Chapter 12

Cancer Stem Cells: Terminology and Implications in Clinical Cancer Biology

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Abstract

The advent and discovery of CSCs[1] have revolutionized our understanding of tumor cell biology, activity, and efficiency of various therapeutic protocols. CSCs with specific properties such as stemness features, self-renewality, and differentiation capacity can control the development, progression, and metastatic behavior even in the presence of conventional therapeutic regimes. Several studies have revealed that CSCs can produce different cell lineages within the tumor parenchyma,

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[1]. Cancer stem cells

leading to therapy resistance and relapse. These cells can engage various intracellular signaling pathways to adapt themselves to the insulting conditions and circumvent the therapeutic protocols to preserve their entities, resulting in the production of enormous neoplastic cells. Here, in this chapter, recent data about CSC features and behavior in the context of tumors will be discussed. Data in this chapter can help us in the proper understanding of CSC biology, activity, and their relevance to tumor development and progression, which is highly significant in human medicine and the selection of correct therapeutic protocols.

Keywords: Tumors; Cancer stem cells; Dynamic Growth and Activity; Therapy.

1. Introduction

CSCs are TICs[1] within the tumor parenchyma. It has been shown that these cells exhibit some stemness features of regular stem cells, such as self-renewal activity and differentiation potential into different cell types [1]. These cells were identified first in leukemic conditions in the late 1990s, with the potential to commit to different lineages, leading to heterogeneity in tumors (**Figure 1**). Several investigations have revealed that CSCs are detected based on the existence of certain biomarkers ($CD133^+$, $CD44^+$, $CD24^-$, etc.) [2]. As a common belief, CSC population ranges between 0.01 to 10% of total tumor cells, causing cancer metastasis, relapse, and failure of chemotherapeutic protocols [3]. Along with these descriptions, detection, monitoring, and exploration of CSCs have opened avenues for the development of *de novo* therapeutic regimes in cancer patients. Besides, a precise study of CSCs in each tumor type helps to understand the underlying challenges associated with malignant types in the clinical setting. Here in this

[1]. Tumor-initiating cells

chapter, we aimed to outline the recent findings related to CSC features and their key roles in the promotion of resistance via different cellular and molecular pathways within the TME[1].

CSCs have the potential to initiate the development and progression of tumor cells via different mechanisms [2]. It seems that CSCs of different tumor types can be identified based on a distinct surface molecular pattern. For instance, in most solid tumors, such as breast cancer, these cells are characterized based on $CD44^{+}/CD24^{-/low}$, while CD133 expression is identical for the identification of CSCs in brain and colorectal cancer [4-6]. In terms of CSC origin, it has been hypothesized that CSCs can originate from normal stem cells or progenitors within the tissues after genetic mutation or changes in environmental stimuli. Besides, others propose that CSCs can derive from differentiated cells following genetic mutation or heterotypic modifications [7]. Besides surface marker assessment, CSCs are also detected based on function and behavior, such as tumoroid and spheroid formation capacity and genetic profiles. Of course, it should not be forgotten that these features are different in CSCs originating from various cancers, making big challenge in the definition and characterization of these cells [8].

[1]. Tumor microenvironment

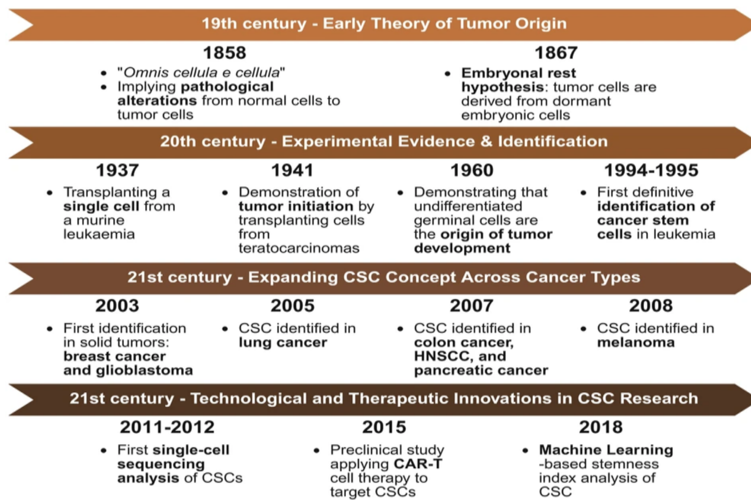

Figure 1. The illustration depicts the historical evolution of CSC research and therapy. Reproduced with permission. [9]. Signal Transduction and Targeted Therapy. 2025.

