

Review

Microenvironmental Regulation of Colorectal Cancer Stemness: Technological Advances, Molecular Basis, and Therapeutic Targets

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Abstract

Stem cell plasticity is crucial for rapidly proliferating tissues, such as the intestine, to cope with microenvironmental stress and maintain homeostasis. This framework may be employed by cancer stem cells (CSCs) to interact with the tumor microenvironment (TME) and give rise to drug resistance, tumor recurrence, and metastasis. Here, we consider colorectal cancer (CRC) as an example to review the technological and conceptual advances in microenvironmental regulation of cancer stemness. Some unique features of CRC, including reprogramming of stromal cells, bacterial niche alteration, and metabolic interplay, were summarized to illustrate how the TME affects the plasticity of CSCs. The key pathways and molecular mechanisms involved in metastasis and drug resistance are reviewed to obtain a deeper understanding of how CSCs may be manipulated for better outcomes in CRC treatment. These findings advance our knowledge of tumor heterogeneity and may provide insights into the development of novel therapeutic strategies.

Keywords: Colorectal cancer; tumor microenvironment; cancer stem cells; intestinal stem cells; stem cell plasticity

1. Introduction

Colorectal cancer (CRC) is a typical tumor type that illustrates the complexity of cancer stem cells (CSCs) [1,2]. In two pioneering studies, the existence of CSCs was suggested by the finding that self-renewing CRC cells could be enriched using the neural stem cell surface marker CD133 [3,4]. Other cross-tumor CSC markers, such as CD44 and epithelial cell adhesion molecule (EpCAM), have also been used to confirm CSC hierarchy in CRC [5]. Additional evidence comes from the lineage tracking of Lgr5, a marker of murine intestinal stem cells (ISCs). Knockout of Lgr5 not only caused dysfunction of ISCs, but also impaired the self-renewal of CSCs in a mouse model of CRC [6]. As a downstream effector of Lgr5, Wnt signaling is presumed to be the key pathway regulating the self-renewal of ISCs and CSCs in CRC [7]. The literature review establishes a framework for the early CSC concept, which states that the growth of CRC cells is fueled by a small subset of cancer cells with self-renewing and multipotent differentiation capacities (**Figure 1**); but it does not explain whether the elimination of CSCs alone is sufficient to eradicate CRC. Recently, a study of human organoids indicated that, although the ablation of LGR5⁺ CSCs led to CRC tumor regression, the spontaneous re-expression of LGR5 in LGR5⁻ cancer cells (*i.e.*, non-CSCs) resulted in tumor regrowth [8]. In addition, our study showed that the transfer of exosomal Wnt from fibroblasts to CD133⁻ cancer cells (non-CSCs) promoted their tumor-initiating capacity and increased the expression of LGR5 in their xenografted progeny [9]. Consistent with the finding that CD133⁻ glioma CSCs also propagated tumors in xenotransplantation assays [10], these results challenged the typical concept of the role of CSCs in solid tumors (**Figure 1**).

In this paper, we review the methodologies that were used to investigate the molecular regulation of CSCs [10,11]. Given that CRC is characterized by enhanced CSC-stromal cell crosstalk, significant exposure to the gut microbiome, and the metabolic interdependence between distinct cell populations within the tumor microenvironment, we discuss how these emerging hallmarks affect CSC plasticity in CRC. Furthermore, we summarize the key molecular pathways by which CSCs induce metastasis and drug resistance in patients with CRC.

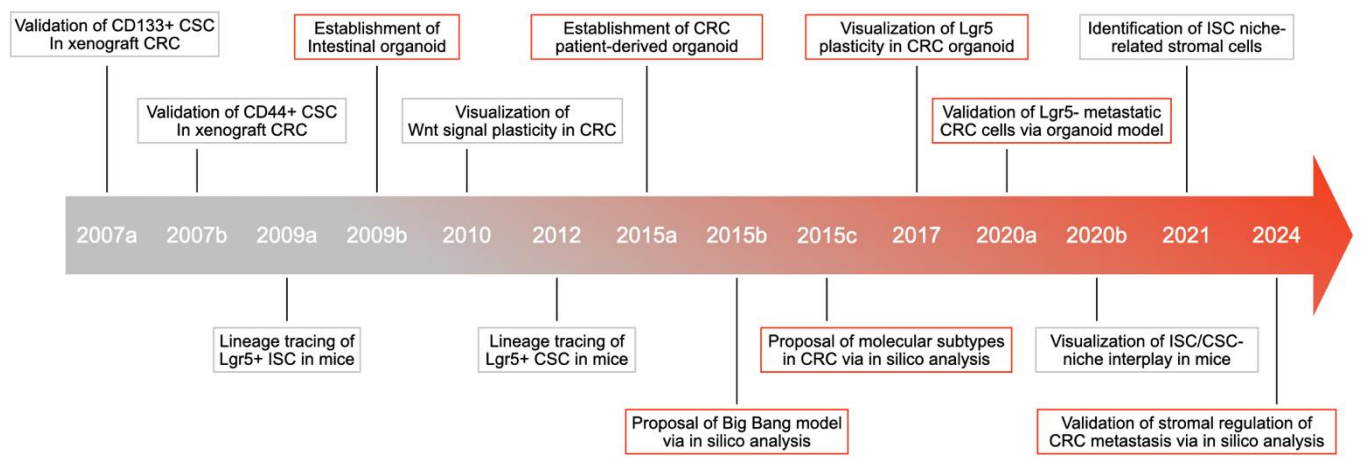


Figure 1 Timeline of the important discoveries clarifying the CSC-niche interplay in CRC.

