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Cancer stem cells and niches: challenges in immunotherapy resistance

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Abstract

Cancer stem cells (CSCs) are central to tumor progression, metastasis, immune evasion, and therapeutic resistance. Characterized by remarkable self-renewal and adaptability, CSCs can transition dynamically between stem-like and differentiated states in response to external stimuli, a process termed "CSC plasticity." This adaptability underpins their resilience to therapies, including immune checkpoint inhibitors and adoptive cell therapies (ACT). Beyond intrinsic properties, CSCs reside in a specialized microenvironment—the CSC niche—which provides immune-privileged protection, sustains their stemness, and fosters immune suppression. This review highlights the critical role of CSCs and their niche in driving immunotherapy resistance, emphasizing the need for integrative approaches to overcome these challenges.

Introduction

For decades, Cancer stem cells (CSCs) have been central to the understanding of tumor biology, playing critical roles in tumor initiation, metastasis, immune evasion, and therapeutic resistance. The concept of CSCs has evolved significantly since their initial identification in 1994 through studies on acute myeloid leukemia (AML), which revealed a $CD34^+/CD38^-$ cell subpopulation with stem cell-like renewal capabilities and high tumor-initiating potential [1]. Unlike their differentiated progeny, CSCs possess a unique ability to sustain the growth of malignant cell populations indefinitely. This property not only drives tumor progression but also endows CSCs with resilience against conventional therapies that target rapidly dividing cells, as CSCs often exist in a quiescent or slow-cycling state, allowing them to evade therapeutic

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elimination. As research advanced, it became increasingly evident that CSCs are not static entities but exhibit remarkable adaptability, enabling them to survive and thrive under diverse therapeutic pressures. This characteristic underpins the "Hierarchical Organization Theory," which posits that CSCs occupy the apex of the tumor's cellular hierarchy [2]. More recently, the concept of "CSC plasticity" has emerged, describing the dynamic ability of CSCs to transition between stem-like and differentiated states in response to external stimuli such as therapeutic interventions, hypoxia, or metabolic stress [3]. Unlike the fixed hierarchical model, this perspective suggests that stemness is not an intrinsic or permanent property but a transient state shaped by external conditions, such as therapy or environmental stressors. This fluidity not only highlights the complexity of CSC biology but also emphasizes their central role in driving therapeutic resistance [4–8]. Moreover, the interactions between CSCs and other tumor cell populations further complicate therapeutic strategies, as non-CSCs can dedifferentiate into CSC-like states under specific conditions, adding an additional layer of heterogeneity and resistance. These insights highlight the urgent need for innovative therapeutic approaches that account for CSC plasticity and its implications for cancer progression and resistance.

Immunotherapy, including immune checkpoint blockade (ICB) and adoptive cell therapies (ACT), has revolutionized cancer treatment, offering unprecedented hope for patients with advanced disease [9]. Yet, the emergence of both intrinsic and acquired resistance has tempered its promise, underscoring significant gaps in our understanding of tumor evolution under immunotherapeutic pressure. In this context, CSCs stand out as pivotal contributors to this resistance, due in part to their immune-privileged status [10]. CSCs possess mechanisms that allow them to evade immune recognition, including low expression of major histocompatibility complex (MHC) molecules, secretion of immunosuppressive cytokines, and the recruitment of regulatory immune cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Under the selective pressure of immunotherapy, CSCs endowed with immune privilege can expand and differentiate into diverse cell types, forming a spatiotemporal continuum of resistance. This process involves not only intrinsic CSC properties but also their dynamic interactions with the tumor microenvironment (TME). Through mechanisms such as adhesion and ligand-receptor signaling, CSCs interact with immune cells, stromal cells, and other TME components to foster immune suppression and promote tumor survival [11–14].

Under physiological conditions, normal stem cells coexist with a specialized microenvironment, known as the "niche," that regulates their self-renewal, quiescence, and differentiation [15–18]. Analogous to normal stem cells, CSCs reside within a unique microenvironment—the "CSC niche"—which plays an indispensable role in sustaining their stemness and immune evasion capabilities. This niche, comprising a heterogeneous array of cell types including immune cells, stromal cells, endothelial cells, pericytes, and fibroblasts, along with cytokines, growth factors, metabolites, and extracellular matrix (ECM) components, creates a protective sanctuary for CSCs, shielding them from external assaults such as immune attacks or therapeutic agents [19]. Furthermore, the CSC niche actively shapes the tumor immune landscape by promoting immune suppression and fostering conditions that favor therapeutic resistance [20–23]. The intricate and dynamic nature of these interactions reflects the profound challenges in effectively targeting CSCs without disrupting the broader tissue microenvironment. As a result, targeting the unique properties of CSCs and their niche has emerged as a pivotal strategy in overcoming immunotherapy resistance. However, such efforts require a nuanced understanding of the interconnected pathways governing CSC behavior and their interactions with the TME. Emerging therapeutic strategies, including the development of niche-targeting agents, immune checkpoint modulators specific to CSCs, and metabolic reprogramming approaches, hold promise in addressing these challenges. Understanding the multifaceted contributions of CSCs to immune resistance demands integrative approaches that bridge basic research and clinical application, leveraging advances in multiomics, single-cell technologies, and computational modeling. This review synthesizes recent advances in CSC biology, emphasizing their dynamic interplay with immune resistance mechanisms, and proposes integrative approaches to translate these insights into clinically actionable strategies.

Immune escape mechanisms of cancer stem cells

CSCs are uniquely equipped to withstand immune system pressures, leveraging their remarkable plasticity and close interaction with the TME to evade immune attacks. Their ability to self-renew and initiate tumors positions them as key players in cancer progression and resistance to therapy. Under the influence of immune selection pressure, CSCs dynamically shift their phenotypes and functional states, employing a spectrum of adaptive responses that ensure their persistence. These adaptive mechanisms are not only intrinsic to the cells themselves but are also shaped by external cues from the TME, including signals from stromal cells, immune cells, and extracellular matrix components. The intricate interplay between CSCs and the TME contributes to immune evasion, allowing CSCs to survive and thrive even under

intense immunotherapeutic stress. This phenomenon is a major obstacle to successful cancer immunotherapy, as it underlies both treatment resistance and tumor relapse.

Intrinsic mechanisms of immune evasion in CSCs

To evade immune surveillance, CSCs deploy a range of intrinsic strategies that highlight their versatility and survival acumen. One of the most prominent mechanisms is the upregulation of immune checkpoint proteins, such as programmed cell death 1 ligand 1 (PD-L1), which suppress T-cell activation and create an immunosuppressive microenvironment [24]. Another strategy involves downregulating antigen-presentation machinery, such as MHC class I molecules, to reduce their visibility to cytotoxic T cells (CTLs) [25]. Furthermore, CSCs undergo extensive epigenetic reprogramming, altering gene expression patterns to evade immune recognition. Epigenetic changes can also enhance the expression of genes associated with immune escape or resistance to apoptosis [26]. Beyond these mechanisms, CSCs actively modulate their secretome, releasing factors such as cytokines, chemokines, and exosomes that can recruit immunosuppressive cells (e.g., Tregs, MDSCs) and dampen antitumor immune responses [27]. Additionally, CSCs often overexpress cancer-testis antigens (CTAs) and oncofetal proteins, enabling them to mimic embryonic or immune-privileged states that evade immune detection. These combined strategies highlight the sophisticated arsenal employed by CSCs to navigate the hostile immune landscape, emphasizing the need for multi-faceted therapeutic approaches to counteract their immune evasive.

Immune checkpoints

Immune checkpoints expressed on tumor cell surfaces interact with ligands on immune cells, suppressing their activity and fostering an immunosuppressive TME. Herein, we provide an overview of immune checkpoints regulation involved in CSCs immune evasion (Fig. 1). A prominent example is PD-L1, which binds to programmed cell death protein-1 (PD-1) on $CD8^+$ T cells, thereby inhibiting T-cell activation and facilitating immune evasion [28]. This mechanism is particularly prominent in CSCs. For instance, the stemness-related transcription factor MYC directly binds to the promoter region of PD-L1 in hepatocellular carcinoma (HCC), driving its transcription and enhancing the immunosuppressive microenvironment. Conversely, the inactivation of MYC leads to a downregulation of PD-L1 expression and strengthens anti-tumor immunity [29]. Similarly, quiescin sulfhydryl oxidase 1 (QSOX1) has been shown to promote the expression of PD-L1 in dormant esophageal cancer stem cells by increasing the levels of reactive oxygen species, thereby facilitating the exclusion of $CD8^+$ T cells [24]. PD-L1 itself also forms a positive feedback loop with the β-catenin signaling pathway, promoting cancer progression by maintaining and expanding tumor stem cells [30]. This interaction underscores the dual role of PD-L1 in both immune evasion and the maintenance of CSC characteristics. In bladder cancer, the stem cell marker aldehyde dehydrogenase 1A1 (ALDH1A1) is positively correlated with PD-L1 expression, linking stemness with immune evasion in this context [31]. Elevated PD-L1 levels have also been reported in CSCs from breast cancer, colon cancer, and human neck squamous cell carcinoma (HNSCC), further highlighting its pivotal role in immune escape [32–36].

