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EDITORIAL

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Cancer stem cells in hepatocellular carcinoma: platforms, updates, challenges and future perspectives

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Hepatocellular carcinoma (HCC) is a pressing global health problem and is the sixth most common cancer and the third leading cause of cancer mortality worldwide. Despite continuous advances in treatment modalities, the 5-year survival rate is low with a high propensity for recurrence and metastasis[1]. This clinical challenge in treating HCC is largely attributed to the heterogeneity and intrinsic therapy resistance of cancer stem cells (CSCs), which are a subpopulation of cells with self-renewal capability and multidirectional differentiation potential to induce tumorigenicity[2]. The behavior and maintenance of CSCs are not autonomous but critically dependent on the complex bidirectional crosstalk between CSCs and the tumor immune microenvironment (TIME)[1]. In this editorial, we summarize the recent progress in characterizing CSCs and the interactions between CSCs and the TIME in HCC. Next, we discuss the emerging therapeutic strategies targeting CSC populations with the ongoing challenges. Finally, we give our perspectives on the future directions in HCC CSC research.

Recent progress in the study of HCC CSCs

Surface markers and defining genes

The primary strategy for identifying HCC CSCs relies on the detection of specific cell surface markers that distinguish HCC CSCs from bulk tumor cells. A study has revealed a core set of surface markers (CD24, ICAM1, CD13, and EpCAM) that are consistently expressed on HCC CSCs[3]. Another study involving resected HCC specimens from 60 patients elucidated the intertumoral heterogeneity of liver CSCs (LCSCs) based on flow cytometry and identified a population of CD24/CD13/EpCAM triple-positive LCSCs in > 50% of the specimens[4]. Transcriptomic analysis on LCSC marker-sorted HCC cells and functional validation experiments pinpointed epidermal growth factor receptor kinase substrate 8-like protein 3 (*EPS8L3*) as a common functional regulatory gene associated with all three LCSC markers. Notably, more effective inhibition of sphere formation was observed following combined, rather than individual, knockdown of CD24, CD13, and EpCAM, suggesting the need to develop multi-targeted therapeutic approaches to overcome intrinsic CSC heterogeneity[4] (**Figure 1**).

Metabolic and transcriptional reprogramming of HCC CSCs

The advent of single-cell RNA sequencing (scRNA-seq) has provided unprecedented resolution in delineating the unique transcriptional landscape of HCC CSCs. Studies have demonstrated that CSCs exhibit marked upregulation of proliferative pathways (e.g., G2M checkpoint, MYC signaling, and E2F targets) and a metabolic shift towards glycolysis coupled with suppression of lipid metabolic pathways, including fatty acid, bile acid, and steroid metabolism[5]. In addition, advanced computational profiling (Dorothea) has revealed that CSCs are defined by upregulated activity of the following specific transcription factors: proliferative regulators (MYC, E2F1, E2F4, and E2F7); hypoxia-inducible factor (HIF-1α); and the redox-determining factor (NRF1), which is essential for mitochondrial homeostasis[5]. This transcriptional reprogramming represents a critical adaptive response to the multifaceted stresses of the advanced HCC tumor niche, including hypoxia, high proliferative demand, and concomitant metabolic and oxidative stress (**Figure 1**).