2. Microenvironmental Regulation of Colorectal Cancer Stemness

2.1 Development of methodologies to assess CRC stemness

In the 1990s, Dick *et al.* employed fluorescence-activated cell sorting (FACS) and xenotransplantation assays to assess the tumorigenic capacity of individual cancer cell subsets in leukemia [12]. This protocol has been widely accepted as the gold standard to evaluate cancer stemness and facilitate the identification of CSC markers in multiple types of tumors, including CRC [10,11]. However, the selection of most cell surface markers is largely dependent on existing knowledge regarding the regulation of stem cells in the brain, breast, and intestines. Anti-CSC strategies based on this data may also impair self-renewal of normal stem cells, particularly those in rapidly proliferating tissues.

Recently, the development of various ‘omics’ and *in silico* analysis approaches has provided powerful strategies to identify the molecular regulators of CSCs [1]. For instance, Guinney *et al.* performed an integrated bioinformatics analysis based on 18 existing gene expression datasets from 4151 patients to visualize the molecular landscape of CRC. They identified four consensus molecular subtypes of CRC, including those associated with microsatellite instability, WNT and MYC overexpression, metabolic dysregulation, and mesenchymal properties. The previously mentioned upregulated CSCs markers were placed in the fourth subtype with mesenchymal properties [13].

This study provides global molecular characterization to validate the existence of CSCs in CRC. Similarly, Li *et al.* performed single-cell RNA sequencing (sc-RNAseq) and spatial transcriptomic analysis of CRC and corresponding liver/ovary metastatic specimens. They identified a stem-like cancer cell cluster, in both primary and metastatic samples, with enhanced expression of the protein tyrosine phosphatase receptor type O (PTPRO) and achaete-like 2 (ASCL2). Notably, the interaction between cancer-associated fibroblasts (CAFs) and endothelial cells via Notch pathways promoted the metastatic capacity of these stem-like CRC cells [14]. In line with these findings, Wang *et al.* investigated genomic and transcriptomic alterations by matching adjacent normal tissues with primary tumors and metastatic CRC tumors. They described how key mutations in genes of CRC cells, such as *KRAS* and *TP53*, modulated PPAR pathways to drive tumorigenesis and metastasis [2]. Although these *in silico* results need further experimental validation, they expand the study of CSCs and provide a rationale for investigating TME regulation of CSC plasticity.

In 2009, another breakthrough in the CSC field took place when Clevers’ lab reported the establishment of intestinal organoid cultures *in vitro* using intestinal stem cell (ISC)-dependent three-dimensional (3D) culture technology [15]. These organoids recapitulated the histology and cellular composition of parental intestinal tissues. CRISPR-mediated loss-of-function mutations of *APC* and *TP53* (the most frequent mutation in CRC) in organoids enhanced their ability to grow as CRC tumors in xenotransplantation assays [16]. Subsequently, Clevers’ group generated many patient-derived CRC organoids from clinical samples. Genomics, transcriptomics, epigenomic sequencing, transplantation, and drug screening assays have systematically confirmed that patient-derived organoids (PDOs) can mimic the genotype and phenotype of the parental CRC

[17,18]. Given these abilities, PDOs provide novel strategies for lineage-tracing studies. As discovered by Shimokawa *et al.*, LGR5⁺ CRC cells in PDOs can serially propagate tumors in xenotransplantation assays and differentiate into KRT⁺ CRC cells. Although genetic ablation of LGR5 protein resulted in CRC regression, unexpectedly a small subset of KRT⁺ cells may replenish the CSC pool if they spontaneously re-repress LGR5 protein [8]. Moreover, in a liver metastasis model based on orthotopic injection of CRC organoids, genetic ablation of LGR5 rarely reduced tumor growth in the liver. Instead, a proportion of LGR5⁺ CRC cells became highly proliferative and continuously replenished the pool of LGR5⁺ CSCs [19,20]. Because the maintenance of the ISCs phenotype in LGR5⁺ cells is regulated by the surrounding stromal niche, it would be interesting to determine if the TME regulates CRC stemness through cancer-stroma crosstalk. In a scRNAseq study based on the co-culture of CRC organoids with corresponding macrophages, overexpression of SPP1 in macrophages promoted CRC development by interacting with CD44 [21]. In other tumors, such as head and neck, breast, and pancreatic cancers, PDOs were further incorporated into CAFs, endothelial cells, neurocytes, and immune cells [22-26]. Undoubtedly, the development of organoid technology will benefit studies on the microenvironmental regulation of CRC stemness (**Figure 2**).