Beyond PD-L1, other immune checkpoints play pivotal roles in CSC-mediated immune evasion. For instance, B7-H4, another immune checkpoint, has also been found to exhibit elevated expression levels in $CD133^+$ glioblastoma stem cells compared to non-CSCs [37]. B7-H4 suppresses T-cell proliferation and cytokine production, further impairing anti-tumor immunity. Similarly, B7-H4 and B7-H3 are utilized to evade immune surveillance during the progression and metastasis of breast CSCs and SCC stem cells, respectively [38, 39]. CD80, a ligand for the cytotoxic T-lymphocyte antigen 4 (CTLA-4), is expressed in stem cells of HNSCC in response to transforming growth factor beta (TGF-β), thereby weakening CTLs toxicity and promoting tumor immune resistance and relapse [40]. Emerging immune checkpoint molecules, such as CD155, have also been implicated in CSC-mediated immune evasion. CD155 interacts with the inhibitory receptor T cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory domains (TIGIT) on T cells, mediates immune escape driven by CD49f-high tumor-initiating cells (TICs) [41, 42]. Similarly, CD24, widely recognized as a CSC marker, functions as an immune checkpoint by directly binding to Siglec-10 on tumor-associated macrophages (TAMs), thereby inhibiting phagocytosis [43, 44]. CD47, as a classic "don't eat me" signal molecule, is upregulated in circulating hematopoietic stem cells and leukemia cells, protecting them from phagocytosis by macrophages [45, 46]. Notably, recent studies have demonstrated that targeting CD47 in combination with PD-L1 blockade can synergistically enhance anti-tumor immunity, highlighting the potential for dual immune checkpoint inhibition in CSC-targeted therapies [47, 48]. In conclusion, CSCs exploit a diverse array of immune checkpoint pathways as a strategy to evade immune surveillance, thereby promoting tumor progression and immune resistance. Elucidating the mechanisms of immune escape in CSCs is essential for developing more effective therapies to overcome their immunosuppressive effects, improve treatment outcomes and overcoming immune resistance.

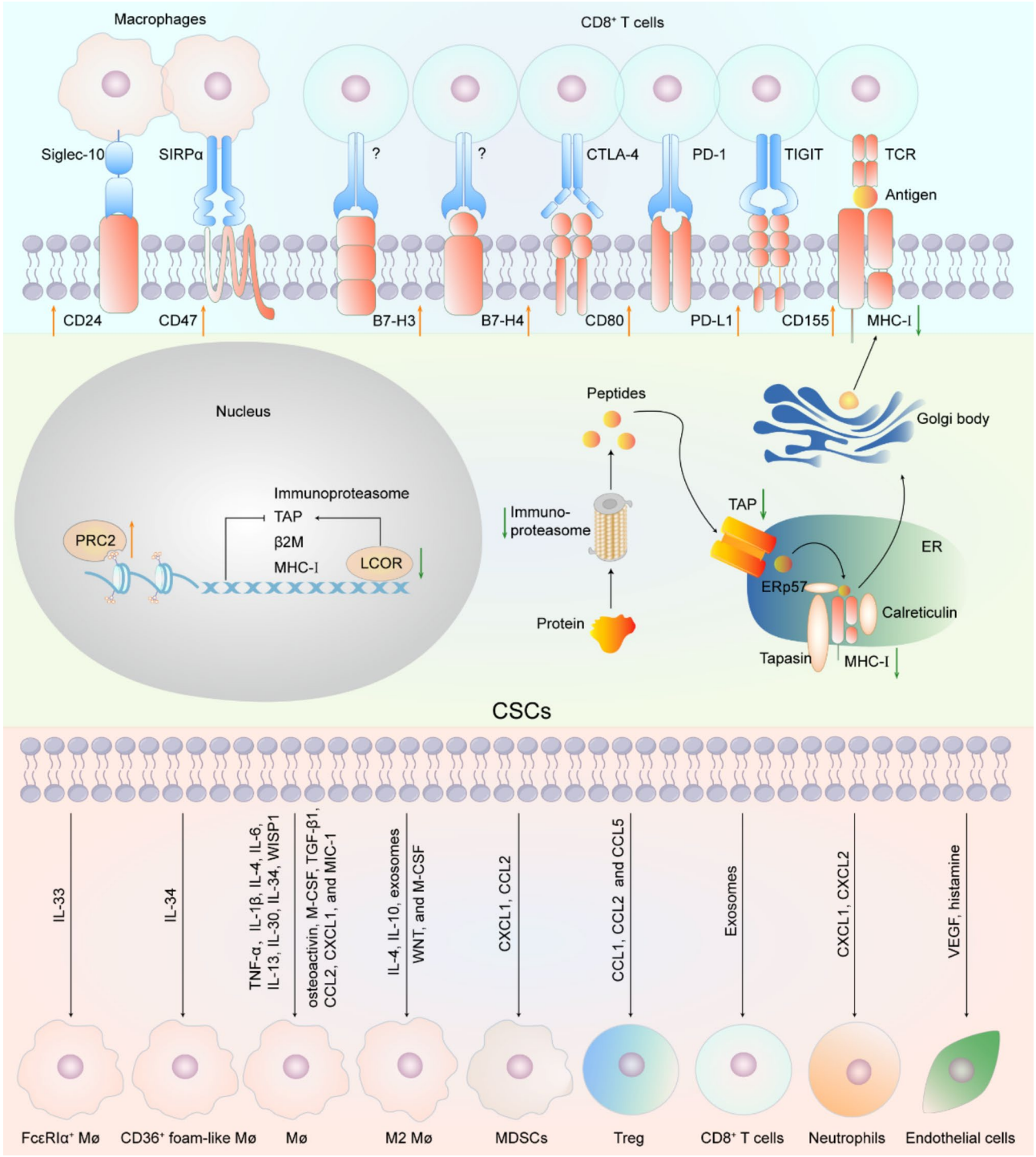

Fig. 1 Immune checkpoints, antigen-presentation machinery, and secretome involved in CSCs immune evasion. The expression of immune checkpoint molecules on CSCs, including CD155, PD-L1, CD80, B7-H3, B7-H4, CD47, and CD24, is significantly upregulated, effectively suppressing anti-tumor immunity. Furthermore, disruptions in antigen presentation pathways, such as impaired MHC-I functionality and TAP-associated protein deficiencies, compromise immune surveillance and facilitate immune evasion. Within the tumor microenvironment, CSCs sustain immunosuppression by secreting abundant cytokines, chemokines, and exosomes, which modulate the activity of immune and endothelial cells in the niche

Antigen processing and presentation

For T cells to recognize tumor cells and generate an immune response, the binding of MHC-I antigens to T cell receptor (TCR) on CTLs is essential [49]. However, prior to this recognition, a series of intricate processes must take place for the successful presentation of tumor antigens. First, tumor antigens are degraded in the proteasome, followed by transport to the endoplasmic reticulum via transporter proteins, where they are loaded onto MHC-I molecules. These MHC-I molecules then travel to the cell surface, where they present the tumor-derived peptides to T cells [50, 51]. Without this precise mechanism of antigen processing and presentation, T cells would lack the necessary cues for identifying and targeting tumor cells. CSCs regulate tumor antigens both by controlling the production of the antigens themselves and by modulating MHC molecules (Fig. 1). Similar to tissue-resident stem cells, which downregulate MHC class I and transporter associated with antigen processing (TAP) proteins to maintain tissue homeostasis, CSCs employ analogous mechanisms to evade immune surveillance [52]. For instance, polycomb repressive complex 2 (PRC2) has been shown to suppresses MHC-I expression at the transcriptional level through epigenetic mechanisms, affecting antigen processing in small cell lung cancer and neuroblastoma [53]. Moreover, in squamous cell carcinoma (SCC), a subset of CSCs responding to TGFβ signaling shows further suppression of antigen presentation, thereby promoting immune escape [40]. Furthermore, tumor spheres cultured from 12 human solid tumor cell lines have demonstrated that the downregulation or loss of human leukocyte antigen class I/II (HLA-I/-II) molecules in CSCs, combined with an absence of response to interferon-gamma (IFN-γ) stimulation, results in impaired antigen presentation. This suggests that impaired antigen presentation due to the downregulation of HLA surface expression may be one of the reasons for CSC immune evasion [54]. A similar pattern of MHC-I downregulation is observed in glioblastoma (GBM) CSCs, where although MHC-I molecules are expressed at lower levels compared to non-CSCs, their upregulation upon stimulation with IFN-α and IFN-γ is limited. Moreover, upon stimulation with IFN-α and IFN-γ, the increase in MHC class I molecules and their heavy chains (i.e., A-HC) as well as β2-microglobulin was greater in non-CSCs than in CSCs [55]. In both colorectal cancer and glioblastoma, the reduced expression of MHC class I molecules on CSCs makes them more susceptible to NK cell-mediated killing compared to their differentiated counterparts, emphasizing the altered immune evasion strategies of CSCs [56–59]. CSCs in other malignancies, including lung cancer, HCC, and melanoma, also exhibit similar immune evasion tactics by downregulating MHC-I molecules, thereby impeding the presentation of neoantigens to T cells [60–62]. A similar phenomenon can be observed in head and HNSCC. $CD44^+$ HNSCC cells exhibit CSC characteristics, along with downregulated expression of HLA-A2, HLA class II molecules, MHC-I and TAP2, indicating impaired antigen presentation and processing functions in these CSCs [63, 64]. These alterations further reinforce the immune-resistant properties of CSCs and their ability to thrive in an immune-suppressive environment. Additionally, melanoma CSCs not only downregulate MHC-related molecules but also reduce the expression of tumor-associated antigens, providing an additional layer of immune evasion [60, 65]. In breast cancer, CSCs exhibit low expression of LCOR, and through a mechanism independent of the IFN signaling pathway, interact with the IFN-stimulated response element, leading to the suppression of genes involved in the antigen processing/presentation machinery, thereby promoting immune evasion and resistance to ICB [66]. In summary, CSCs adopt sophisticated strategies to evade immune detection by disrupting antigen presentation and modulating MHC-related pathways. These adaptations not only hinder T cell recognition but also foster the overall immunosuppressive environment, where CSCs persist and contribute to tumor progression. Therefore, understanding and targeting these immune evasion mechanisms are pivotal for the development of novel therapeutic strategies aimed at overcoming CSC-mediated immune resistance.