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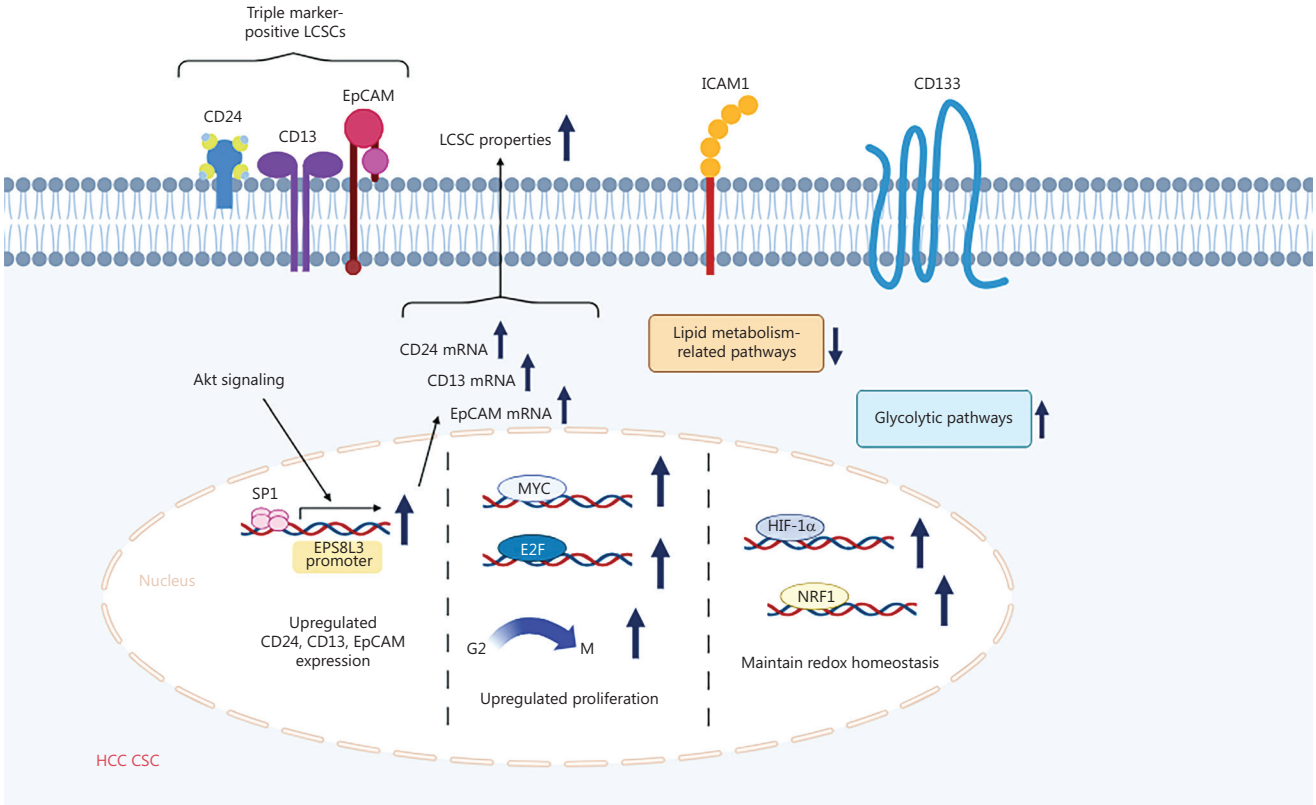


Figure 1 Unique markers and pathways of HCC CSCs. HCC CSCs commonly express surface markers, such as CD24, CD13, and EpCAM, and are regulated by signaling pathways, including EPS8L3, MYC, E2F, HIF-1α, and NRF1. CSCs, cancer stem cells; EPS8L3, epidermal growth factor receptor kinase substrate 8-like protein 3; HCC, hepatocellular carcinoma; LCSC, liver cancer stem cell.

Crosstalk between HCC CSCs and the microenvironment

CSCs maintain an immunosuppressive niche by inducing M2 polarization and T cell exhaustion through the ICAM signaling pathway[3]. CSCs release chemokines (CCL3, CCL16, and CCL15) that target CCR1, which is expressed on SPP1$^+$ macrophages, thereby promoting recruitment of SPP1$^+$ macrophages to create an immunosuppressive tumor microenvironment (TME)[5].