2. CSC self-renewal and differentiation

As above-mentioned, CSCs exhibit two distinctive characteristics, self-renewal and differentiation, which can be compared to the behavior of normal stem cell counterparts. Calling attention, these features help CSCs to maintain their population during the tumor dynamic growth and increase the size of the tumor mass via phenotype shifting into neoplastic cells [10]. The self-renewal activity of CSCs is done via engaging both symmetric and asymmetric cell division to ensure their presence within the tumor parenchyma in different insulting conditions [11]. To be specific, using asymmetric cell division, CSCs promote the tumor growth and expansion via generating daughter cells to preserve the CSC pool and another that acquire a more specialized neoplastic phenotype [9]. In line with this potential, CSCs can produce diverse progeny contributing to cell heterogeneity and complexity inside the tumor parenchyma (**Figure 2**).

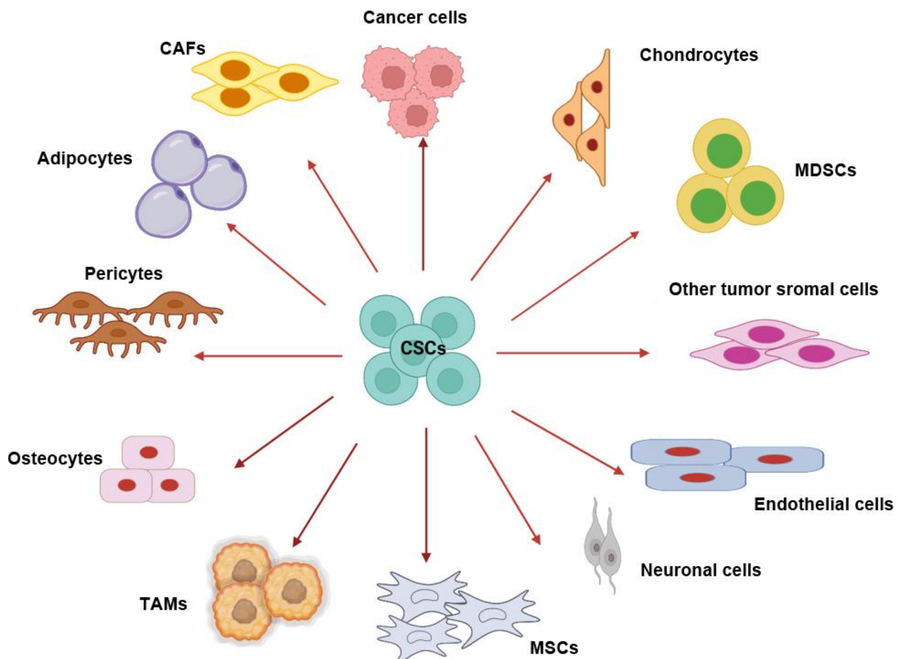

Figure 2. CSCs can produce different progenies and lineages, contributing to tumor heterogeneity and therapeutic resistance. Abbreviations: CSCs: Cancer stem cells; CAFs: Cancer-associated fibroblasts; TAMs: Tumor-associated macrophages; MSCs: Mesenchymal stem cells; MDSCs: Myeloid-derived suppressor cells. Created by BioRender's web-based software. 2025.

It is thought that the stimulation and provocation of various molecular cascades associated with different signaling pathways can potentiate CSCs in the generation of distinct cell phenotypes. For instance, the Wnt[1]/β-catenin, Notch, JAK[2]/STAT3[3], PI3K[4]/Akt[5], and Hedgehog signaling pathways have abnormal activity when compared to normal stem cell counterparts (Figure 3a and b) [2].