Regulation of secretome

Intercellular communication mediated by cytokines and extracellular vesicles (EVs) plays a crucial role in enabling tumors to interact with their microenvironment. The secretome of CSCs is crucial for immune evasion, invasive progression, and drug resistance [67]. Next, we will primarily outline the regulation of the secretome of CSCs on the niche (Fig. 1). Interleukin-33 (IL-33), under normal physiological conditions, is primarily localized in the nucleus of CSCs. However, in TGF-β-responsive TICs of SCC, IL-33 is released into the extracellular space through nuclear factor erythroid 2-related factor 2 (NRF2)-mediated antioxidant mechanisms. IL-33 derived from TICs induces the differentiation of immature bone marrow cells into $FcεRIα^+$ macrophages, which contribute to the formation of an immunosuppressive microenvironment [68]. Whereas in HCC-CSCs, the inactivation of P53 leads to the aberrant high-level secretion of IL-34, which induces a population of $CD36^+$ foam-like protumor macrophages, thereby promoting tumor immune escape [69]. In cholangiocarcinoma-CSCs, IL-13, IL-34, and osteoactivin are secreted into the microenvironment to promote macrophage differentiation, promoting immune suppression and tumor progression [20]. In ovarian cancer, CSCs have been shown to increase

the secretion of pro-tumor cytokines such as IL-10 and WNT, which in turn promote the activation of M2 macrophages, supporting immune evasion [70]. Upregulated phosphorylation of signal transducer and activator of transcription 3 (STAT3) in glioma CSCs promotes the production of IL-6, IL-10, colony-stimulating factor (CSF)-1, TGF-β1, and MΦ inhibitory cytokine-1, which are cytokines that can recruit and polarize macrophages/microglia phagocytosis to form an immunosuppressive microenvironment, thereby promoting immune evasion [37, 71]. In colorectal cancer (CRC), $CD133^+$ CSCs protect themselves from chemotherapy-induced cell death by secreting IL-4 [72]. Meanwhile, IL-4 induces the formation of M2 macrophages in CRC, contributing to the establishment of an immunosuppressive microenvironment [73]. Membrane-anchored IL-30 expressed by CRC-CSCs has been shown to be associated with lymphocyte infiltration and survival in CRC patients [74]. Additionally, in breast CSCs, the autocrine IL-30 shapes the immune landscape by regulating the expression of IL-23 and CXCL10, which are crucial for immune response modulation [75]. The secretion of macrophage colony-stimulating factor by CSCs, under the regulation of the transcription factor IFN regulatory factor 5 (IRF5), promotes the generation of pro-tumor M2 macrophages, further supporting tumor growth and immune evasion [76]. In non-small cell lung cancer (NSCLC) -CSCs, upregulation of ubiquitin-specific protease 17 (USP17) enhances the production of cytokines TNF-α, IL-1β, and IL-6, promoting macrophage infiltration [77]. Similarly, in bladder cancer-CSCs, mutations causing the loss of lysine demethylase 6 A (KDM6A) function promote the secretion of IL-6 and CCL2, driving macrophage recruitment and contributing to tumor progression [78].

Vascular endothelial growth factor (VEGF) plays a key role in promoting vascular permeability and angiogenesis and binds to VEGF receptors on endothelial cells, thereby stimulating angiogenesis [79]. CSCs can also regulate the immune microenvironment by secreting VEGF, contributing to tumor vascularization and immunotherapy resistance [80–82]. Chemokines, another major class of secreted proteins, are integral in connecting tumor cells to their surrounding microenvironment [83]. For example, CD49f has been identified as a marker of HCC-CSCs, which secrete CXCL2 to recruit neutrophils and acquire immune privilege, evading immune surveillance [41]. Similarly, CXCL1, as an autocrine chemokine of breast CSCs, primarily triggers tumor progression and immune evasion-related pathways by regulating tumor-promoting and immunosuppressive factors [84]. Treg cells, as the main subset of suppressive T cells, play a central role in tumor immunobiology. Meanwhile, CSCs secrete chemokines CCL1, CCL2, and CCL5 to actively recruit Treg cells [26, 85–88]. In glioblastoma, histamine, a metabolite preferentially secreted by glioma stem cells (GSCs), regulates endothelial cell activity, thereby promoting angiogenesis in the GSC microenvironment [89]. Moreover, the Wnt/β-catenin signaling pathway plays multiple roles in stem cells and CSCs, including promoting the secretion of chemokines [90]. In lymphoma, overactivation of the Wnt/β-catenin signaling pathway promotes the chemotaxis of lymphoma cells toward endothelial cells, enhancing adhesion and promoting tumor progression [91]. In melanoma, lung cancer, and colon cancer, activation of the Wnt/β-catenin signaling inhibits T cell infiltration and promotes tumor growth and therapeutic resistance by regulating the secretion of CCL4 and CCL5 [92, 93]. In breast cancer, CSCs secrete higher levels of IL-6, IL-8, CSF2, and CCL2, which activate their own NF-κB and Wnt/β-catenin pathways, forming an autocrine inflammatory feedback loop that further enriches drug-resistant cancer cells and CSCs [94]. In GBM-CSCs, Wnt-induced signaling protein 1, activated by Wnt/β-catenin signaling, is a secreted protein that can promote tumor progression by recruiting tumor-supportive TAMs [95].

Additionally, CSCs also release another significant type of membrane-bound EVs into the TME [96]. These EVs efficiently transfer signaling molecules from the originating cells to neighboring cells, thereby influencing their characteristics, such as promoting metastasis, stimulating angiogenesis, and modulating immune responses [27, 97]. Exosomes, a subset of EVs secreted by GBM tumor stem cells, are enriched with proteins from the STAT3 signaling pathway and can activate PD-L1 expression in $CD14^+$ monocytes, promoting their differentiation into M2 macrophages [98]. Tumor-derived exosomes, rich in PD-L1, also contribute to the systemic exhaustion of $CD8^+$ T cells, further promoting immune evasion [99]. In summary, CSCs utilize a variety of secreted factors, including cytokines, chemokines, and EVs, to shape the TME and facilitate immune evasion. Through autocrine and paracrine signaling, CSCs not only promote immune suppression but also enhance tumor progression, metastasis, and resistance to treatment. The interplay between these secreted molecules and the immune cells, is crucial for the establishment of an immunosuppressive microenvironment that supports tumor survival and recurrence.

Epigenetic reprogramming and chromatin architecture

Epigenetic reprogramming is one of the fundamental characteristics of tumors, particularly in the context of their plasticity, which involves alterations in DNA methylation, histone modifications, and chromatin architecture [100–103]. These modifications are essential not only for tumor initiation and progression but also for the immune evasion mechanisms orchestrated by CSCs,

which contribute to the creation of an immunosuppressive TME (Fig. 2A).

DNA and RNA methylation DNA methyltransferase 1 (DNMT1) is closely related to stemness, and its interaction with B-cell lymphoma/leukemia 11 A (BCL11A) has been shown to suppress the stemness of triple-negative breast cancer, while BCL11A has also been reported to affect immune infiltration in breast cancer [104–106]. Furthermore, DNMT1 regulates the activation of the Wnt/β-catenin signaling pathway through brain-expressed x-linked protein 1 (BEX1), which is essential for the self-renewal and maintenance of liver CSCs [107]. The maintenance of β-catenin signaling plays a crucial

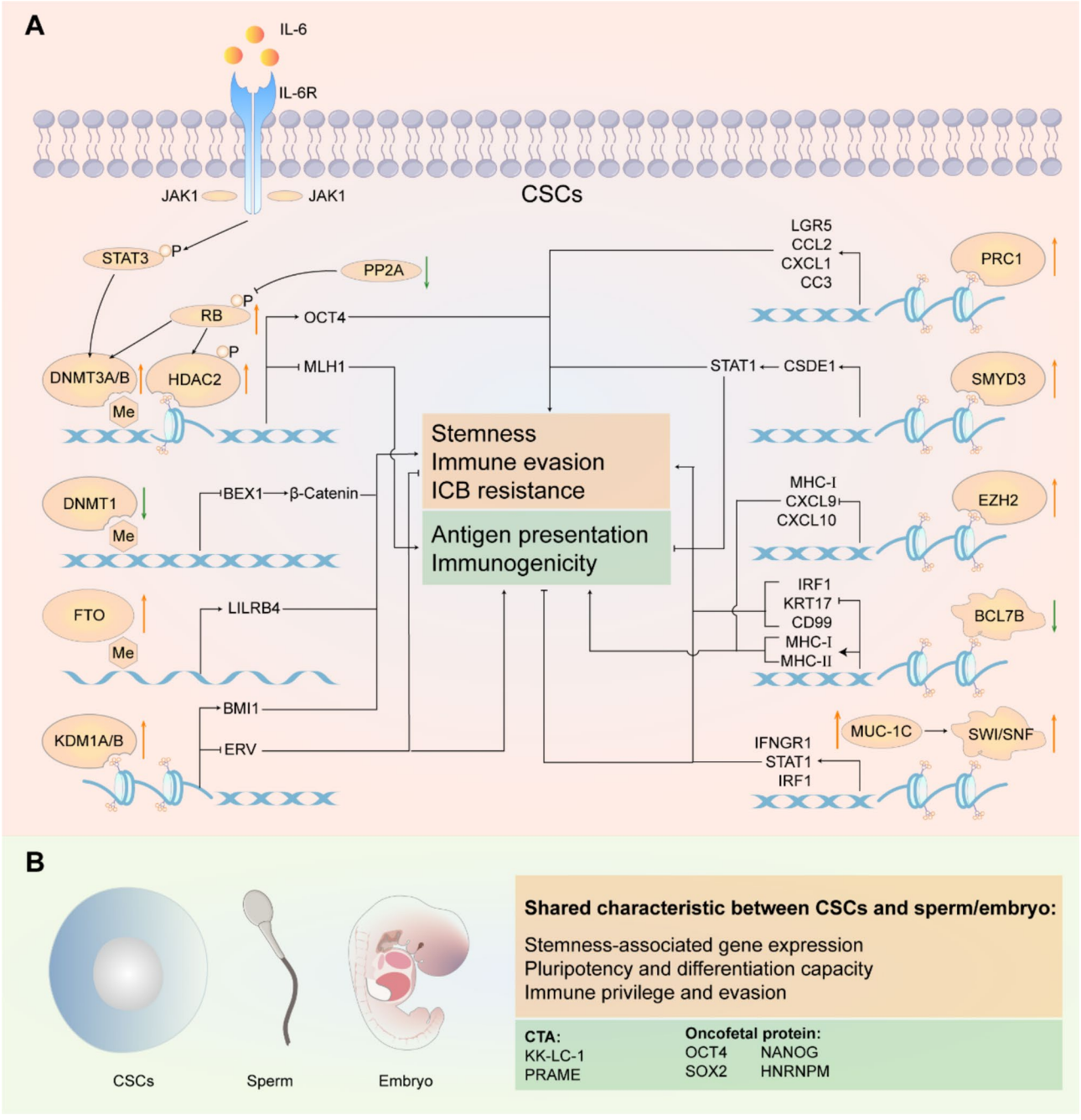

Fig. 2 Epigenetic reprogramming, CTA, and oncofetal protein involved in CSCs immune evasion. (**A**) DNA&RNA methylation, histone modifications, and chromatin architecture collectively regulate molecules associated with stemness and immune evasion in cancer stem cells (CSCs). These modifications not only maintain the stemness characteristics of CSCs but also promote their immune evasion abilities. (**B**) CSCs share certain features with the testis and embryo, such as the expression of stemness-related genes, pluripotency, differentiation capabilities, and immune privilege and evasion mechanisms. These shared characteristics further endow CSCs with an enhanced ability to acquire immune privilege