In addition to soluble factors, extracellular vesicles (EVs), especially exosomes and small EVs (sEVs), are key mediators of intercellular communication in HCC. Exosomes and sEVs contribute to the disease by maintaining CSC properties and modulating the TME through the transfer of various exosomal cargos to recipient cells. For example, a search for exosomal circRNAs identified circ-AFAP1 expression to be significantly higher in tumor tissues and positively correlated with CD133. Subsequent functional validation demonstrated the contributing role of circ-AFAP1 in tumor progression by stemness enhancement and epithelial-mesenchymal transition (EMT) promotion[2]. Another study showed that CD90$^+$ Huh7 cells released sEVs containing lncRNA H19, which upon internalization by recipient endothelial cells, promoted H19 overexpression and stimulated VEGF production, thus increasing pro-metastatic angiogenesis to permit metastasis of the CSCs[6]. In addition, RAB27A-mediated sEV secretion from liver CSCs upregulates NANOG to expand immunosuppressive Treg populations[1]. sEVs from CD133$^+$ CSCs carry the RNA demethylase, ALKBH5, which activates the SOX4/SHH signaling axis and contributes to additional immunosuppressive mechanisms in HCC[1]. Together these findings suggest active modulation of the TME by the HCC CSCs.

In contrast, reprogrammed stromal components enhance CSC aggressiveness through multiple approaches. For example, SPP1$^+$ macrophages, which are often spatially co-localized with CSCs in the tumor area, foster a pro-tumorigenic niche that enhances extracellular matrix remodeling, angiogenesis, and cell adhesion through HIF-1α signaling[5]. Furthermore, TGF-β1 secretion from tumor-associated macrophages (TAMs) at the edge of the tumor potently enhances core CSC properties, such as epithelial-mesenchymal transition, invasion, and tumorigenicity[7]. Moreover, CSC apoptosis can be regulated by TAM-secreted factors. Specifically, CXCL1 and CXCL2 from M2-polarized TAMs upregulate anti-apoptotic

BCL-2, while suppressing pro-apoptotic BAD and BAX to confer significant sorafenib resistance[8]. Similarly, TAM-derived IL-6 activates pro-survival STAT3 signaling in CSCs, further promoting expansion and enhancing chemoresistance[1]. Collectively, this reciprocal relationship progressively amplifies tumor malignancy and creates an immunosuppressive TME (**Figure 2**).

Clinical implications for CSC-targeted immunotherapeutic strategies

Clinically, elevated CSC scores and higher SPP1$^+$ macrophage infiltration are consistently displayed in patients who are non-responsive to cabozantinib-nivolumab therapy[5]. The co-occurrence of the above two events in non-responsive patients underscores the critical necessity to develop co-targeting strategies that simultaneously address both CSCs and CSC conducive niche components to overcome therapeutic resistance. In fact, therapeutic strategies are evolving to co-target CSCs and the immune system. For example, bispecific antibodies, such as those targeting EpCAM on CSCs and CD3 on T cells, have shown promise in preclinical models, demonstrating potent immune-mediated cytotoxicity and tumor elimination[9]. Second, chimeric antigen receptor- (CAR-) T therapies targeting CSC markers have currently been the focus of the following clinical trials: a phase II trial of CAR-CD133 T cells (NCT02541370) in advanced HCC showed a manageable safety profile and encouraging preliminary efficacy [median overall survival (OS) = 12 months with hyperbilirubinemia the most common grade 3 adverse event]; and a separate phase I/II trial in the patient recruitment phase targeting EpCAM