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[1]. Wingless-type MMTV integration site family
[2]. Janus kinase
[3]. Signal transducer and activator of transcription 3
[4]. Phosphoinositide-3-kinase
[5]. Protein kinase B

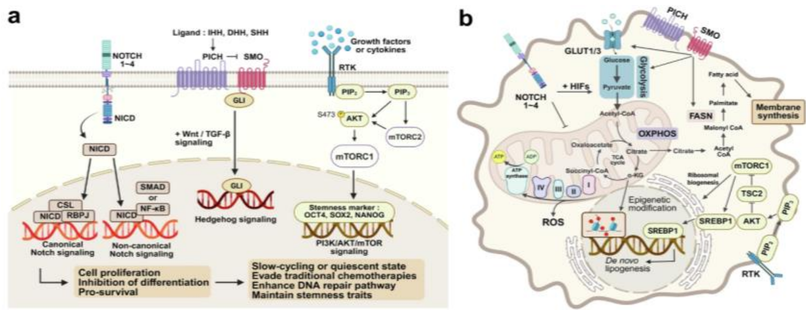

Figure 3. The involvement of various signaling pathways and metabolic switches in CSCs. Different signaling pathways involved in the stability and maintenance of CSCs (**a**). It is suggested that Notch, Hedgehog, and PI3K/AKT/mTOR pathways actively control self-renewal, quiescence, therapy resistance, and survival features of CSC. The activation of the Notch signaling pathway following NOTCH1-4 receptors leads to the promotion of NICD-CSL-RBPJ complex via the canonical pathway. While the non-canonical route is stimulated via the interaction of SMAD[1] and NF-κB[2]. Both signaling axes can control CSC plasticity. Along with this signaling pathway, Hedgehog signaling is stimulated after attachment of IHH[3], DHH[4], and SHH[5] with concomitant activation of GLI transcription, leading to tumorigenesis. Along with these molecular cascades, the PI3K/AKT/mTOR[6] pathway increases CSC entity by engaging mTORC1 and mTORC2 complexes. Of note, the mTORC2 effector is activated by the PI3K signaling pathway, which in turn activates mTORC1, resulting in upregulation of OCT4, SOX2, and NANOG, and CSC dormancy. Additionally, the therapy failure and DNA repair are high under such conditions. Metabolic status in CSCs and their interaction with signaling pathways (**b**). These cells possess metabolic plasticity with the potential to shift between glycolysis, OXPHOS[7], and lipid metabolism in response to ECM[8] clues. The hypoxic conditions and HIFs[9] activate GLUT1/3[10] to uptake glucose to support glycolysis and the TCA[11] cycle. PI3K/AKT signaling inhibits TSC2[12]and stimulates mTORC1, which in turn provokes SREBP1[13]-related *de novo* lipogenesis to increase CSC growth. FASN[14]-associate lipid synthesis can promote CSC viability while the OXPHOS system produces ROS[15], resulting in epigenetic modifications. These data highlight the putative capacity of CSCs in adaptation into different metabolic states depending on external ECM stimuli. Reproduced with permission. [9]. Signal Transduction and Targeted Therapy. 2025.

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[1]. Suppressor of mother against decapentaplegic
[2]. Nuclear factor kappa-light-chain-enhancer of activated B cells
[3]. Indian hedgehog
[4]. Desert hedgehog
[5]. Sonic hedgehog
[6]. Mammalian target of rapamycin
[7]. Oxidative phosphorylation
[8]. Extracellular matrix
[9]. Hypoxia-inducible transcription factors
[10]. Glucose transporter-1/3
[11]. Tricarboxylic acid cycle
[12]. Tuberous sclerosis complex 2
[13]. Sterol regulatory element binding protein 1
[14]. Fatty acid synthase
[15]. Reactive oxygen species

The activation of Wnt/β-catenin in breast CSCs leads to the increase of OCT4 and SOX2, promoting the self-renewal activity [3]. Notch signaling controls phenotype acquisition and is overexpressed in glioblastoma CSCs, leading to enhanced proliferation [6]. The promotion of the Hedgehog signaling pathway maintains the pancreatic CSCs via engaging GLI transcription factors , and thereby increases the malignant features [8]. Due to the involvement of different molecular machineries in CSCs, the selection and efficiency of conventional and nascent cancer therapies will be challenging. The genetic modifications, such as DNA methylation and histone acetylation, can fine-tune transcriptome patterns to preserve self-renewal. In this regard, in AML[1], CSCs hypo-methylate stemness-related genes to increase their expression [12]. HDACs[2] potentially regulate stemness features in which HDAC inhibitors diminish CSC population in breast cancer via concomitant differentiation into neoplastic cells with less tumorigenicity [13]. Of note, H3K9 acetylation of glioblastoma cells is associated with CSC plasticity. It was suggested that HDAC inhibitors can diminish H3K9ac levels in glioblastoma CSCs, thereby blunting stemness traits and sensitizing cancer cells to irradiation [14].