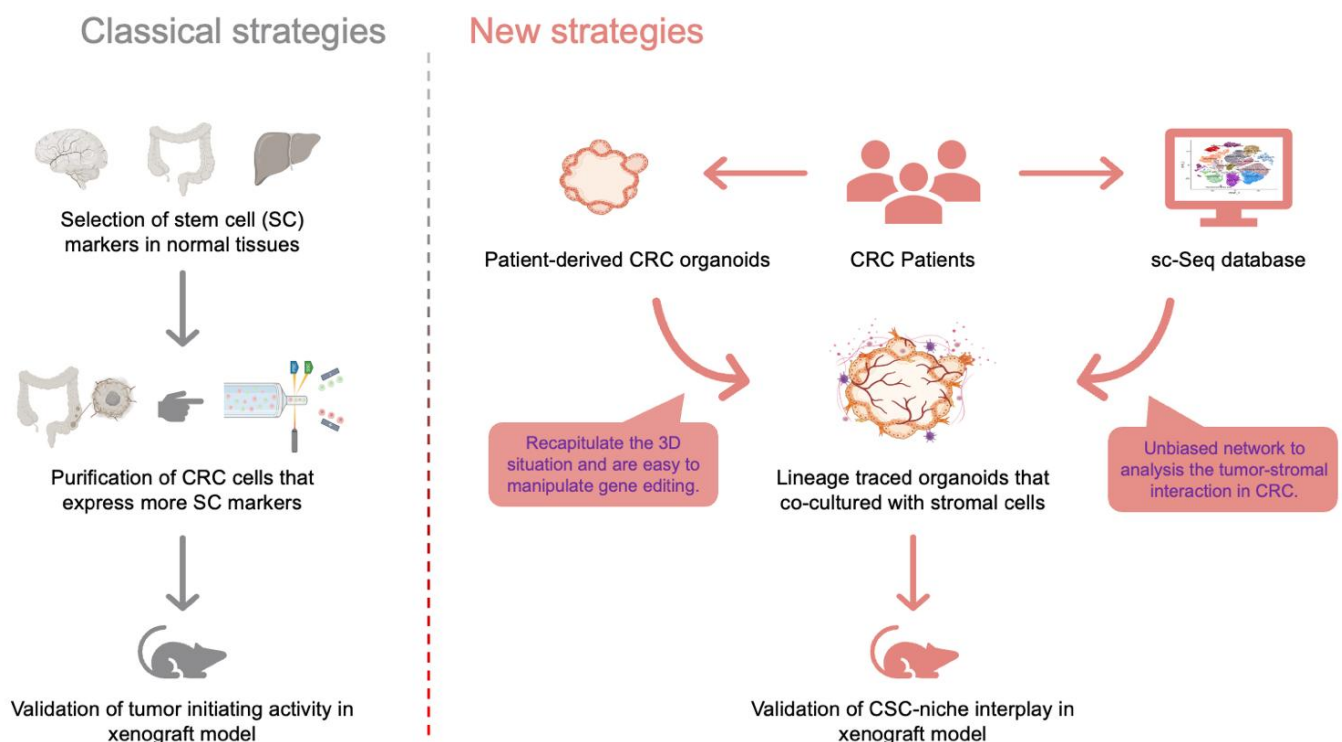


Figure 2 Comparison of classical and new strategies for studying and validating the properties and phenotypic plasticity of CSCs. The development of new technologies, such as single cell sequencing and organoid modeling is expected to advance our knowledge of the role and mechanisms of the influence of CSCs on CRC.

2.2 Emerging hallmarks of the CSC niche in CRC

CRC is characterized by an abundance of stromal cells, which counteract microenvironmental stress by secreting cytokines and chemokines to reshape the extracellular matrix (ECM), revascularize the tissue, and harmonize the immune response [27]. Reprogramming of stromal cells is correlated with the formation of a CSC niche. Using scRNA-seq analysis based on the mouse

intestine, Roulis *et al.* found that fibroblasts expressing Ptgs2 (also known as COX-2) constitutively processed arachidonic acid into intermediate prostaglandin H₂ (PGH₂), which was rapidly converted into highly labile prostaglandin E₂ (PGE₂) by downstream enzymes such as PTGES. This PGE₂ signaling promoted the clonal expansion of Sca-1⁺ reserve-like stem cells through the Ptger4/Yap cascade. Specific ablation of Ptgs2 in fibroblasts or Ptger4 in Sca-1⁺ stem cells reduced intestinal regeneration in genetically engineered mice (GEM) and alleviated Apc-induced sporadic tumor initiation in both GEM and PDO models [28]. In another study based on xenotransplantation and 3D co-culture models, secretion of PGE₂ by intestinal enteric glia was augmented by tumor cell-derived interleukin-1, and more importantly, promoted the spheroid and xenograft initiating capacity of CD44/CD24⁺ CRC cells (*i.e.*, CSCs) [29]. Thus, the functional differences in tumorigenic capacities between intestinal stem cells (ISCs) and CRC cells, whose genomes are nearly identical except for the tumor-specific mutations, are primarily governed by divergent gene expression programs shaped through interactions with the surrounding mesenchymal niche (**Figure 3**).

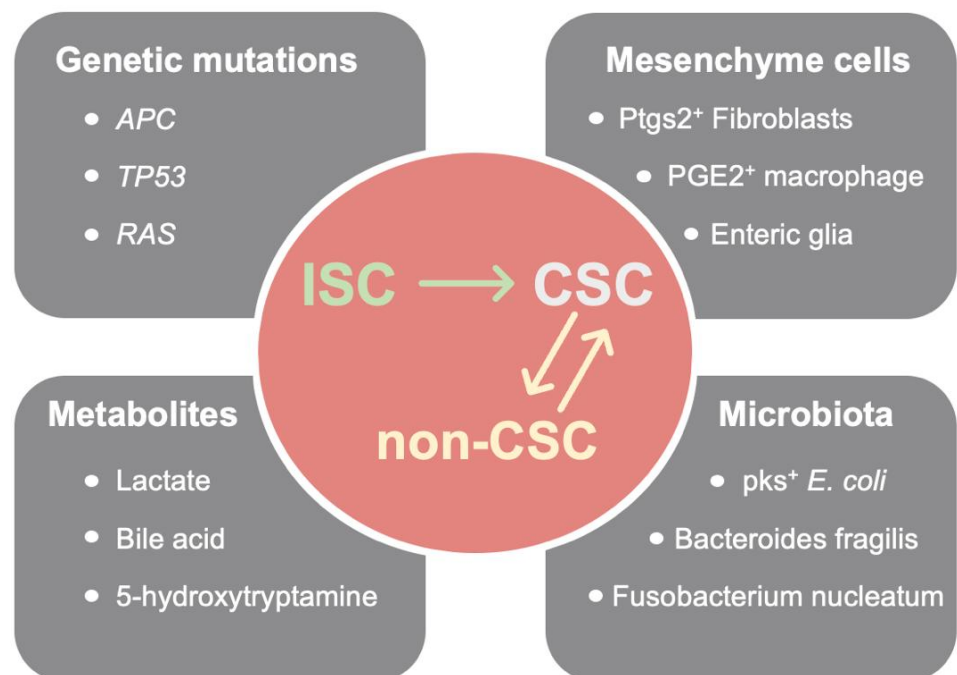


Figure 3 Overview of the emerging hallmarks of tumor microenvironment (TME) that correlate with the regulation of phenotype plasticity of CSCs in CRC.

