and romidepsin can modulate histone acetylation and disrupt CSC self-renewal and differentiation [151]. EZH2, a key Polycomb repressive complex 2 (PRC2) member, is often overexpressed in CSCs [152]. Inhibitors like tazemetostat are being explored to target EZH2 and prevent CSC maintenance [153]. Bromodomain and extra-terminal domain (BET) inhibitors like JQ1 target proteins that regulate gene expression via histone acetylation, showing potential in eliminating CSCs by modulating transcriptional networks critical for stemness [154].

CSCs play a critical role in mediating resistance to anti-cancer therapies through a variety of mechanisms **(Figure 1)**. Furthermore, pharmacological repurposing and the integration of micronutrients are capable of targeting both malignancies and cancer stem cells. However, ongoing research has led to the development of various approaches aimed at targeting and eradicating these cells [155,156]. CSCs often rely on aerobic glycolysis for energy production (the Warburg effect). Targeting enzymes like hexokinase 2 or pyruvate kinase M2 can inhibit glucose metabolism and reduce CSC viability [157]. While inhibiting fatty acid oxidation or metabolism, it can also target CSCs, as they depend on this pathway for maintaining stemness and growth [158]. Targeting mitochondrial functions, such as metformin or IACS-010759, can disrupt the metabolic networks that sustain CSCs [159]. Agents like retinoids, vitamin D analogs, and histone deacetylase inhibitors (HDACi) can promote the differentiation of CSCs, decreasing their ability to self-renew and initiate tumors [7,160]. Bone morphogenetic protein (BMP) signaling can promote differentiation and decrease stemness in

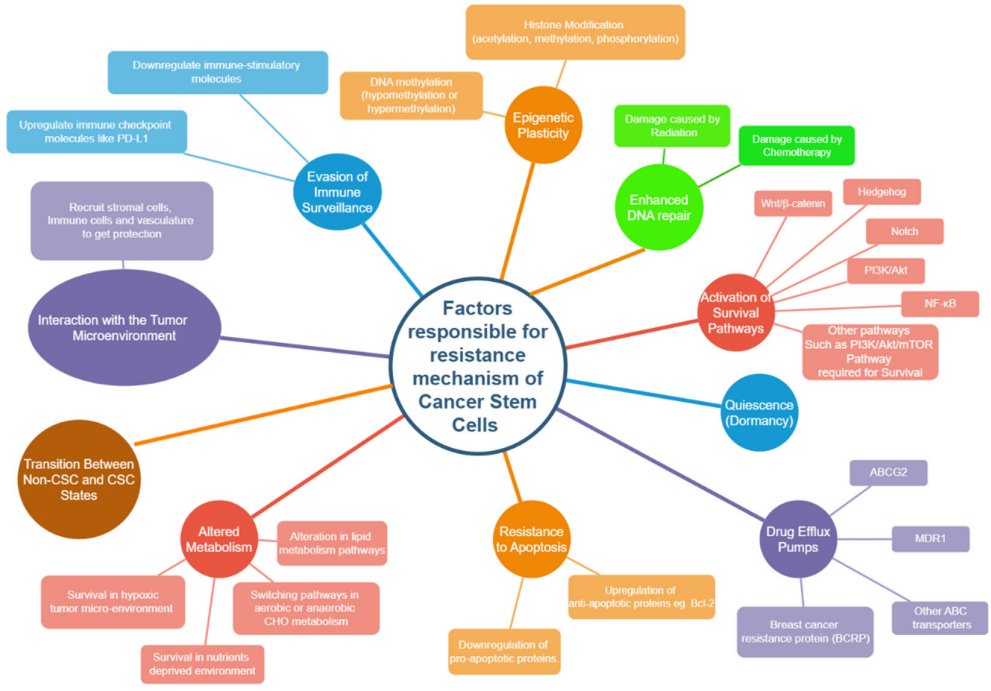


Figure 1. Various mechanisms responsible for mediating resistance to anti-cancer therapies by CSCs.

CSCs. Activating this pathway by BMP agonists is being studied as a potential therapy [161]. Drugs targeting immune checkpoints like PD-1/PD-L1 and CTLA-4 can enhance anti-tumor immunity and potentially eliminate CSCs [162,163]. Targeting CSC-specific antigens through cancer vaccines could provide a strategy to selectively activate immune responses against TSCs [164]. Engineered viruses can be designed to specifically target and eliminate cancer stem cells while preserving normal cells. For example, oncolytic adenoviruses have been designed to target CSCs specifically [165]. Nanocarriers can deliver gene therapies that target key genes involved in CSC self-renewal and survival [166].