Commensurate with these descriptions, therapeutic approaches should target the genetic program of CSCs to control their plasticity and differentiation properties. To be specific, the reciprocal and dynamic interaction between self-renewal and differentiation features highlights the necessity of novel therapies targeting both to effectively kill CSCs. The occurrence of cell heterogeneity is a hallmark of various cancer types, which is mainly controlled by CSC activity and hierarchical organization,

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[1]. Acute myeloid leukemia
[2]. Histone deacetylases

producing different cell lineages with distinct functions and phenotypes [15]. Therefore, the hierarchical properties of CSCs can contribute to intertumoral and intratumoral diversity, making the diagnosis and therapy of cancer problematic. Of course, the emergence and advent of sophisticated technologies with accurate and precise sensitivity, like scRNA-seq[1], yield high-throughput profiling of CSC subsets within the tumor parenchyma [16]. In general, CSC subsets have a unique gene expression profile involving proliferation, dormancy, immune system activity, and resistance mechanisms [16]. In TNBC[2], using the scRNA-seq technique, different CSC subsets have been identified with certain EMT[3] properties and stemness features associated with metastatic behavior and poor clinical outcomes. It is believed that EMT is involved in tumor cell invasion and acquisition of stem-like properties, leading to prominent plasticity and stability of CSC phenotype [17]. Besides, the metabolic status of CSCs can be altered via EMT activity. In support of this notion, some pancreatic CSC subsets closely depend on OXPHOS[4], while other subsets prefer the glycolytic pathway for the production of energy [18]. The metabolic switch between two states can help CSCs to adapt in response to different therapeutic protocols.

3. CSC identification methods

To date, several approaches have been used for the identification and phenotype characterization of CSCs. In this regard, flow cytometry is the most common analytical modality to detect and enrich CSCs based on specific surface markers such as CD44, CD133, or ALDH[5] activity, helping

[1]. Single-cell RNA sequencing
[2]. Triple-negative breast cancer
[3]. Epithelial-mesenchymal transition
[4]. Oxidative phosphorylation
[5]. Aldehyde dehydrogenase

in the precise estimation of CSC populations within total tumor cells [19, 20]. Besides surface markers, the purification of CSCs is also done based on intracellular Hoechst 33342, the rhodamine exclusion method [21]. This approach enables us to isolate side population, CSCs, based on their capacity to exclude the fluorochromes via the activity of ABC[1] transporters highly expressed in these cells, while exclusion properties are blunt in mature or non-CSC population [22]. Tumor spheroids or tumorspheres are unique in vitro platforms for cancer cell study and enrichment of CSCs [23, 24]. Tumor spheroids are generally induced in non-adherent and serum-free conditions to increase the absolute CSC number while preserving their self-renewal properties and stemness feature [25]. Calling attention, using the lineage tracing technique in various animal models, it is possible to monitor the fate of each cell type and how and by which mechanisms CSCs orchestrate tumor growth and cell heterogeneity [26]. For this purpose, cells are labeled with genetic tags or fluorescent reporters and can be monitored phenotypically over time [27]. For example, researchers investigated the dynamic bioactivity of $LGR5^+$ colon cancer cells in a mouse model [28]. Additionally, the Nestin-Cre model was also used for monitoring CSC hierarchies and heterogeneity in brain tumors [27].

Flow cytometry has been extensively used for the identification and characterization of CSCs within tumors or cultured cells [29]. The isolation and enrichment of CSCs by FACS[2] is done using fluorescent-tagged antibodies that attach to specific surface markers. The tagged CSCs can be isolated and sorted from heterogeneous cell populations [30]. Of course, the sorting strategy should be defined for CSCs of various tumors. For instance, breast CSCs have a unique phenotype ($CD44^+/CD24^{-/low}$