Intestinal tissues are also specialized by their exposure to a highly dynamic microbiome niche. The ISC-niche interplay can be regulated by reprogramming the gut microbiota. Using GEM and intestinal organoid models, Zhu *et al.* found that microbiota-derived valeric acid promoted the secretion of 5-hydroxytryptamine (5-HT) in enteric serotonergic neurons to trigger the activation of PGE₂⁺ macrophages, which in turn facilitated Wnt/ β -catenin signaling in Lgr5⁺ ISCs [30]. In their follow-up study of CRC, the connection between 5-HT and the cell surface markers HTR1B/1D/1F suppressed the axin-mediated degradation of β -catenin, and thereby, exacerbated the tumorigenic capacity of CSCs in CRC [31]. The oncogenic properties of *Fusobacterium nucleatum* (Fn), a typical periodontal disease pathogen, have been thoroughly

investigated in recent years. As shown by Zepeda-Rivera *et al.*, the presence of the specific Fn subtype, Fna C2, can be detected in more than 50% of patients with CRC [32]. Zhang *et al.* employed a genome-wide screening method to determine whether the binding of RadD to CD147 enabled the colonization of Fn in CRC [32]. In addition, binding of Fn-specific FadA to E-cadherin in CRC cells promoted β -catenin signaling [33]. Other intestinal bacteria such as *Bacteroides fragilis* and *pks*⁺ *Escherichia coli* are also associated with the development of CRC [34]. Investigating the regulation of this niche by the microbiome may improve our understanding of how the intestinal TME modulates CRC stemness.

The metabolic properties of ISCs differ from those of differentiated cells. Specifically, ISCs employ mitochondrial metabolism of glucose and fatty acids to sustain self-renewal, whereas their daughter cells utilize aerobic glycolysis to rapidly fuel their proliferation [35]. The transfer of lactate as a by-product of this metabolic symbiosis can support intestinal tissue homeostasis. Using metabolomic analysis based on an organoid model, Rodríguez-Colman *et al.* showed that Paneth cell-derived lactate enhanced p38/MAPK signaling in Lgr5⁺ ISCs by elevating mitochondrial ROS levels. Maintenance of this metabolic interplay contributed to stable intestinal organoid reconstitution [36]. Because ISCs and the CSCs in CRC show similar expression levels of many genes, it is presumed that the same metabolic crosstalk exists in CRC. As a case in point, we compared the metabolic phenotypes of sphere/Wnt⁺ (CSCs) and adherent/Wnt⁻ cells (non-CSCs) in CRC PDOs. We found that Wnt⁻ cells were proficient in producing lactate to support mitochondrial activity and the ROS/AKT/ β -catenin pathway in Wnt⁺ cells. In transplantation assays with co-implanted spheres and adherent cells, the tumor-initiating activity was reduced when the lactate exporter, MCT4 in non-CSCs, or the transport protein, MCT1 in CSCs was silenced or inhibited [37]. In our follow-up study, the lactate metabolism of CSCs *in vivo* appeared to be regulated by the oxygen-mediated suppression of HIF-1 α and the activation of PGC1- α . As the source of oxygen in the TME, the vasculature in tumors provides a previously overlooked mechanism of regulating CSC phenotypes [38]. Collectively, the metabolic features of individual cell subsets form a complex network that affects CRC stemness (**Figure 3**).

Dedifferentiation is the process by which differentiated cells are reprogrammed to acquire the ability to self-renew. Investigations of dedifferentiation in CRC have advanced our understanding of stem cell plasticity in solid tumors. Using a WNT reporter system, Vermeulen *et al.* showed that myofibroblasts secreted growth factors such as HGFs to restore the CSC phenotype in more differentiated CRC cells, both *in vitro* and *in vivo*, via a β -catenin-dependent transcriptional network [39]. In line with this, our study showed that secretion of exosomal WNT3A was enhanced in CAFs compared with that in normal fibroblasts, and co-injection of CAFs promoted the tumor-initiating capacity of CD133⁻ CRC cells (non-CSCs) in a xenotransplantation assay [9]. It follows that tumor-initiating capacity is more likely to be described as cancer stemness, which emphasizes it as a flexible state rather than a constant phenotype. Further studies are required to clarify the molecular mechanisms underlying CRC cell dedifferentiation. Hall *et al.* performed RNAseq analysis in an *Apc*-deficient mouse model and found that the RNA-splicing factor SRSF1 controlled the plasticity of CRC cells by regulating the splicing level of *Kras4b*. Moreover, *SRSF1* expression affected the reconstitution

of CRC PDOs and correlated with the CSCs markers in human CRC samples [40,41]. Hwang *et al.* isolated colon spheres from primary CRC tissues and profiled their gene expression patterns using microarray analysis. Consequently, the EMT activator, SNAIL, which regulates the expression of IL8 and other genes to sustain cancer stemness in CRC cells [34] was identified. It would be interesting to investigate whether TME signals regulate CRC stemness through these molecular nodes.