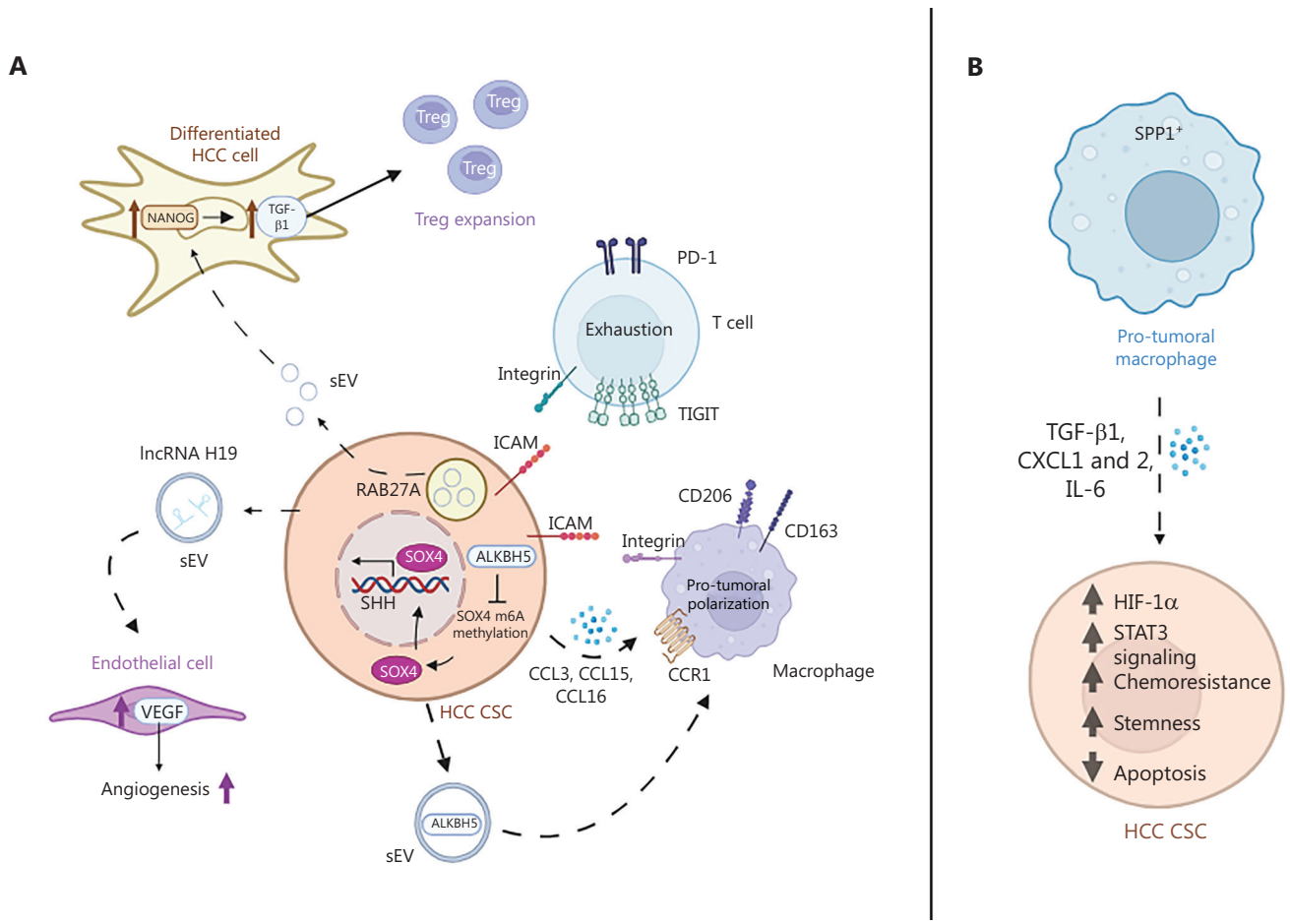


Figure 2 Bidirectional crosstalk between HCC CSCs and TME. (A) HCC CSCs drive ICAM-dependent M2 polarization and recruitment, T-cell exhaustion, Treg expansion, endothelial cell angiogenesis, and HCC EMT *via* chemokine secretions and sEV cargo transfer. (B) Pro-tumoral macrophages further promote HCC CSC EMT, chemoresistance, and survival *via* secretion of chemokines (TGF-β1, CXCL1 and 2, and IL-6). CSC, cancer stem cells; EMT, epithelial-mesenchymal transition; HCC, HCC, hepatocellular carcinoma; sEV, small extracellular vesicle; TME, tumor microenvironment.