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[1]. ATP-binding cassette
[2]. Fluorescent activated cell sorting

lineage) with active resistance mechanisms to chemotherapeutics [31]. In colorectal cancer, CD133 has been used to enrich the CSCs via FACS. In this regard, Li and colleagues applied this technique to purify $CD133^+$ CSCs from real tumor samples. This modality enables us to precisely concentrate on the dynamic and tumorigenic behavior of CSCs [32]. In brain glioblastoma, CD133 and nestin were used for the enrichment of CSCs ($CD133^+$/$nestin^+$) [33]. It was suggested that this CSC population is actively involved in tumor recurrence and relapse [33]. Despite several advantages associated with CSC isolation using FACS, the existence of specific markers and the possible impact of ECM on biomarkers can influence the CSC population and entity. Along with FACS, MACS[1] was also used for the enrichment of CSCs in *in vitro* and *in vivo* samples [29]. Akbarzadeh et al used the MACS technique and CD133 microbeads to purify SKOV3 ovarian CSCs for different biological analyses in a laboratory setting [29]. The isolated CSCs express SOX-2 and yielded numerous CSC spheroids cultured on stem cell culture medium [29]. The MACS technique isolation is based on the isolation of target cells after the attachment of magnetic bead-conjugated antibodies [34]. Pouyafar and co-workers used CD133 microbeads for the isolation of colorectal cancer HT29 CSCs. Data indicated a relatively high purification rate reaching 90% [35]. The isolated cells had appropriate clonogenic properties to generate CSC spheroids in the *in vitro* setting (**Figure 4**) [35].

[1]. Magnetic Activated Cell Sorting

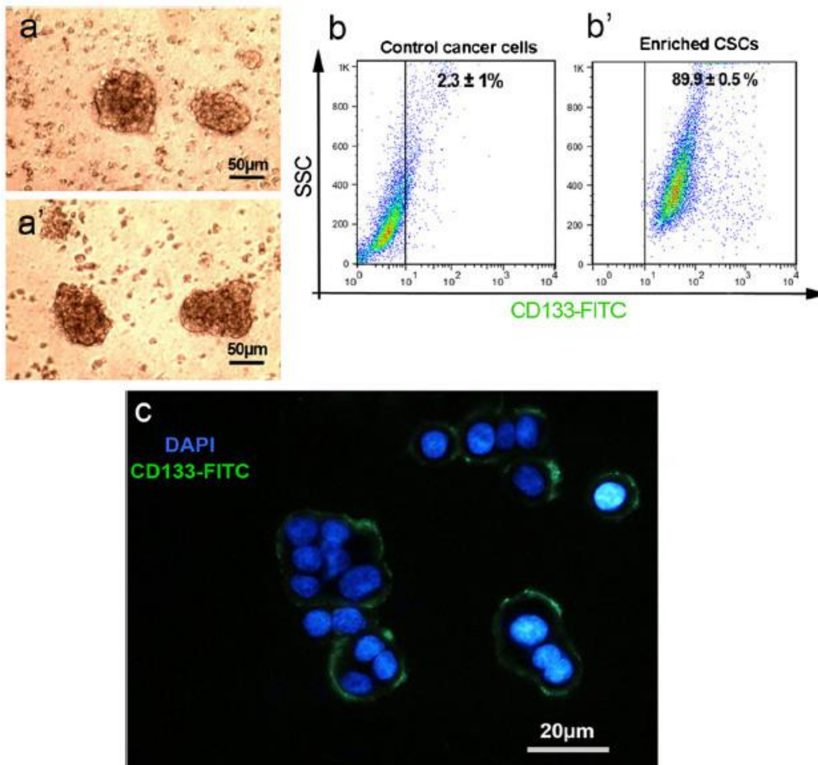

Figure 4. Bright-field imaging of HT-29 CSC spheroids following enrichment by MACS and CD133 microbeads (**a**, **a'**). The purity and isolation efficiency of MACS were evaluated by FITC[1]-conjugated CD133 antibody via a flow cytometric approach, CD133 (n = 3; **b, b'**). The CSC spheroids were also characterized by immunofluorescence imaging (**c**). Reproduce with permission. [35]. Cell and Tissue Research. 2019.

Tumorsphere or spheroid assays have become a conventional in vitro assay to study CSCs in non-adherent, serum-free conditions compared to the 2D culture system [36]. The spheroid culture system potentiates CSCs to proliferate without attachment while preserving their self-renewal activity and control Anoikis [37]. It is thought that spheroid-based assays are valuable for expanding and functionally characterizing CSCs [37]. These platforms can offer deep insights into mechanisms associated with the