2.3 Molecular regulation of CSC plasticity

The elucidation of normal ISC signaling pathways has made great progress in recent years. However, studies on the abnormal signaling pathways in colorectal CSCs are still in their infancy. Here, we focus on four critical pathways that regulate colorectal CSCs: the Wnt, Hedgehog, BMP (bone morphogenetic protein), and Notch pathways.

2.3.1 The Wnt pathway and plasticity of CSCs

Wnt signaling is an essential pathway regulating normal development and physiology and has become adapted to perform various roles in cancer [42,43]. Wnt signal transduction is involved the Wnt/ β -catenin pathway, the planar cell polarity (Wnt/PCP) pathway, and the Wnt/ Ca^{2+} signaling pathway [44,45]. Abnormalities in Wnt pathway components have been identified as drivers of cancer and potential targets for treatment, particularly in CRC [17,46]. WNT growth factors are important for the regulation of both normal and malignant stem cells. APC or Wnt/ β -catenin mutations exist in 90% of CRCs, increasing Wnt target gene transcription. However, abnormal β -catenin is not sufficient to produce CRC, and other mutations, epigenetic silencing, microenvironmental signals, and cross-pathways help increase nuclear β -catenin to induce tumorigenesis. CRC with Wnt/ β -catenin mutations show different levels of Wnt activation, and only high levels of Wnt activation show nuclear localization of β -catenin and possess CSCs characteristics. The Wnt signaling pathway plays a crucial role in CRC cell survival, proliferation, and self-renewal, with dysregulation observed in CSCs [47,48]. ISC dynamics are influenced by several endogenous and exogenous stimuli, including dietary and niche factors. Wnt target genes have the leucine-rich repeat-containing G-protein coupled receptor 5 (Lgr5), the first functional marker of ISCs. Lgr5⁺ cells, which are an important component of the epithelial stem cell niche, capable of long-term self-renewal and possessing multilineage differentiation potential. The key signaling pathway controlling ISC function is the Wnt/ β -catenin pathway, and the Wnt and R-spondin ligands are extensively secreted in the niche, reaching their highest levels at the bottom of the crypt.

Colorectal cancer-related stem cells (CRC-SCs) exhibit distinctive characteristics, including significant heterogeneity and plasticity, contributing to drug resistance and cancer recurrence [49]. When treating patients with CRC, the genetic composition of SCs and their microenvironment aberrantly activate Wnt signaling pathways. CRC-SCs are resistant to both chemotherapy and radiotherapy. LGR5⁺ CSCs exhibit chemotherapy resistance by entering a quiescent state that allows them to evade drug treatment [50]. The activation of the *LRP5* gene further promotes CSC-like phenotypes, including tumorigenicity and resistance to platinum-based drugs in CRC cells, via the canonical Wnt/ β -catenin and IL-6/STAT3 signaling pathways [51]. In 2010,

Medema *et al.* identified a CRC that exhibited highly active Wnt signaling in CSCs. This finding suggested that elevated Wnt signaling can be employed as a marker for CRC-SCs, with the Wnt signaling pathway being regulated by the TME [40]. Research has demonstrated a close relationship between Wnt/ β -catenin signaling and the ABC transporter of CSCs; also, a critical role of the c-Myc-ABCB5 axis has been implicated in 5-FU resistance in CRC cells. Side population (SP) cells display heightened resistance to 5-FU and irinotecan compared to non-SP cells, in conjunction with the increased activation of the Wnt signaling pathway, inhibition of β -catenin significantly reduced the SP cells [52]. Our study demonstrated that transferring exosomal Wnt from fibroblasts to CD133⁺ cells (non-cancer stem cells) enhanced their tumor-initiating capacity and increased Lgr5 expression in their progeny xenografts [9,53]. Concurrently, we observed that lactate derived from differentiated cells enhanced the Wnt activity of CSCs and promoted their self-renewal in CRC organoids [38,54].

2.3.2 The Notch pathway and CSC plasticity

Notch signaling is pivotal in many cellular processes, including stem cell maintenance, cell specification, differentiation, proliferation, and apoptosis [55]. Understanding the intricacies of Notch signaling in its natural context is crucial for uncovering how these pathways may be hijacked in cancer [56]. Numerous studies have elucidated the roles of various Notch components in the regulation of stem cell properties. This raises the question of whether Notch ligand-receptor specificity influences specific subpopulations of stem cells such as CSCs [57]. The heterogeneity of Notch receptors, effectors, and pathways may contribute significantly to CSC diversity [58]. The Notch pathway has been recognized for its modulation of stemness and the tumor-initiating phenotype in CRC; however, results vary depending on the study, model employed, and specific components of the Notch pathway examined [59]. While Notch signaling is often perceived as relatively straightforward, owing to the involvement of only a limited number of proteins, diverse signaling outcomes arise from various combinations of interactions among different ligands and receptors. The role of the Notch pathway in tumors is contingent on the spatial and temporal context of Notch activation and the status of other signaling pathways within cells. This contextual variability likely explains why studies examining the effect of different receptors on CRC stemness have reported a general enhancement of CSC phenotypes despite the presence of non-redundant or even antagonistic effects among the various molecular components involved [60].