(NCT03013712) with outcome data and status currently unavailable[9]. Third, natural killer (NK) cell-based immunotherapies represent another promising strategy for selectively targeting CSCs in HCC. Multiple phase I/II clinical trials are currently exploring the efficacy of autologous or allogeneic NK cell infusions, either as monotherapy or in combination with other treatments (NCT03319459, NCT04162158, and NCT03592706), anti-MUC1 CAR-NK cells (NCT02839954)[9]. Notably, studies indicate that conventional therapies, such as chemotherapy or radiation, can have a dual effect. While conventional therapies have been shown to enrich the CSC population in various tumors, conventional therapies also upregulate stress-induced ligands, like MICA and MICB on the CSC surface, thus activating the NKG2S receptor on NK cells to promote NK cell recognition and cytotoxicity against CSCs[9]. This finding suggests that combining NK cell-based immunotherapies with conventional treatments, particularly when strategically timed, can synergize to eliminate CSCs more effectively and improve therapeutic outcomes in HCC.

Hurdles and challenges: CSC specific markers and CSC-associated pathway inhibitors

Current approaches that utilize liver CSC surface markers aim at facilitating drug targeting for enhanced CSC selectivity, such as conjugating nanoparticles with anti-CD133 or anti-CD144 antibodies[10]. However, because most CSC surface markers are glycoproteins, the glycosylation patterns might affect receptor recognition, protein stability, and intracellular trafficking. In addition to glycosylation, other post-translational modifications should be considered when designing CSC-targeting therapeutics, antibodies, or CAR-T approaches.

In addition to targeting liver CSC markers, the canonical signaling pathways found to promote or initiate HCC progression, including TGF-β and Wnt/β-catenin pathways, are also crucial in liver development, immune regulation, and homeostasis under normal physiologic conditions, making the targeting of these pathways not ideal for the development of CSC-specific therapeutics. Moreover, some CSC-related signaling pathways, like the Wnt/β-catenin signaling pathway, are difficult to target. For example, *CTNNB1* is one of the most frequently mutated genes in HCC with frequent mutations of the serine or threonine residues in exon 3. The mutations enable β-catenin to escape phosphorylation by GSK-3β and CK1α and subsequent ubiquitination and degradation. As a result, these mutations promote β-catenin stabilization for nuclear translocation and binding to TCF/LEF transcription factors, leading to activation of various genes to promote cell proliferation, stemness, and metabolic changes. Any treatment approaches that function upstream of β-catenin nuclear translocation will have limited efficacy in the presence of these constitutively stable β-catenin mutant proteins. Even though many studied molecules that target Wnt signaling receptor, Frizzled receptors, or β-catenin degradation are complex and have undergone clinical trials for treatment of many cancers, such as pancreatic and breast cancers[11], the molecules have limited clinical benefit in treating HCC. Designing drugs to target β-catenin was thought to be impossible due to the unusually highly flexible protein structure rooted from various post-translational modifications, intrinsically disordered N- and C-termini, and confirmational adaptivity, which allows β-catenin binding to different effector proteins, such as E-cadherin and TCF/LEF, CREB-binding protein (CBP), and TBL1[11]. Fortunately, many small molecule-based inhibitors have been designed and are currently undergoing clinical trials for HCC management. These inhibitors aim to block the interaction between β-catenin and CBP or between β-catenin and TBL1 (NCT04008797 and NCT05797805) and have shown manageable or low toxicity in trials[12].

In addition to the β-catenin pathway, the Notch pathway is another well-studied CSC pathway that contributes to tumor initiation, drug resistance, and metastasis in HCC. However, no clinical trials were conducted to assess the safety or efficacy of Notch-associated inhibitors in HCC, potentially due to the involvement of Notch signaling in tissue homeostasis, high potential systemic toxicity, as well as the absence of biomarkers for stratifying HCC patients with Notch signaling alteration.