[1]. Fluorescein isothiocyanate

formation of tumor mass, chemotherapy resistance, and the generation of CSCs and drug-resistant cells within the tumor matrix. It has been indicated that the existence of micron-sized dimensions and biological barriers in the structure of tumor spheroids makes radial gradients, limiting the access of oxygen and nutrients to cells located in deep layers [23]. These cells are prone to hypoxia the similar to *in vivo* conditions, contributing to the activation of angiogenesis, tumorigenic traits, and emergence of resistant cells [23]. Due to the existence of such insulting conditions (lack of sufficient O_2, glucose, and acidic conditions), the number of CSCs can be increased, which coincides with the elimination of non-resistant non-CSCs [38]. Besides these facts, CSCs *per se* can generate tumor spheres with the activation of certain genes such as *SOX2* and *NANOG,* which correlate with poor prognosis and tumor development [39]. In colorectal cancer, tumorspheres are suitable platforms for the identification of CSCs with higher ALDH1 activity. Data have confirmed that $ALDH1^+$ CSCs can easily generate tumor spheroids and exhibit higher metastatic behavior [40].

4. Mechanisms of resistance to therapy

Using intrinsic and extrinsic mechanisms, CSCs can resist the conventional treatments, resulting in tumor relapse and a poor prognosis [1]. It has been shown that CSCs are armed with biological tools to control quiescence, DNA repair, and drug efflux pumps to withstand therapeutic stress [1]. In quiescence or a dormant state, CSCs can temporarily rest in G0 phase to circumvent the insulting conditions such as therapies [41]. In HCC[1], $CD13^+$ CSCs are usually quiescent with the potential to resist after treatment

[1]. Hepatocellular carcinoma

with 5-FU[1] via the reduction of DNA replication, indicating to target these cells should be targeted in future treatment strategies [42]. The quiescence property is tightly controlled by microenvironment signals, such as TGF-β[2] and IL-6[3], by simultaneous activation of STAT3, repressing genes associated with proliferation [43]. Likewise, quiescent leukemic CSCs express high levels of BCL-2[4], an anti-apoptotic factor that accelerates host cell viability during chemotherapy [44]. The induction of HIF-1α under hypoxic microenvironments helps CSCs to remain within the glioblastoma mass [45]. Strategies targeting quiescent CSCs aim to dictate cell proliferation via the application of BCL-2 inhibitors[5] or similar suppression of other signaling pathways. Cell cycle effectors like p27 and p21 can force CSCs to be in a dormant state. In this scenario, pancreatic CSCs have higher p27 activity with the potential resistance to chemotherapeutics such as gemcitabine [46]. Despite these descriptions, it should not be neglected that CSC dormancy is a reversible phenomenon, and these cells can enter active dynamic growth after therapy, leading to tumor relapse [47].

CSCs can easily adapt to the insulting conditions largely due to the existence of DNA repair mechanisms, resulting in failure of therapeutic protocols [9]. The abnormal activity of the p53 gene allows CSCs to suppress DNA damage checkpoints and resist genotoxic compounds [48]. In a similar way, glioblastoma CSCs have the potential to stimulate DNA damage response pathways, especially via ATM[6] and ATR[7] signaling axes to repair double-strand breaks following radiotherapies [49]. Along with the

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[1]. 5-fluorouracil
[2]. Transforming growth factor beta
[3]. Interkeukin-6
[4]. B-cell leukemia/lymphoma 2
[5]. Venetoclax
[6]. Ataxia-Telangiectasia Mutated
[7]. Ataxia telangiectasia and Rad3-related protein

exploitation of numerous intracellular mechanisms, extracellular factors and components can also help CSCs to restore their function. For instance, TAMs are an eligible cell source to foster DNA repair in CSCs via the TOP2A[1]/β-catenin/YAP1[2] signaling pathway, which reduces CSCs' sensitivity against the genotoxic stress [50, 51]. Therefore, CSC DNA repair mechanisms using PARP[3] inhibitors help make CSCs vulnerable to chemotherapies in BRCA[4]-mutated tumor cells. In addition, the control of epigenetic factors involved in DNA repair, such as HATs[5] , i.e., KAT2B[6], in breast cancer increases the therapeutic outcomes [52]. Thus, a combination of HDAC inhibitors with simultaneous DNA-damaging therapies can yield better tumoricidal properties via the reduction of CSC resistance in the clinical setting [53].