A positive correlation has been established between the activation of NOTCH3 and NOTCH1 receptors in CRC. Specifically, NOTCH3 activation occurs by binding the DLL4 ligand, which inhibits the NUMB protein, a known inhibitor of Notch-dependent gene expression. This inhibition of NUMB facilitates the activation of the NOTCH1 receptor, leading to a positive feedback loop that enhances NOTCH3 expression and activation [60]. Notch ligands, particularly JAG1 and DLL4, augment stemness-related characteristics. However, numerous studies investigating the Notch pathway in other pathophysiological contexts have demonstrated distinct or opposing functions of JAG1 and DLL4 ligands, especially regarding their roles in angiogenesis. Both JAG1 and DLL4 ligands are expressed in the embryonic aorta and activate the NOTCH1 receptor, leading to the establishment of hematopoietic and endothelial cell fates,

respectively. This ligand-specific lineage differentiation underscores the existence of ligand-receptor specificity within Notch signaling, which is further influenced by crosstalk between Notch ligands [61]. This crosstalk occurs in the intestinal epithelium, where the inhibition of DLL4 or DLL1 does not affect ISCs. However, their simultaneous inactivation disrupts pluripotency and leads to a loss of stem cells (Olfm4+, Lgr5+, and Ascl2+). Nevertheless, the presence of Lgr5⁺ cells in the intestinal tract of Hes-1, -3, and -5 conditional knockout mice, comparable to that in wild-type mice, indicates that HES transcription factors are not the sole targets of the Notch signaling involved in maintaining pluripotency [62].

Despite numerous studies illustrating the differential effects of the Notch pathway on CRC-SCs, crosstalk among the various components of the Notch pathway and their specific effects complicates the investigation of the effect of these individual proteins on stemness. Few studies have focused on multiple Notch pathway proteins, which are essential for a comprehensive understanding of the influence of the Notch pathway on stemness and self-renewal. These limitations and several other factors must be considered when exploring the relationships among the Notch pathway, stemness phenotypes, CSC heterogeneity, and treatment resistance.

2.3.3 The Hedgehog pathway and plasticity of CSCs

The Hedgehog signaling pathway, which is essential for normal embryonic development, is dysregulated in cancer, leading to tumorigenesis and maintenance of CSCs within the TME [63]. The complex interaction between CSCs and their microenvironment involves various molecular signals that dictate stem cell behavior and fate [64]. Recent studies have highlighted how the Hedgehog pathway influenced CSC functionality by modulating the plasticity in response to microenvironmental cues [65]. For example, specific ligands can activate the Hedgehog signaling cascade, which regulates the expression of genes necessary for maintaining stemness and promoting tumor growth [66]. This signaling directly affects CSCs and alters the surrounding stromal cells, creating a supportive niche that fosters tumor progression and metastasis [67]. Moreover, TME is characterized by a dynamic interplay of various factors, including inflammatory cytokines and the ECM, which can enhance Hedgehog signaling [68]. This interaction can increase the CSC population, contributing to therapeutic resistance and tumor heterogeneity [69]. Understanding these mechanisms is vital for developing targeted therapies to disrupt the CSC niche and improve treatment outcomes for patients with CRC. Zhu *et al.* reported that TSPAN8 expression was upregulated in breast CSCs, promoted the expression of the stemness genes *NANOG*, *OCT4*, and *ALDH1*, and was correlated with therapeutic resistance. Mechanistically, TSPAN8 interacts with PTCH1 and inhibits degradation of the SHH/PTCH1 complex by recruiting the de-ubiquitinating enzyme ATXN3 [70]. Gu *et al.* revealed that circIPO11 drives the self-renewal of liver CSCs and promotes the propagation of HCC (hepatocellular carcinoma) via activation of the Hedgehog signaling pathway. Antisense oligonucleotides (ASOs) against circIPO11 combined with the TOP1 inhibitor camptothecin (CPT) exerted a synergistic antitumor effect [71]. Do *et al.* discovered that expression of the long non-coding RNA (lncRNA), LOXL1-AS1, was detected in MYCN-expressing Daoy cells and MYCN-amplified SHH-MB (sonic-hedgehog medulloblastomas), and its

presence was significantly correlated with reduced survival rates in patients with SHH-MB. Functionally, LOXL1-AS1 enhances cell migration and cancer stemness in SHH-MB cells *in vitro*. In murine models, MYCN-expressing Daoy cells demonstrated a high metastatic rate and negative effect on survival, both of which were mitigated by perturbation of LOXL1-AS1 [72].

2.3.4 BMP signaling in CSC plasticity

In CRC, abnormal activation of BMP signaling is closely related to tumor progression and the maintenance of stem cell properties [73]. The BMP signaling pathway affects the self-renewal and differentiation abilities of CSCs through transcriptional inhibition mediated by Smad4 [74]. Specifically, BMP signals inhibit transcriptional activity by recruiting the histone deacetylase, HDAC1, to the promoters of stem cell marker genes. In addition, BMP signaling interacts with the Wnt/beta-catenin pathway to regulate CSCs dryness and plasticity of CSCs [75]. Colon CSCs are the main cause of tumor recurrence and drug resistance, and their properties are similar to those of normal stem cells, with the ability to self-renew and undergo multidirectional differentiation [76]. The BMP signaling pathway influences the properties and behavior of CSCs by regulating the stem cell microenvironment and cell-cell interactions. Studies have shown that BMP4 can induce the differentiation of colon CSCs and enhance their responsiveness to chemotherapy [27]. In a mouse model, the administration of BMP4 significantly improved the sensitivity of colon CSCs to chemotherapy drugs, indicating that the BMP signaling pathway has potential applications in regulating the plasticity and therapeutic response of CSCs [77]. Additionally, BMP signaling maintained colon stem cell homeostasis by interacting with Wnt signaling. The Wnt signaling pathway plays an important role in the self-renewal of colon stem cells, and BMP signaling regulates the proliferation and differentiation of stem cells by inhibiting Wnt signaling [78]. This mutually interactive mechanism may be an important regulator of CSCs plasticity in CRC.