role in both immune exhaustion and immune exclusion in HCC, further contributing to immune resistance [108, 109]. Beyond DNMT1, DNA methyltransferase 3 A/3B (DNMT3A and DNMT3B) are responsible for the de novo methylation of DNA, a heightened process in embryonic cells and development [110–113]. In mouse colorectal cancer $Lgr5^+$ stem cells, the deletion or inactivation of Protein phosphatase 2 A (PP2A) leads to the phosphorylation of retinoblastoma protein, which subsequently affects the levels of DNMT3A/B, thereby influencing the lymphocyte infiltration levels in CRC [114]. Furthermore, RB phosphorylation of RB also affects the phosphorylation of HDAC2, which subsequently decreases H3K9 acetylation (H3K9ac), leading to the epigenetic silencing of mutL homolog 1 (MLH1). This process weakens CTL infiltration in CRC and induces resistance to ICB therapy. Moreover, the activation of p-STAT3 increases the expression of OCT4 mediated by DNMT3B, with STAT3 playing a crucial role as an IFN-related transcription factor in cancer stemness and sorafenib-resistant HCC patients [115]. In breast CSCs, the silencing of TAP1 caused by promoter hypermethylation contributes to immune evasion [116]. Fat mass and obesity-associated protein (FTO), the first identified RNA N6-methyladenosine demethylase, removes m6A from RNA via α-ketoglutarate and exerts oncogenic effects in various cancers [117]. Genetic deletion and pharmacological inhibition of FTO significantly impair the self-renewal of stem/initiation cells and enhance antitumor immunity by suppressing the expression of immune checkpoint genes, particularly leukocyte immunoglobulin (Ig)-like receptor B4 (LILRB4) [118].

Histone modifications Histone modifications are another intrinsic mechanism deeply involved in the immune escape of CSCs. As a histone demethylase, the dysregulation of lysine-specific histone demethylase 1 A (LSD1/KDM1A) plays a crucial role in maintaining tumor stem cells and resistance to ICB therapy [119, 120]. Mechanistically, high expression of LSD1 is critical for maintaining CSCs properties by regulating the expression of BMI1, a stemness marker [121, 122]. LSD1 can also inhibit the activation of endogenous retroviruse (ERV) elements by demethylating Argonaute-2 (AGO2), thereby reducing the cytoplasmic RNA expression of ERVs and suppressing interferon-mediated antitumor immune responses [119]. Similarly, the dysregulation of lysine-specific histone demethylase 1B (LSD2/KDM1B) plays a role in maintaining CSC stemness under the stimulation of type I interferons [123]. The SET domain bifurcated histone lysine methyltransferase 1 (SETDB1), which is enriched in CSCs, has been shown to promotes immune evasion in melanoma through epigenetic suppression dependent on endogenous retroelements [124–126]. In double-negative prostate cancer, Polycomb repressive complex 1 (PRC1) catalyzes the monoubiquitination of histone H2A, thereby promoting the expression of LGR5, CCL2, CXCL1, and CC3, playing a critical role in coordinating stemness, immune evasion, and angiogenesis [26]. Enhancer of zeste homolog 2 (EZH2), a subunit of the PRC2 complex and a histone methyltransferase, is instrumental in silencing the expression of multiple components of the antigen-presenting machinery (APM), including MHC class I molecules, in tumors derived from stem cells, such as melanoma, embryonal carcinoma, neuroblastoma, and AML, thereby promoting immune evasion [53, 127, 128]. Another important methyltransferase, the methyltransferase SET and MYND domain containing 3 (SMYD3) has been found to downregulate genes associated with the APM through CSDE1/STAT1 signaling pathway in melanoma and breast cancer CSCs, further contributing to immune evasion [129].

Chromatin architecture SWI/SNF chromatin remodeling complexes, also known as the BAF complex, is frequently implicated in human cancers and plays a crucial role in maintaining stemness, involving proliferation, metastasis, and other malignant traits [130, 131]. B-cell lymphoma 7B (BCL7B), as a component of the SWI/SNF complex, is highly expressed in cancer cells, imparting cancer stem cell-like characteristics and promoting the acquisition of an immune evasion phenotype [132]. Mechanistically, BCL7B silencing leads to the downregulation of antigen presentation genes MHC-I, MHC-II, IRF-1, as well as stemness-related genes KRT17 and CD99, thereby promoting the stemness and immune evasion of gastric cancer CSCs. MUC1-C-induced lineage plasticity and dedifferentiation in prostate cancer contribute to an immunosuppressive TME, a process that is dependent on the SWI/SNF complexes [133]. In conclusion, chromatin regulation and epigenetic reprogramming are key drivers of immune evasion in CSCs. By altering DNA methylation patterns, histone modifications, and chromatin architecture, CSCs can dynamically reshape their immune interactions, promoting immune resistance and tumor progression.

Cancer-testis antigen and oncofetal protein

The process of immune evasion mediated by tumor cells shares similarities with immune tolerance mediated by organs such as the embryo and testes (Fig. 2B). CSCs often hijack characteristics associated with the testes and embryo to evade attacks by the immune system. CTAs are a class of multifunctional proteins that exhibit unique expression patterns in germline cells and various types of cancer cells. These CTAs are involved in regulating cellular processes related to development, stem cell differentiation, and tumor initiation [134]. In addition, CTAs are also considered unique stem cell markers. The CTA

score generated from 201 CTA genes, has been shown to have a strong positive correlation with the stemness score within tumors. Furthermore, this CTA score displays a negative correlation with immune infiltration characteristics, a relationship that holds true across all eight major tumor types [135]. For example, one specific cancer-testis antigen, KK-LC-1, demonstrates a negative correlation with $CD4^+$ T cells, macrophages, and dendritic cells in lung adenocarcinoma (LUAD) [136]. Macrophages and dendritic cells, crucial for antigen presentation, are often suppressed in the presence of high levels of such antigens. In breast cancer, the expression of cancer-testis antigen PRAME is associated with poorer survival prognosis, particularly in immune-unfavorable tumors. Silencing preferentially expressed antigen in melanoma (PRAME) reduces the expression of immune checkpoints and ligands, such as PD-1, lymphocyte activation gene 3 (LAG3), PD-L1, CD86, galectin-9 (Gal-9), and V-domain immunoglobulin suppressor of T-cell activation (VISTA) [137]. Interestingly, many embryonic genes and developmental signaling pathways that regulate the characteristics of embryonic stem cells (ESCs) are reactivated in CSCs. These are referred to as "oncofetal drivers," linking tumors to ESCs [138]. For instance, OCT4, a key transcription factor, is highly expressed in liver tumors, breast cancer, and lung cancer [139–141]. Similarly, SOX2 is overexpressed in osteosarcoma, glioblastoma, and SCC [142–144], while NANOG is highly expressed in brain tumors, colon cancer, and liver tumors. These oncofetal proteins are pivotal stemness-associated transcription factors [145–147]. These classic oncofetal protein have all been proven to be associated with an immunosuppressive microenvironment. In glioblastoma, for instance, OCT4 and SOX2 function as transcription factors that regulate multiple immunosuppressive checkpoints, cytokines, and chemokines, thereby promoting the establishment of an immunosuppressive microenvironment [148]. Furthermore, recent studies have identified additional oncofetal proteins that further regulate the positive correlation between cancer stemness and immune evasion. For instance, heterogeneous nuclear ribonucleoprotein M (HNRNPM) influences β-catenin through the alternative splicing of methyl-CpG-binding domain (MBD2) in HCC-CSCs, thereby modulating immune evasion [149]. In summary, CSCs employ these mechanisms to evade immune detection, and this ability to "revert" to an embryonic-like state is one of the defining features of CSCs, known as their plasticity. This plasticity enables CSCs to persist and thrive despite immune surveillance and treatment pressures, ultimately contributing to tumor progression, metastasis, and therapy resistance.

Extrinsic mechanisms: remodeling of the CSC niche to facilitate immune evasion

Extrinsically, the remodeling of the CSC niche creates a favorable environment for immune evasion, such as recruiting immunosuppressive cells like Tregs and M2 macrophages, secreting cytokines like TGF-β, and creating metabolically hostile environments [87, 150, 151]. The CSC niche is a dynamic and multifaceted microenvironment, consisting of diverse cellular and non-cellular components. These include immune cells, stromal cells, endothelial cells, pericytes, cancer-associated fibroblasts (CAFs), and ECM components [19]. Additionally, soluble factors like cytokines, chemokines, growth factors, and metabolites interplay within the niche to orchestrate complex signaling networks. Importantly, non-CSCs residing within the niche can also be co-opted by CSCs to support tumor progression, either by contributing to an immunosuppressive microenvironment or by providing structural and biochemical support for CSC survival and proliferation. This section primarily analyzes how these diverse components within the CSC niche synergistically contribute to CSC-mediated immune evasion, enhance treatment resistance, and ultimately facilitate tumor persistence and progression.