It has been indicated that CSCs are armed with other biological weapons to resist the insulting conditions. The upregulation of ABC transporters helps CSCs to actively extrude chemotherapeutic compounds [54]. Among them, P-glycoproteins such as ABCB1[7] and ABCG2 reduce intracellular drug concentrations, leading to MDR[8]. NSCLC[9] CSCs are characterized by the expression of CD44 and CD133 and elevated ABCG2 levels. Targeting the mentioned transporters blunts MDR activity and improves therapeutic outcomes [55]. Similarly, breast cancer CSCs overexpressing ABCB1 and ALDH1 possess resistance against paclitaxel [56]. The enhanced ABCG2 activity with simultaneous lncRNA H19 levels

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[1]. DNA topoisomerase II alpha
[2]. Yes1 Associated Transcriptional Regulator
[3]. Poly (ADP-ribose) polymerase
[4]. BReast CAncer gene 1
[5]. Histone acetyltransferase
[6]. Lysine Acetyltransferase 2B
[7]. ATP binding cassette subfamily B member 1
[8]. Multidrug resistance
[9]. Non-small cell lung cancer

heightens MDR potential in colorectal CSCs [57]. Although some compounds, such as verapamil and tariquidar, have indicated successful preclinical outcomes via the inhibition of ABC transporters, their clinical application is under investigation due to putative side effects on healthy tissues and cells [58, 59].

Among various extracellular factors, TME, with an intricate and complicated entity, composed of immune cells, TAMs, DCs[1], CAFs[2], MSCs[3], stromal cells, ECs[4] , and diverse ECM components, can control the behavior of CSCs (**Figure 5**) [60]. The reciprocal juxtacrine interaction between CSCs and TME components can contribute to the stimulation of relevant signaling cascades involved in CSC stemness features, dynamic growth, etc., blunting the therapeutic protocols [61]. It is thought that hijacking TME biochemical and structural cues enables us to control CSC viability, stemness features, and thereby resistance to conventional therapies. Within the TME, certain cell lineages, such as CAFs, TAMs, and MSCs, release cytokines such as IL-6 and TGF-β to maintain CSC stemness and tumor expansion.

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[1]. Dendritic cells
[2]. Cancer-associated fibroblasts
[3]. Mesenchymal stem cells
[4]. Endothelial cells

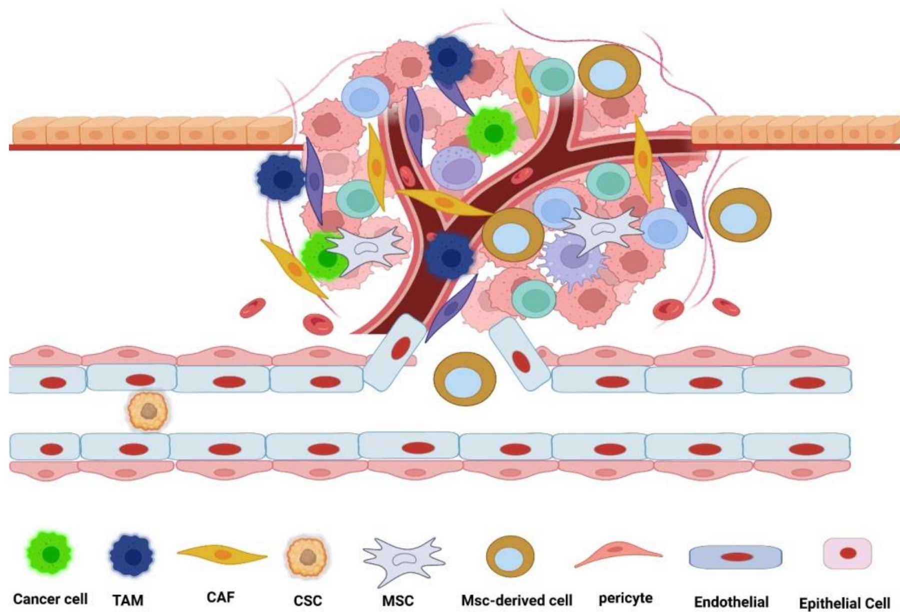

Figure 5. TME is an intricate milieu with different cellular components involved in CSC maintenance and stability. Created by BioRender's web-based software. 2025.