In summary, the regulation of CSC plasticity by the TME through the Hedgehog pathway represents a promising area of research with implications for therapeutic strategies targeting CSCs and the TME.

2.3.5 Epigenetic regulation of CSC phenotype

The primary distinction between stem cells and other cell types lies in their epigenetic architecture [79,80]. Epigenetic regulators, transcription factors, and microRNAs (miRNAs) are crucial for maintaining stem cell self-renewal. The pervasive aberrant epigenetic regulation observed in tumors indicates a strong association between epigenetic mechanisms and cancer [81]. Advances in sequencing technologies have significantly enhanced the detection of rare yet functionally significant epigenetic events, thereby contributing substantially to the precise targeting of cancer cells [82]. Epigenetic regulatory mechanisms play a pivotal role in the plasticity of CSCs, and the TME has a significant influence [83]. The interplay between epigenetic modifications and the microenvironment can determine the fate of CSCs, affecting their self-renewal capacity, differentiation potential, and contribution to tumor heterogeneity [84]. Wang *et al.* reported that BEX1 played a key role in regulating CSCs properties in different types of liver cancer. Targeting BEX1-mediated Wnt/ β -catenin signaling may help address the high recurrence rate and heterogeneity

of liver cancer [85]. The TME comprises diverse cellular and non-cellular elements encompassing the ECM, stromal cells, and immune cells, all of which provide biochemical and mechanical cues that shape the epigenetic profile of CSCs. For instance, changes in ECM rigidity and composition can alter the chromatin structure and gene expression, thereby promoting a more adaptable state in cancer cells. This adaptability enables CSCs to respond to the dynamic milieu of the tumor microenvironment, facilitating processes such as metastasis and therapy resistance.

DNA methylation is one of the most prevalent epigenetic modifications and involves DNA methyltransferases (DNMTs) which add methyl groups to the fifth carbon atom of the cytosine ring to form 5-methylcytosine (5mC) [86,87]. In normal cells, DNA methylation primarily occurs in CpG dinucleotide sequences on CpG islands and plays a role in gene silencing and preserving genomic stability [88,89]. In contrast, tumors simultaneously exhibit global hypomethylation and hypermethylation of CpG islands, resulting in altered gene expression profiles that can foster cancer initiation and progression [90,91]. Within the TME, stress signals such as hypoxia, inflammation, and cytokine release can trigger the upregulation of DNMT expression, leading to hypermethylation of the promoter regions of crucial stemness-related genes such as *Oct4*, *Sox2*, and *Nanog* [92], which inhibits the self-renewal capacity of the CSCs. Conversely, the TME can lower the overall genome methylation level by diminishing the activity of DNMTs or activating demethylases, thereby reactivating previously silenced oncogenes and potentially enhancing the aggressiveness and resistance of CSCs to chemotherapy.

2.3.6 Histone modification and plasticity of CSCs

Histone modification is a crucial epigenetic regulatory mechanism encompassing acetylation, methylation, ubiquitination, phosphorylation, and SUMOylation [77,93]. These modifications affect DNA accessibility and binding efficiency of transcription factors by reshaping the chromatin structure, thereby orchestrating gene expression [85,87]. Histone acetylation is typically associated with an open chromatin state that promotes active gene expression [94]. At the same time, the effects of methylation with its complex regulation, is contingent upon the specific histone residues altered and the extent of modification [95]. Within the TME, various enzymes involved in histone modification, such as histone deacetylases (HDACs), histone demethylases, lysine-specific methyltransferases (KMTs) and demethylases undergo modulation, thereby reshaping the expression profile of stem cell-related genes in CSCs. Bi *et al.* found that HDAC11 suppressed LKB1 expression in HCC to promote cancer stemness, progression, and sorafenib resistance, suggesting the potential of targeting HDAC11 to treat HCC and overcome kinase inhibitor resistance [96]. Notably, HDAC inhibitors have been shown to reverse the stemness of CSCs, diminish the efficiency of tumor spheroid formation, and increase their sensitivity to chemotherapeutic agents. Caslini *et al.* proposed that the inactivation of HDAC7, either directly or via the inhibition of HDAC1 and HDAC3, may lead to the suppression of the CSCs phenotype by downregulating several super-enhancer-associated oncogenes. The selective targeting of CSCs by this mechanism and the potential to concurrently inhibit multiple oncogenes underscores the importance of developing HDAC7-specific inhibitors as promising research objectives [97].

2.3.7 Noncoding RNA and plasticity of CSC

Owing to their distinctive roles in gene expression regulation, regulatory networks mediated by noncoding RNAs have gained much attention recently, particularly miRNAs and lncRNAs [98]. MicroRNAs function by negatively regulating gene expression through complementary base pairing with the 3'UTR of the target mRNA, leading to either translation inhibition or mRNA degradation [99]. In contrast, lncRNAs act as competitive endogenous RNAs (sponges) for miRNAs or interact with transcription factors, RNA polymerase II (Pol II), and other epigenetic regulators to positively or negatively modulate the expression of target genes [100]. In the TME, factors such as hypoxia, inflammatory mediators, and intercellular communication can alter the expression levels and activities of non-coding RNAs, consequently affecting the proliferation, migration, chemotherapeutic resistance, and other functions of CSCs [101]. For example, several miRNAs, including miR-145, miR-34a, and members of the let-7 family, are downregulated in various types of cancer. Overexpression of these miRNAs suppresses the expression of CSC markers, reduces the formation of tumor spheroids, and inhibits tumorigenesis and chemotherapy resistance *in vivo*. The lncRNAs, MALAT1, HOTAIR, and H19, have been implicated in CSC regulation within the TME [102]. These lncRNAs act as miRNA sponges or cooperate with histone-modifying enzymes to regulate downstream target gene expression, thereby influencing the fate and functional traits of CSCs.