Immune cells in the CSC niche

The interaction between immune cells within the CSC niche and CSCs plays a crucial role in promoting immune evasion and tumor progression [152]. Various immune cells, including macrophages, T cells, and MDSCs, contribute to maintaining CSC properties and facilitating immune escape, thereby enhancing tumor aggressiveness and treatment resistance (Fig. 3). For instance, $FcεRIα^+$ macrophages secrete TGF-β, which acts on SCC-CSCs to promote the invasive progression and drug resistance of SCC [68]. Furthermore, using single-cell spatial transcriptomics technology, it was discovered that in residual lesions of HCC, $PD\text{-}L1^+$ M2-like macrophages interact with stem-like tumor cells and release TGFβ1, which mediates the persistence of stem-like tumor cells and the exhaustion of $CD8^+$ T cells, ultimately leading to HCC recurrence [14]. TAMs are also crucial in sustaining CSC populations in various cancers. For example, in breast cancer, TAMs support CSC survival through direct interaction between Ephrin and the EPH receptor A4. This triggers CSCs to secrete inflammatory cytokines such as IL-1, IL-8, and IL-6, which further support tumor growth and immune resistance [22, 153]. Similarly, MDSCs provide a supportive niche for CSCs by inhibiting immune cell activity in the TME. In ovarian cancer, MDSCs has been shown to enhance CSC-like traits by upregulating microRNA-101, which drives the expression of genes linked to stemness, thus promoting immune evasion and tumor progression [154]. Within the niche, MDSCs

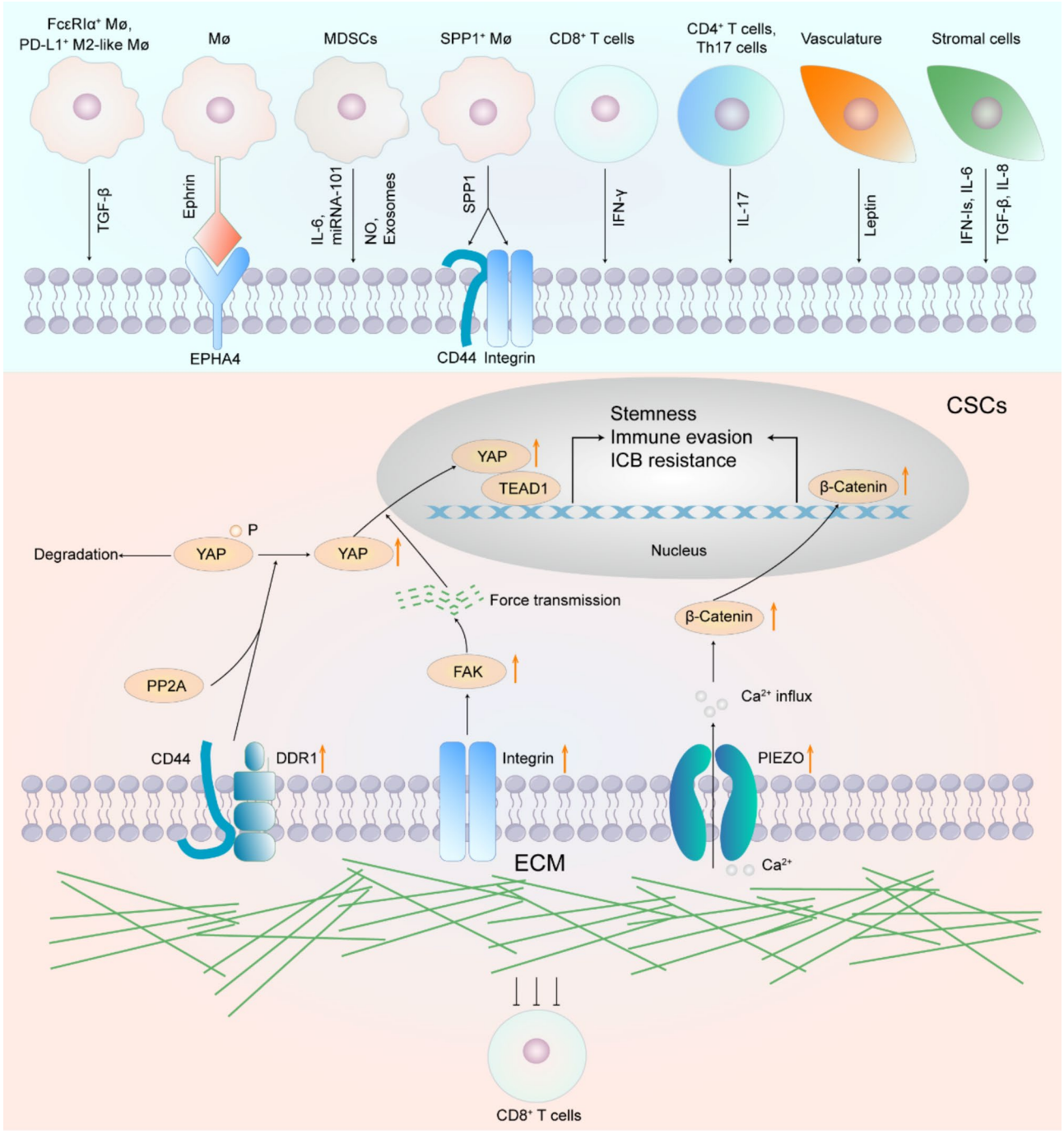

Fig. 3 Role of Extracellular Signals and Mechanical Forces in the Tumor Stem Cell Niche. Cell types within the CSCs niche promote CSC stemness and immune evasion through ligand-receptor interactions or the secretion of cytokines and exosomes. Meanwhile, mechanical signals in the niche are transmitted via PIEZO, YAP/TAZ, or integrins, further enhancing CSC stemness and immune evasion

further promote tumor immune evasion by inducing STAT3 phosphorylation through IL6 and activating NOTCH via nitric oxide, which enhances the stem cell-like properties of breast cancer cells and inhibits T cell activation [155]. Similarly, in CRC-CSCs, MDSCs promote stemness by secreting exosomal S100A9. This mechanism is primarily achieved through the activation of the STAT and NF-kB pathways in CSCs [156]. Spatial transcriptomics analysis in HCC has demonstrated that CSCs co-localize with SPP1$^+$ macrophages, with the SPP1-CD44 and SPP1-ITGA/ITGB ligand-receptor pairs identified as key mediators of this interaction. Interestingly, this communication leads to the exclusion of CD8$^+$

T cells from tumor regions, further exacerbating the immune-exhaustive environment [157].

IFNγ, a key cytokine produced by T cells during immunotherapy, can directly convert non-CSCs into CSCs and sustain their stemness [8]. This process has been linked to branched-chain aminotransferase 1 (BCAT1), which serves as an intermediary molecule in the IFNγ-induced polyoma middle T plasticity transformation. A similar phenomenon has also been observed in NSCLC, where low-dose IFNγ can maintain stemness through the PI3K/AKT/NOTCH1 pathway, thereby enhancing tumor malignancy [158]. Furthermore, IL-17 from Th17 cells or $CD4^+$ T cells can also promote the stemness of ovarian cancer, pancreatic cancer, and gastric cancer CSCs by activating the NF-kβ, p38 MAPK, and STAT3 pathways [159–161]. Beyond secreting cytokines, T cells regulate CSC stemness through direct cell-to-cell contact mechanisms in breast cancer. Among them, the cognate non-lytic interactions between $CD8^+$ T cells and cancer cells can promote the stemness of cancer cells [162]. In preclinical models, such as in a mouse SCC model driven by $HRAS^{G12V}$, single-cell transcriptomics and lineage tracing have shown that abnormal crosstalk between CSCs and their niche promotes the elevation of leptin receptor levels, mediated by stromal TGF-β and vascularly-mediated tissue leptin. This leads to the activation of the LEPR-leptin signaling pathway, which in turn triggers the PI3K-AKT-mTOR pathway in CSCs, driving malignant invasion and metastasis [163]. CAFs represent a highly heterogeneous cellular component within the TME, characterized by remarkable plasticity. They play a crucial role in maintaining CSC stemness and facilitating immune evasion [164]. In bladder cancer, CAF subpopulations characterized by the overexpression of SLC14A1 can induce and maintain stemness through type I IFN signaling, leading to treatment resistance and recurrence [165]. Additionally, $CD10^+GPR77^+$ CAFs sustain cancer stemness and chemoresistance by secreting IL-6 and IL-8 [166]. These complex interactions within the CSC niche establish an immunosuppressive microenvironment that supports CSC survival, immune evasion, and tumor recurrence, highlighting the need to unravel these mechanisms to develop targeted therapies that overcome treatment resistance and enhance therapeutic outcomes.