Notably, the production of CXCL12 by colorectal cancer TAMs provokes the Wnt/β-catenin pathway, leading to enhanced self-renewal and tumor growth properties of CSCs [62]. In HCC, CAF-related IL-6 activates STATs in CSCs and increases resistance mechanisms [63]. The upregulation of HIF-1α and HIF-2α, in hypoxic conditions, is integral to increased breast and glioblastoma CSC maintenance [64]. The close interaction of ECM hyaluronan with CSC CD44 receptor activates specific downstream effectors such as Nanog, thereby promoting tumorsphere formation [65]. Besides these elements, the release of nanosized vesicles, namely EVs[1], i.e., exosomes, and microvesicles, with a certain molecular signature can control the dynamic activity of CSCs in a paracrine manner

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[1]. Extracellular vesicles

[66, 67]. For example, CAF exosomes harboring miR-21 can precisely control pancreatic CSC stemness by inhibiting PTEN[1] [45, 68]. Recent research emphasizes the importance of exosomes in communication between the niche and CSCs. For instance, CAF-derived exosomes containing miR-21 enhance CSC stemness in pancreatic cancer by targeting PTEN, which is involved in the failure of cancer therapy [69]. Therefore, one can hypothesize that niche factors provided by TME are crucial to support the CSC entity and bioactivity.

In terms of immune modulatory properties, CSCs can use several strategies to evade the immune system. For example, these cells suppress MHC-I[2] molecule levels to impair T-cell recognition and antigen presentation [70]. For example, this effect is related to the suppression of LCOR[3] in breast CSCs to circumvent the adaptive immunity. Notwithstanding, glioblastoma CSCs overexpress PD-L1[4], a checkpoint ligand, to suppress the function of CD4 and CD8 lymphocytes [71, 72]. The release of various immunosuppressive factors like IL-10 and TGF-β by CSCs contributes to the homing of MDSCs[5] and Tregs[6] into the tumor parenchyma, hampering the tumoricidal properties of immune cells [69, 73]. These factors can be transferred using EVs from donor CSCs to recipient TEM cells. For instance, melanoma CSCs can release EVs with high levels of PD-L1 to non-CSCs with the potential to suppress immune response [69, 73].

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[1]. Phosphatase and tensin homolog
[2]. Major histocompatibility complex class I
[3]. Ligand dependent nuclear receptor corepressor
[4]. Programmed Cell Death Ligand 1
[5]. Myeloid-derived suppressor cells
[6]. Regulatory T Cells

5. Therapeutic implications

Epigenetic therapies additionally focus on CSC pathways. For instance, EZH2 inhibitors decrease CSC stemness in breast cancer by reversing H3K27me3-mediated gene silencing [74]. Combining pathway inhibitors with epigenetic drugs improves treatment effectiveness, as demonstrated in AML preclinical studies [75]. In recent years, several attempts have been made to use pre-treated immune cells in cancer therapy. For example, CART[1]-cell therapy is a promising cell-based approach in cancer candidates that use engineered T lymphocytes to accurately target CSC-specific markers such as CD133 and ALDH1. Preclinical studies related to the application of CAR T cells have indicated the reduction of glioblastoma $CD133^+$ CSCs and enhanced survival rate of tumor-suffering creatures [76]. Notably, simultaneous anti-PD-1 agents such as nivolumab or BMI1[2] inhibitors can intensify T-cell responses against $PD\text{-}L1^+$ CSCs in HNSCC[3] cases [77, 78]. Dual inhibition of glycolysis using 2-deoxyglucose and N-acetylcysteine can efficiently disrupt the metabolic heterogeneity of CSCs [18]. Taken together, the multimodal approaches are a relatively promising strategy in overcoming CSC resistance and yielding cancer atresia [79].

6. Conclusion

CSCs can create cell heterogeneity and promote therapy resistance. Although CSCs resemble normal stem cell counterparts, these cells use certain signaling pathways to promote tumor malignancy and metastasis. The reciprocal CSC-TME interaction is pivotal in preserving CSC self-renewal, differentiation, and tumor growth. Besides, the existence of various resistance mechanisms, such as the DNA repair system, efflux

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[1]. Chimeric antigen receptor
[2]. Polycomb complex protein
[3]. Head and neck squamous cell carcinomas

properties, and distinct epigenetic traits, helps CSCs to evade immune system detection and activity. Commensurate with these descriptions, targeting intracellular and TME-derived signaling pathways in CSCs with simultaneous immunotherapy can increase the tumoricidal properties. To achieve better regenerative outcomes, the development of sophisticated diagnostics, such as advancing single-cell sequencing, along with accurate manipulation of gene profiles, helps pave the way for personalized cancer therapies.

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