Combining traditional chemotherapy with CSC-targeting agents (e.g., Wnt inhibitors, HDAC inhibitors) can enhance the effectiveness of treatment and prevent tumor recurrence [167]. Combining immune checkpoint inhibitors with epigenetic modulators can potentially enhance the immune response to CSCs by modifying their immune profile [168]. Blocking the formation of blood vessels (angiogenesis) in the tumor microenvironment can starve CSCs of nutrients and oxygen, making them more vulnerable to treatment. Drugs like bevacizumab (anti-VEGF) are being explored [169]. Intervening with the stromal cells in the tumor microenvironment, such as fibroblasts and mesenchymal stem cells, can disrupt the supportive niche and reduce CSC survival [170]. Gene editing technologies such as CRISPR/Cas9 can directly inactivate genes critical for cancer stem cell self-renewal, survival, or metastasis. Focusing on oncogenes or tumor suppressors that govern stemness may diminish CSC viability and avert recurrence [171]. Also, matrix metalloproteinase inhibitors target enzymes involved in tissue remodeling and could impact the supportive microenvironment for CSCs [172]. CSCs' heterogeneity and varying markers make developing one-size-fits-all treatments challenging. Careful targeting is necessary to avoid damaging normal stem cells or causing significant side effects. The study emphasizes the importance of understanding and overcoming the resistance mechanisms of CSCs to various therapies, as they are often more resistant to conventional treatments [173].

Concluding Remarks

Researchers are working on better ways to identify and isolate CSCs to understand their biology and develop targeted therapies. Additionally, finding reliable biomarkers for CSCs is crucial for early detection and monitoring treatment response. CSC markers can be used for early detection of cancer, as they may be present in circulating tumor cells or biopsy samples before conventional markers become evident. The presence and proportion of CSCs often correlate with a more aggressive disease course and poorer prognosis. While several cancer stem cell biomarkers are being studied and utilized in clinical trials, few have received formal FDA approval for direct therapeutic targeting. However, CD44, ALDH1, HER2, and Trop2 represent the most clinically significant CSC markers currently used to guide treatment decisions or included in FDA-approved therapies (e.g., trastuzumab for HER2+ cancers, sacituzumab govitecan for Trop2-expressing cancers). The clinical utility of CSC markers is rapidly evolving as research continues to uncover new potential targets and therapies aimed at eradicating cancer stem cells and improving patient outcomes. Developing drugs that specifically target CSCs, or their pathways can potentially improve treatment outcomes and reduce relapse rates. Overall, understanding the role of tumor stem cells is essential for developing more effective cancer treatments and improving patient outcomes.

Abbreviations

ALDH: Aldehyde Dehydrogenase; AR: Androgen Receptor; ABC: ATP-Binding Cassette; BRCA1/2: Breast Cancer Susceptibility genes; BET: Bromodomain and Extra-Terminal Domain; BMP: Bone Morphogenetic Protein; SIL: Silibinin; CBX: Cabazitaxel; CSCS: Cancer Stem Cells; CAR: Chimeric Antigen Receptor; CAR-T: Chimeric Antigen Receptor T-cell; CD: Cluster Domain; CTLA-4: Cytotoxic T Lymphocyte Antigen-4; CK: Cytokeratin; DCs: Dendritic Cells; ESA: Epithelial-Specific Antigen; EVS: Extracellular Vesicles; HER2: Human Epidermal Growth Factor Receptor 2; HDACI: Histone Deacetylase Inhibitors; KRAS: Kirsten Rat Sarcoma Viral Oncogene Homolog; NK-Cells: Natural Killer Cell; OVS: Oncolytic Viruses; PD-1: Programmed Cell Death Protein 1; PD-L1: Programmed Death Ligand 1; PIK3CA: Phosphatidylinositol-4, 5-bisphosphate 3-kinase Catalytic Subunit Alpha; PTPRC: Protein Tyrosine Phosphatase Receptor Type C; TIM-3: T Cell Immunoglobulin and Mucin Domain-Containing Protein 3; TP53: Tumor Protein p53; TSCS: Tumor Stem Cells; Sox2: SRY-Box Transcription Factor 2

Declarations

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author contributions

Conceptualization: Linz Buoy George; Study design: Dhara Jani; Original draft preparation and analysis: Urja Joshi; Formal analysis and investigation: Hyacinth Highland; Review and editing: All authors.

Data, material, and/or code availability

Not applicable.

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