Mechanotransduction signaling in the CSC niche contributes to immune evasion of cancer

Abnormal tumor biomechanics represents a pivotal physical characteristic of tumors, and its influence on maintaining tumor stemness is increasingly recognized [167–170]. The ECM, a complex network composed of proteins and glycosaminoglycans, plays a critical role in all physiological processes of multicellular organisms. Its mechanical properties, such as stiffness and elasticity, can significantly impact cellular behaviors, including proliferation, differentiation, invasion, and migration, through mechanotransduction signaling [171, 172]. These mechanical signals are vital in regulating the TME and the behavior of CSCs (Fig. 3). SMYD3 mediates the trimethylation of H3K4 at the CSDE1 locus, thereby influencing the immunogenicity of TICs and promoting their immune evasion. This process is regulated by mechanotransduction through the ECM and cell-to-cell contact [129]. Discoidin domain receptor 1 (DDR1), a collagen receptor with tyrosine kinase activity, contributes to immune exclusion by promoting the alignment and remodeling of ECM [173]. DDR1 signaling is particularly relevant in HCC-CSCs, where the co-receptor CD44 enhances type I collagen-induced DDR1 activation, facilitating the recruitment of PP2A. This, in turn, dephosphorylates MST1/2, leading to the activation of YAP and its translocation to the nucleus, where it maintains the stem cell phenotype [174]. YAP and TAZ, two key downstream effectors of the Hippo signaling pathway, are highly responsive to mechanical cues from the ECM and function as mechanosensors, detecting forces such as shear stress, cell shape, and matrix stiffness, and transduce these signals into specific transcriptional profiles that regulate stem cell behavior and tissue regeneration [175]. In the TME, increased ECM stiffness inhibits T cell cytotoxicity and proliferative capacity through YAP signaling [176]. However, some studies have shown that softer ECM can attenuate T-cell cytotoxicity, as cell softness may prevent pore formation induced by CTLs, thereby enabling them to evade CTL-mediated cell killing [177]. Hardening soft cancer cells and stem cell-like cancer cells can achieve effective killing induced by CTLs [169]. This duality highlights the heterogeneity of the TME and suggests that ECM properties can be tailored to either promote or hinder immune responses. In addition to the YAP/TAZ signaling pathway, deregulated integrin signaling in tumors is also closely associated with mechanotransduction, stemness, epithelial plasticity, and therapeutic resistance [178]. Ligand-bound integrins (primarily the αLβ2 subtype, LFA-1) serve as spatial signals to attract lytic granules containing perforin and granzymes and induce their fusion with the plasma membrane to release their contents. Thus, lymphocytes utilize an integrin-dependent mechanical inspection mechanism to enhance their cytotoxic capacity and precision [179]. Although this phenomenon has not been studied in CSCs, it has been reported that integrins can regulate tumor stemness and chemoresistance via the FAK/TAZ pathway [180]. In summary, it is reasonable to speculate that integrin-mediated mechanical forces may influence the tumor stem cell niche by regulating stemness and immune evasion. The PIEZO signaling pathway can also sense mechanical signals to determine stem cell fate and

lineage differentiation, a process primarily dependent on the influx of $Ca2^{+}$ signals [181]. The latest studies using transgenic mice combined with single-cell sequencing have revealed that PIEZO channels play a decisive role in the intestinal stem cell niche [182]. Notably, Piezo1 in macrophages can also sense changes in stiffness, enhancing CD11b expression and Ca^{2+} influx, thereby regulating macrophage morphology and function [183, 184]. This mechanism may be involved in modulating tumor immunity.

In summary, tumor biomechanics—through mechanotransduction pathways like YAP/TAZ, integrin signaling, and PIEZO—plays a critical role in shaping the TME and regulating CSC behavior. The mechanical properties of the CSC niche not only influence stem cell maintenance and tissue regeneration but also modulate immune cell function. The dynamic interplay between biomechanical forces and immune responses presents an exciting avenue for future research, with the potential to develop innovative approaches that target both the mechanical and immunological aspects of tumor biology.

CSC niche-driven metabolic reprogramming contributes to immune evasion of cancer

Tumors commonly exhibit increased glycolytic flux under aerobic conditions, a phenomenon known as the Warburg effect, which is crucial for sustaining their malignant phenotype and promoting uncontrolled proliferation [185]. However, CSCs display distinct metabolic characteristics compared to non-CSCs, not only in terms of their phenotype and function but also at the metabolic level. Unlike their non-CSC counterparts, which predominantly rely on glycolysis, CSCs exhibit a preference for mitochondrial oxidative phosphorylation (OXPHOS), a key metabolic pathway for ATP production in normal cells [186, 187]. This shift toward OXPHOS is believed to confer certain advantages, such as increased resistance to glycolysis inhibitors, and the ability to utilize mitochondrial fatty acid oxidation (FAO) for energy production, thereby promoting cellular survival and metabolic flexibility [187–189]. Consequently, CSCs with OXPHOS characteristics may gain an evolutionary advantage in the TME due to their more efficient utilization of limited nutrients. This metabolic adaptation allows CSCs to thrive even under nutrient-limited conditions, providing them with an evolutionary advantage. Interestingly, lactate, which is produced by more differentiated non-CSCs relying on glycolysis, can serve as valuable fuel for OXPHOS in CSCs, establishing a metabolic symbiosis system [187, 190]. This interdependence creates a metabolic microenvironment that enhances the survival and stemness properties of CSCs, ultimately contributing to tumor progression. However, similar to the plasticity inherent in stem cells, the metabolic characteristics of CSCs are not fixed. Glycolytic and OXPHOS traits can coexist within CSCs, with the balance between the two pathways likely influenced by the cellular state and external cues from the TME [191–195]. For instance, in the quiescent state of CSCs, glycolysis plays a crucial role in sustaining their antioxidative capacity, maintaining stemness, and supporting self-renewal [196, 197]. Moreover, tumors consume glucose in large amounts through glycolysis, competitively limiting T cell effector function, thereby promoting tumor progression [198, 199]. Although direct evidence linking this competitive metabolic mechanism to the CSC niche remains elusive, it is an area of ongoing investigation. Notably, factors such as PPARγ, HIF-1α, and mTOR, which are known to regulate metabolic pathways in immune cells, have also been implicated in the regulation of Treg differentiation, suggesting a complex interplay between CSCs, immune cells, and metabolic regulation [200–203]. Tregs, which are key modulators of immune responses, could potentially influence the immune landscape within the CSC niche, contributing to immune evasion and tumor progression [204]. Next, we will primarily outline the effects of energy sources and metabolites within the niche on CSCs' immune evasion (Fig. 4).

A fascinating example of metabolic reprogramming occurs in pancreatic ductal adenocarcinoma (PDAC), when the exogenous carbon source is switched from glucose to galactose, PDAC cells rely more on OXPHOS for energy production. This metabolic shift promotes the enrichment of CSCs, as evidenced by increased expression of CSC markers and pluripotency genes, enhanced invasiveness, and upregulation of immune evasion factors such as PDL1, CD206, and CD47 [205]. Additionally, mitochondrial FAO has been identified as a major source of bioenergy and, similar to other metabolic pathways implicated in cancer, its dysregulation supports various cancer hallmarks, including proliferation, survival, stemness, drug resistance, and metastasis [206]. Furthermore, FAO is reprogrammed in cancer-associated immune and host cells, potentially contributing to the creation of an immunosuppressive, tumor-promoting microenvironment [207]. For instance, Leptin derived from adipocytes maintains the self-renewal and therapeutic resistance of breast cancer stem cells (BCSCs) by activating the JAK/STAT3 pathway, which subsequently upregulates the expression of carnitine palmitoyltransferase 1B (CPT1B), a key enzyme in FAO [208]. Additionally, the FAO metabolite acetyl-CoA enhances the acetylation level of H3K27Ac in the stemness gene (NANOG, SOX2, and OCT4) promoters, thereby increasing stemness and lymph node metastasis in the lipid-rich lymph node environment [209].

Other metabolites in the CSC niche have also been shown to influence immune evasion. For example,

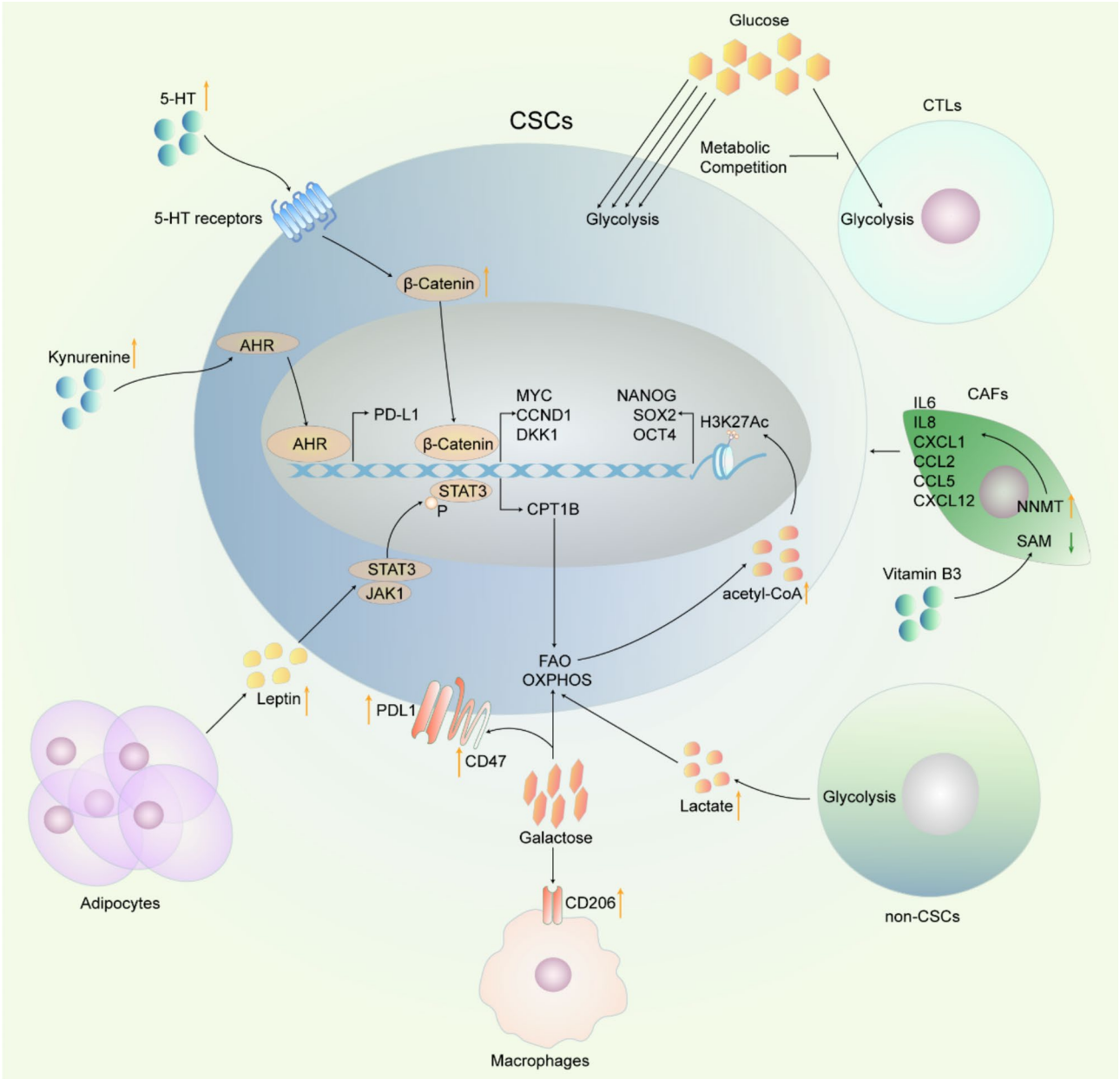

Fig. 4 Niche-driven metabolic reprogramming involved in CSCs immune evasion. Similar to the plasticity inherent in stem cells, the metabolic characteristics of CSCs are not fixed. Glycolytic and OXPHOS traits can coexist within CSCs, with the balance between the two pathways likely influenced by the cellular state and external cues from the TME. The energy sources and metabolic products within the CSC niche promote CSC stemness and immune evasion by regulating metabolic competition or intracellular signaling