Another signaling pathway not as well-studied as Notch and β-catenin pathways in HCC is TGF-β signaling, which has gained more research interest in recent years with new insights on the role in driving regorafenib resistance[13], inducing DNMT3A- and DNMT3B-mediated genome-wide DNA methylation, and subsequent induction of CD133 and tumor initiation[14]. Challenges in targeting TGF-β pathways arise from dual functions during tumor development because TGF-β induces cell cycle arrest and cell death in early stage of tumorigenesis but switches to promote EMT and anti-inflammatory immunosuppression as tumor progress. For example, in the phase II clinical trials (NCT02178358 and NCT01246986) involving an inhibitor of TGF-β receptor I kinase, LY2157299, in HCC patients, little therapeutic benefit but high adverse effects were demonstrated in combination therapy with sorafenib. Given the prominent functions of TGF-β in tumor progression and establishment of a pro-tumoral microenvironment, more selective TGF-β inhibitors targeting only late-stage HCC cells or CSCs might be needed to determine if selective TGF-β inhibitors alone or in combination with other therapeutics might have clinical potential.

In addition, the efficacy of current treatment options for advanced HCC is restrained by tumor heterogeneity and an acquired drug resistance mechanism. Current research has identified many CSC-associated pathways that contribute to

therapeutic resistance in HCC cells and suppression or elimination of CSCs might be able to resolve drug resistance[15]. Tumor heterogeneity, however, is a more difficult property to target. Because HCCs commonly arise from cirrhotic, inflamed, or metabolically overwhelmed liver environments, the complex environment can add huge survival pressure on the malignant cells. This selective pressure can be exacerbated as tumors proliferate, limiting oxygen and nutrients. As a result, under the dynamic and severe survival pressure, different subclones are selected, thrive, and form tumor clones. Moreover, because *TERT* is the most frequently mutated gene in HCC, overactive *TERT* activity also leads to genetic instability, contributing to even higher intra-tumoral heterogeneity. Therefore, HCC tumors contain various subclones with unique transcriptomics, thus giving rise to high CSC plasticity and drug resistance.

Future directions in CSC-related research in HCC

Most *in vitro* models assessing cancer stemness to date rely on quantification of CSC markers, sphere formation assays, and *in vivo* limiting-dilution assays to determine the frequency of tumor initiation. scRNA-seq and ST are increasingly favored for an ability to localize CSCs and adjacent TME and pinpoint the plasticity-related pathways in the context of bioinformatics analyses. In addition, because HCC exhibits high intra-tumoral heterogeneity, scRNA-seq is favored due to a capacity to resolve malignant subclones. When combined with data on wider tumor regions, clonal architecture or evolutionary trajectories can also be delineated. In addition to transcriptomics analysis, epigenetic modification warrants research attention. Recently, many epigenetic regulators, such as RNA N6-methyladenosine (m6A) reader[16] and histone lactylation[17], have been shown to associate with stemness, radiotherapy resistance, recurrence, and prognosis. In the future, *in vivo* platforms that allow lineage tracing of CSCs or pre-CSCs before and after treatments as well as offering a holistic understanding of the cellular interplay within the TME will be needed in HCC CSC research.

Due to the strong plasticity and heterogeneity of HCC cells, simple eradication of CSCs may drive de-differentiation of the non-CSCs into new subclones of CSCs in HCC. In addition, because CSCs share common surface markers with normal liver progenitor cells or normal stem cells (SCs), CSC removal strategies may lead to large systemic toxicity. As a result, rather than eradicating the CSCs, suppressing relevant CSC-associated signaling is a safer and more effective approach. For example, Guo et al.[18] performed a trajectory analysis on HCC scRNA-seq and ST data that revealed the evolution of metabolism- and EMT-subtype tumor cells from the proliferation subtype, suggesting inhibition of different CSC pathways may be more effective according to different tumor stages. In addition, Guo et al.[18] revealed the ability of HCC cells to activate and recruit fibroblasts, which in return activates TGF-β signaling in HCC cells, underscoring the need to re-invigorate the TME while inhibiting CSC function. Therefore, to achieve optimal clinical benefit, combination therapy of drugs that suppress CSC pathways and drugs that modify the immune microenvironment are promising.