kynurenine, catalyzed by indoleamine 2,3 dioxygenase 1 (IDO1) and tryptophan 2,3 dioxygenase 2 (TDO2), can promote cancer progression by impairing host immune surveillance [210, 211]. Mechanistically, TDO2-mediated immune evasion and the maintenance of stem cell characteristics promote liver metastasis of colorectal cancer through the regulation of PD-L1 by mediating aryl hydrocarbon receptor (AHR) activity [211]. Neurotransmitter 5-hydroxytryptamine (5-HT), a metabolite of tryptophan, regulates the Wnt/β-catenin signaling pathway and drives the self-renewal of CSCs in CRC by binding to 5-HT receptors HTR1B, HTR1D, and HTR1F on CSCs [212]. Previous studies have also demonstrated the significant role of 5-HT in regulating tumor immunity [213]. The abnormal metabolic reprogramming of vitamin B3 can promote the secretion of pro-stemness and immunosuppressive factors from CAFs, thereby increasing the abundance of CSCs and immunosuppressive cells while reducing the infiltration of CTLs [214]. Mechanistically, the abnormal metabolism of vitamin B3 leads to an

increase in NNMT and a decrease in SAM, which in turn promotes the upregulation of IL6, IL8, CXCL1, CCL2, CCL5, and CXCL12 through epigenetic reprogramming. In conclusion, CSCs adopt distinct metabolic adaptations, including metabolic plasticity and niche metabolite interactions, which not only sustain their survival in the TME but also enhance their stemness and immune evasion, distinguishing them from non-CSCs.

Dynamic plasticity in cancer stem cells: immune selection as a driver

Immunotherapy has shown remarkable success in treating many malignancies; however, the ability of CSCs to adapt under therapeutic pressure remains a critical barrier to long-term efficacy. Under the pressure of immune therapy, the dynamic plasticity of CSCs is likely to contribute to the development of immune therapy resistance (Fig. 5). Dynamic plasticity, one of the fundamental characteristics of CSCs, and resultant phenotypic heterogeneity enable tumors to maintain an invincible position during aggressive progression, therapeutic resistance, and recurrence [215, 216]. The stemness index constructed for CRC effectively evaluates the capacity of CRC stem cell phenotypes to undergo transitions under selective pressure. Sequential sampling from a subset of patients in the FOxTROT cohort enables a robust assessment of the continuous dynamic changes influenced by chemotherapy-induced selective pressure. In this unique cohort, the stemness index demonstrated that the dynamic plasticity of stem cells is associated with a reduced response to treatment [217]. This further demonstrates the impact of selective pressure on the plasticity of CSCs, and this mechanism of CSC adaptation to therapeutic pressure is highly likely to also exist in immunotherapy.

When treating mouse SCC with ACT-based immunotherapy, tumor-initiating stem cells (tSCs) that respond to TGF-β demonstrate exceptional resistance to ACT and become the root cause of tumor relapse [40]. This is primarily because immune pressure selectively induces the expression of CD80, a ligand typically expressed on immune cells, in tSCs. CD80 subsequently binds to CTLA4, thereby suppressing the cytotoxicity of CTLs [218]. Despite the remarkable success of ICB therapy, most cancer patients remain unresponsive. Immunotherapy can even drive stem cell-like properties in tumors. After ICB therapy, a subset of patients may develop hyperprogressive disease (HPD), characterized by accelerated tumor growth and reduced overall survival despite $CD8^+$ T cell infiltration and activation. In melanoma and non-small cell lung cancer, IFNγ secreted by $CD8^+$ T cells upregulate c-myc expression through FGF2/Wnt/β-catenin signaling, while the stemness marker CD133 is also activated [219]. This indicates that HPD following immunotherapy is not only associated with FGF2 and β-catenin activation but also with increasing in tumor stemness. Coincidentally, in osteosarcoma, breast carcinoma, bladder cancer and PyMT tumors, interferons can also promote tumor cell stemness and enhance therapeutic resistance [8, 123, 165]. In HNSCC, similar to the gradual enrichment of $Bmi1^+$ CSCs under cisplatin treatment, $Bmi1^+$ CSCs also gradually enrich under combined treatment with cisplatin and PD1 [220, 221]. Mechanistically, this is primarily mediated by BMI1's inhibition of the cGAS-STING pathway and suppression of H2AUb. H2AUb binds to the promoters of CCL5, CXCL9, CXCL10, and CXCL11, leading to transcriptional repression, which overall suppresses the CTLs killing ability [220]. Single-cell transcriptomic analysis of organoid tumor spheroids derived from tumors of mice treated with PD1 blockade revealed the presence of a subgroup resistant to $CD8^+$ T cell-mediated immunity. These cells express Snai1 and stem cell antigen 1, exhibiting a mixed epithelial-mesenchymal phenotype characteristic of a stem cell-like state [222]. Atezolizumab plus bevacizumab is now the standard-of-care first-line therapy for HCC; however, patients with continued progression after treatment still exist [223–225]. CTC (circulating tumor cell) testing of patients receiving this regimen shows that the non-responder group has a stronger stem cell phenotype [226]. This suggests that the enrichment of CSCs under this combination treatment may be a reason for the unfavorable response rate. Another study used spatial transcriptomics to sequence samples from HCC patients following PD1 treatment and found that cells in tumor regions with poor immune infiltration exhibited high expression of a CSC signature [227].

Given the inherent adaptive mechanisms of CSCs, therapeutic strategies targeting CSC plasticity must incorporate immune modulation to achieve durable treatment responses. CSCs are characterized by their ability to transition between quiescent and proliferative states, evade immune surveillance, and resist conventional therapies, making them a critical driver of tumor recurrence and metastasis. To disrupt these adaptive processes, combining targeted therapies with ICB has shown promising results in preclinical and clinical settings. In HNSCC, the inhibition of BMI1—a key regulator of CSC self-renewal and stemness—combined with anti-PD1 immune checkpoint therapy, has demonstrated the ability to prevent $BMI1^+$ CSC-mediated tumor recurrence [220]. This combination not only disrupts the self-renewal capacity of CSCs but also enhances the immune system's ability to eliminate residual tumor cells. Similarly, in HCC, targeting CD155, a molecule associated with immune evasion and CSC maintenance, in conjunction with anti-PD1 monoclonal antibodies, effectively weakens the resilience of CSCs and improves therapeutic outcomes [41]. These strategies highlight the importance of addressing both

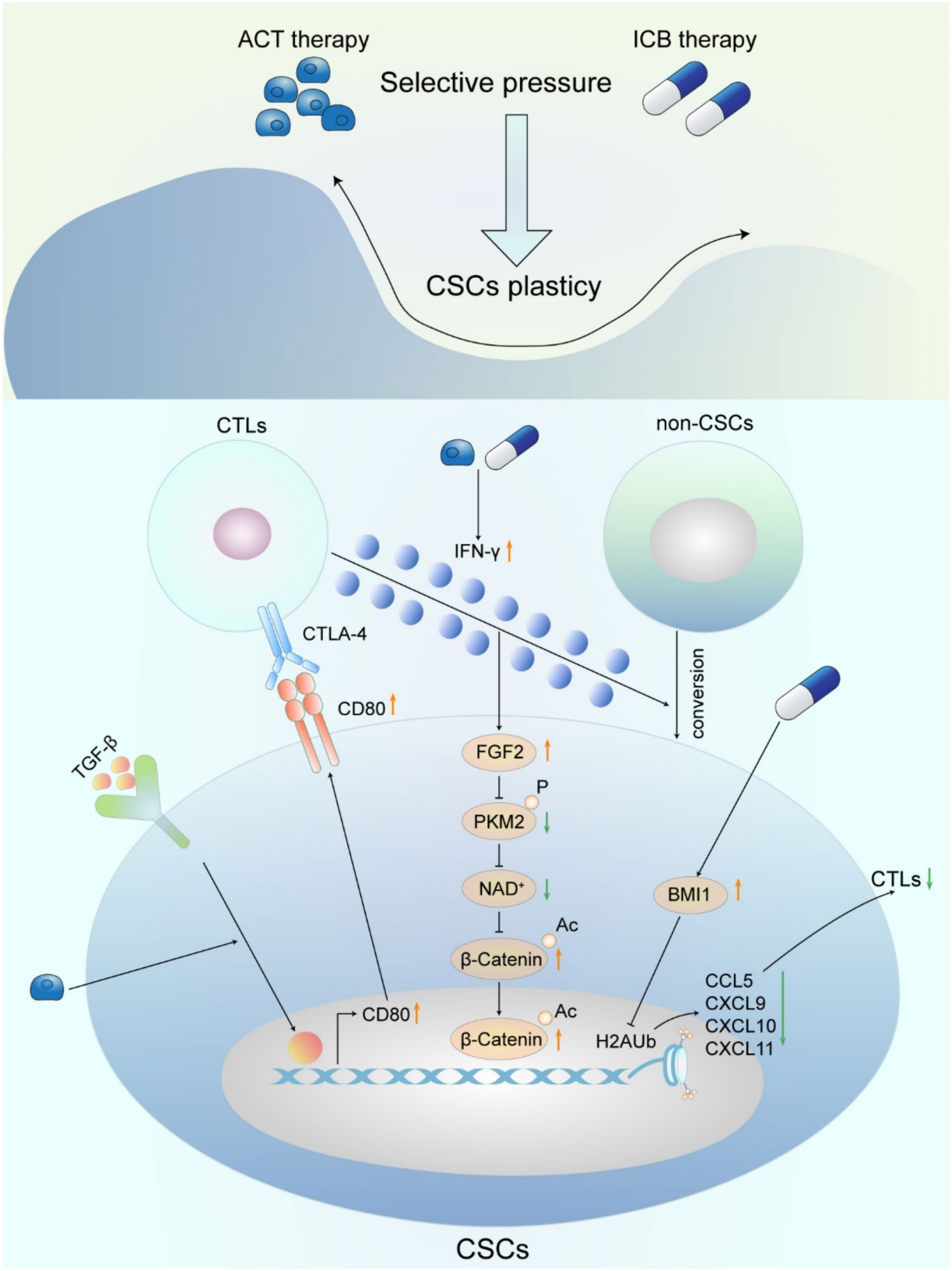

Fig. 5 Dynamic plasticity in cancer stem cells: immune selection as a driver. Dynamic plasticity and resultant phenotypic heterogeneity enable tumors to maintain an invincible position during aggressive progression, therapeutic resistance, and recurrence. Under the pressure of immune therapy, the dynamic plasticity of CSCs is likely to contribute to the development of immune therapy resistance