In addition to the clinical trials aimed at CSC-associated pathways (mentioned in previous sections), clinical investigations are underway to use CSCs as tumor vaccines in HCC treatments. For example, CSCs can be used as antigen presenting cells to prime dendritic cells (DCs), which can be injected as vaccines to boost anti-tumoral immunity. Tumor cells with a high aldehyde dehydrogenase (ALDH) level were isolated and regarded as CSCs In the NCT02089919 trial. DCs were isolated from peripheral blood mononuclear cells, primed with ALDH-high CSCs, then re-infused to patients to trigger a CSC-targeted immune response. However, the outcomes of this trial are not available. Beyond DC-based vaccines, CAR-T cell therapies have been increasingly investigated (as mentioned in the above section), even though currently only a limited number of trials have been conducted in treating HCC. In addition, scRNA-seq and ST analysis can be utilized to identify neoantigens specific to CSCs for the development of next-generation CAR-T therapies. Because T cells are often excluded from the HCC tumor mass or with activities suppressed due to CSC signaling, combining the CAR-T therapy with agents that foster a pro-activation and pro-inflammatory TME is equally crucial. To this end, scRNA-seq and ST analysis can be utilized to facilitate the identification of critical immunomodulatory cells or pathways in the CSC niche.

In addition, a pioneering clinical trial (NCT03896958) has explored drug efficacy testing on patient-derived CSCs. In the trial patient CSCs were extracted *ex vivo*, exposed to a panel of therapeutic agents, and assessed for drug responsiveness. The results were used to guide patient treatment decisions. The trial is expected to reach its completion but the outcome data is not available. Beyond antineoplastic agent screening, developing patient-derived organoid (PDO) co-culture models that incorporate immune cells to better recapitulate the TME can be utilized during high-throughput drug screening. In addition to efficacy, safety remains the biggest issue in clinical investigations. Indeed, establishment of CSC-related biomarkers and investigation of potential link between the biomarker and treatment response of immune therapies possess huge clinical benefits.

Conclusions

In summary, the intrinsic characteristics of CSCs and the dynamic interplay with the TIME are the important therapeutic targets for tumor development, advancement, and therapeutic resistance. A core feature is metabolic and transcriptional

reprogramming, which is characterized by upregulated glycolysis and proliferative pathways, permitting enhanced adaptability to stress in the tumor niche. The malignancy of HCC is aggravated by a bidirectional crosstalk between CSCs and the TIME. CSCs foster an immunosuppressive niche *via* exosomal signaling and macrophage recruitment, while TME components, like TAMs, reciprocally reinforce CSC properties. Significant hurdles impede the translation of these insights into therapies due to the inaccessibility of intracellular stemness markers, shared stemness marker expression, and physiologically important pathways with normal SCs. These hurdles complicate the targeting of CSCs and raise safety concerns. Moreover, profound tumor heterogeneity and CSC plasticity drive therapeutic resistance. Therefore, future therapeutic efforts must prioritize precise targeting and safety. Promising strategies include combination therapies that suppress CSC pathways and remodel the TIME simultaneously, such as CSC-targeted CAR-T/NK cells and dendritic cell vaccines. Finally, validation of biomarkers to predict treatment response and the development of more physiologically relevant models to understand CSC dynamics will be important for personalizing therapies to achieve durable clinical benefits with limited toxicity.

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the paper: YMT and ION
Wrote, reviewed and revised the paper: JL, DCO, YMT, and ION.

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