CSC-intrinsic pathways and the CSC niche. In SCC, the use of CTLA4- or TGF-β-blocking antibodies has shown potential in sensitizing CSCs to treatment [40]. TGF-β, in particular, plays a dual role in promoting immune suppression and maintaining CSC plasticity, making it a pivotal target in strategies aiming to integrate immune modulation. By disrupting the signaling networks that sustain CSCs, these therapies can overcome treatment resistance and reduce the likelihood of tumor relapse. Despite these advances, challenges remain in effectively targeting CSCs due to their heterogeneity and dynamic interplay with the immune system. Future therapeutic strategies must aim to refine our understanding of CSC biology, identify novel biomarkers for CSC subpopulations, and develop more precise combination therapies. Targeting CSC plasticity through combined therapies involving targeted treatment and immune modulation offers a promising strategy to overcome the limitations of current cancer treatments, with the potential to reduce tumor recurrence and metastasis while enhancing patient survival, thereby advancing the fight against cancer.

Conclusion and future directions

CSCs are one of the critical driving factors of tumors, characterized by their potent self-renewal capacity, immune evasion properties, and drug resistance. These attributes position CSCs as pivotal players in tumor progression, recurrence, and resistance to immunotherapy. Although modern immunotherapies, such as immune checkpoint inhibitors and cellular immunotherapies, have achieved remarkable success across various cancer types, the presence of CSC niche remains one of the fundamental reasons why immunotherapy has not yet been able to completely cure tumors. The CSC niche plays a crucial role in orchestrating these interactions, creating a dynamic environment that safeguards CSCs while modulating the immune landscape to favor tumor persistence. This dynamic environment, characterized by the heterogeneity and adaptability driven by the plasticity of the CSC niche, ultimately determines their differential responses to immunotherapy.

The concept of the resistance continuum, which describes the gradual adaptation to PARP-inhibitor olaparib treatment mediated by a series of ovarian cancer cell state transitions, each transition involves a progressive shift in cellular states reinforced by genetic expression programs and epigenetic reprogramming [228]. The deeper implication of these shifts includes the adaptation of stemness programs to stress. Similar to the concept of a resistance continuum observed in response to other therapies, CSCs under immunotherapy pressure may undergo gradual transitions reinforced by transcriptional and epigenetic reprogramming. These shifts enable CSCs to maintain their plasticity, thereby contributing to immunotherapy resistance. Future studies should address whether these dynamic transitions represent a distinct "immune resistance continuum" specific to CSCs. However, with the rapid development of cutting-edge technologies such as single-cell omics, spatial transcriptomics, lineage tracing, immunomes, 3D tumor models, and evolving data science, researchers are gradually uncovering the immune escape mechanisms and resistance characteristics of CSCs. These technologies provide precise tools for analyzing CSC immune phenotypes and microenvironments, enabling the possibility of personalized treatment strategies. Single-cell RNA sequencing can unravel CSC heterogeneity by identifying subpopulations with distinct immune evasive properties, while spatial transcriptomics reveals the spatial organization of CSCs and immune cells within the TME. Lineage tracing enables researchers to track the dynamic state transitions of CSCs under therapeutic pressure, offering insights into the temporal progression of resistance mechanisms. Additionally, immunoprofiling and 3D tumor models are instrumental in recreating the complexity of the TME, enabling the functional evaluation of potential therapeutic targets in physiologically relevant settings. The integration of these technologies is not only advancing our understanding of CSC biology but also paving the way for personalized therapeutic strategies. By leveraging high-resolution data, researchers can identify novel CSC-specific biomarkers and therapeutic vulnerabilities. For instance, computational modeling and artificial intelligence can accelerate the analysis of large-scale datasets, uncovering hidden patterns that drive immune escape and resistance. These insights are critical for designing combination therapies that disrupt CSC plasticity while simultaneously modulating the immune landscape to enhance treatment efficacy.

In conclusion, eradicating CSC-mediated therapeutic resistance demands dual targeting of their cell-autonomous plasticity and the spatiotemporal dynamics of their immune-microenvironment crosstalk. Advances in single-cell spatial profiling and lineage tracing now provide the resolution needed to deconvolute this complexity, empowering rationally designed combinatorial regimens that dismantle CSC survival niches while resensitizing tumors to immune attack—a strategy poised to achieve durable remission in treatment-refractory malignancies.

Abbreviations

5-HT	5-hydroxytryptamine
AML	Acute myeloid leukemia
ACT	Adoptive cell therapies
APM	Antigen-presenting machinery
ALDH1A1	Aldehyde dehydrogenase 1A1
AGO2	Argonaute-2
AHR	Aryl hydrocarbon receptor
BCL7B	B-cell lymphoma 7B
BCL11A	B-cell lymphoma/leukemia 11A
BEX1	Brain-expressed x-linked protein 1
BCAT1	Branched-chain aminotransferase 1
BCSCs	Breast cancer stem cell
CAFs	Cancer-associated fibroblasts
CSCs	Cancer stem cells
CTAs	Cancer-testis antigens

CPT1B	Carnitine palmitoyltransferase 1B
CSF	Colony-stimulating factor
CRC	Colorectal cancer
CTLA-4	Cytotoxic T-lymphocyte antigen 4
CTLs	Cytotoxic T lymphocytes
DDR1	Discoidin domain receptor 1
DNMT1	DNA methyltransferase 1
DNMT3A and DNMT3B	DNA methyltransferase 3A/3B
ESCs	Embryonic stem cells
ERV	Endogenous retroviruse
EZH2	Enhancer of zeste homolog 2
ECM	Extracellular matrix
EVs	Extracellular vesicles
FTO	Fat mass and obesity-associated protein
FAO	Fatty acid oxidation
Gal-9	Galectin-9
GBM	Glioblastoma
GSCs	Glioma stem cells
HCC	Hepatocellular carcinoma
HNRNPM	Heterogeneous nuclear ribonucleoprotein M
HDAC2	Histone deacetylase 2
HNSCC	Human neck squamous cell carcinoma
HLA-I and HLA-II	Human leukocyte antigen class I/II
HPD	Hyperprogressive disease
IRF5	IFN regulatory factor 5
ICB	Immune checkpoint blockade
IDO1	Indoleamine 2,3 dioxygenase 1
IFN-γ	Interferon-gamma
IL-33	Interleukin-33
LILRB4	Leukocyte immunoglobulin (Ig)-like receptor B4
LAG3	Lymphocyte activation gene 3
KDM6A	Lysine demethylase 6A
LSD1/KDM1A	Lysine-specific histone demethylase 1A
LSD2/KDM1B	Lysine-specific histone demethylase 1B
LUAD	Lung adenocarcinoma
MHC	Major histocompatibility complex
MBD2	Methyl-CpG-binding domain
MLH1	MutL homolog 1
MDSCs	Myeloid-derived suppressor cells
NSCLC	Non-small cell lung cancer
NRF2	Nuclear factor erythroid 2-related factor 2
QSOX1	Quiescin sulfhydryl oxidase 1
OXPHOS	Oxidative phosphorylation
PDAC	Pancreatic ductal adenocarcinoma
PP2A	Protein phosphatase 2A
PRC1	Polycomb repressive complex 1
PRC2	Polycomb repressive complex 2
PRAME	Preferentially expressed antigen in melanoma
PD-1	Programmed cell death protein-1
Tregs	Regulatory T cells
SMYD3	SET and MYND domain containing 3
SETDB1	SET domain bifurcated histone lysine methyltransferase 1
STAT3	Signal transducer and activator of transcription 3
SCC	Squamous cell carcinoma
TCR	T cell receptor
TIGIT	T cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory domains
TGF-β	Transforming growth factor beta
TAP	Transporter associated with antigen processing
TDO2	Tryptophan 2,3 dioxygenase 2
TAMs	Tumor-associated macrophages
TICs	Tumor-initiating cells
tSCs	Tumor-initiating stem cells
TME	Tumor microenvironment
USP17	Ubiquitin-specific protease 17
VEGF	Vascular endothelial growth factor
VISTA	V-domain immunoglobulin suppressor of T-cell activation

Author contributions
Study concept and design: Y.P., C.Y., and Z.D. Collecting references: Y.P., C.Y., and Z.D. Original drafting of the manuscript: Y.P. and C.Y. Figure preparation and editing: C.Y. and C.Z. Writing review and editing: Y.P., C.Y., and C.Z. Critical revision of the manuscript: Z.D., J.L., C.S., L.X., G.W., and X.C. Project administration: Z.D., J.L. and B.Z. All authors have reviewed and approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval
Not applicable.

Competing interests
The authors declare no competing interests.

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