2.3.8 Chromatin remodeling and plasticity of CSCs

In addition to the epigenetic mechanisms discussed earlier, the role of chromatin remodeling complexes in CSC plasticity is crucial [103]. These complexes consist of a set of proteins that manipulate the position of nucleosomes via ATP hydrolysis [104]. They either expose or conceal transcription initiation sites in DNA, consequently regulating gene expression [105,106]. Within the TME, factors such as hypoxia, cytokines, and ECM components modulate the localization of CSCs, consequently affecting the chromatin accessibility and activity of crucial genes [107]. For instance, Portney *et al.* demonstrated that a mere two days of transient induction of ZSCAN4 (zinc finger and SCAN domain-containing 4) resulted in an increased frequency of CSCs both *in vitro* and *in vivo*, accompanied by the upregulation of pluripotency and CSC-associated factors. Notably, we elucidated, for the first time, the role of ZSCAN4 in modulating the epigenetic landscape and regulating chromatin configuration. Our findings indicated that ZSCAN4 induced functional hyperacetylation of histone three at the *OCT3/4* and *NANOG* promoters, thereby facilitating the upregulation of CSC factors [108]. The SWI/SNF family members are important chromatin remodeling factors capable of opening densely packed heterochromatin regions, facilitating the access of transcription factors to DNA, thereby promoting the transcription of downstream genes related to plasticity [109]. However, in certain instances, the SWI/SNF complex participates in heterochromatin assembly and suppresses the expression of specific genes. Members of the ISWI family can also alter the TME by compacting chromatin, repressing gene transcription, and restricting the maintenance, proliferation, and differentiation of CSCs (**Figure 4**).

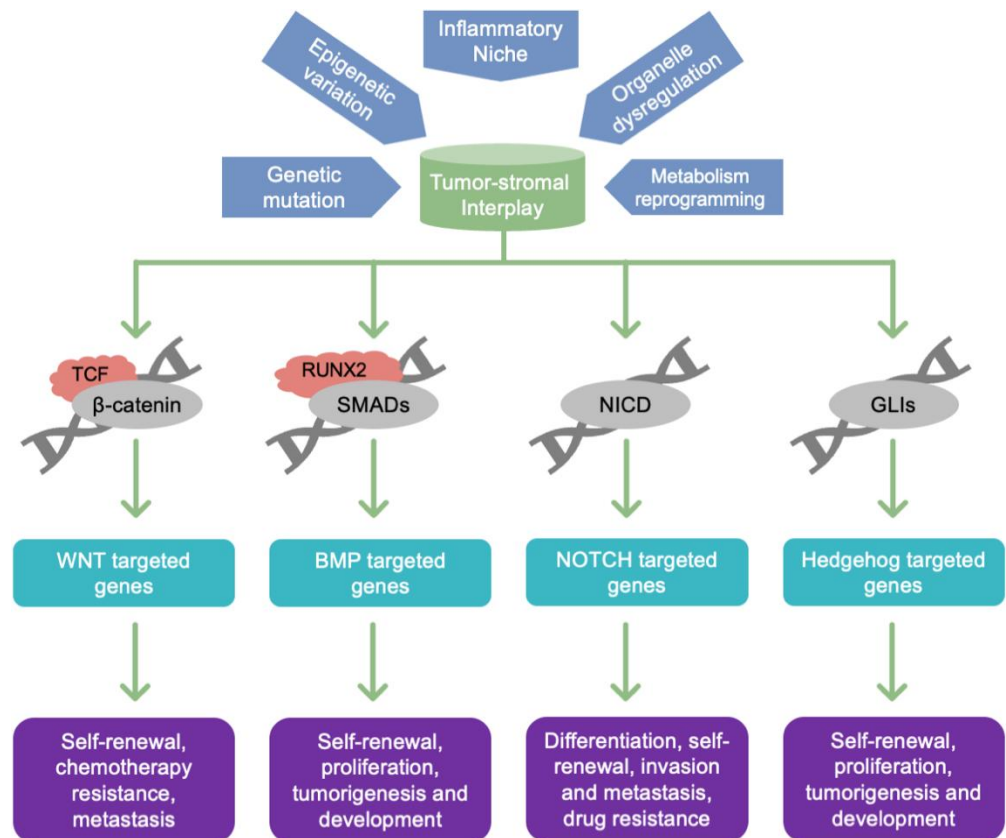


Figure 4 Key functional pathways of CSC action as TME pivots during the course of tumor progression in patients with CRC.

3. Therapeutic Implication

3.1 The role of CSCs in metastasis

Metastasis is a major cause of cancer-related death worldwide. Several studies have reported the correlation between CSCs and CRC metastasis. Using spatial transcriptomics (ST) technology, Zhou *et al.* compared the tissue-wide transcriptome information of primary CRC with that of corresponding metastatic liver specimens. The expression of CSC markers is enriched in metastatic tissues, and FOXD1 was selected as a marker to predict metastatic potential [110]. In a xenotransplantation model, overexpression of protease-activated receptor 2 (PAR2) enhanced the self-renewal and metastatic capacity of CSCs by triggering β -catenin-mediated transcription of periostin, a metastasis-related ECM protein [111]. Similarly, Wang *et al.* showed that PGE2 induced CSCs expansion by activating the EP4-PI3K/MAPK/NF- κ B signaling axis and promoted the formation of liver metastases in GEM and orthotopic transplantation models [112]. These studies provided clues for targeting CSCs to prevent metastasis. But whether targeting CSCs alone is sufficient to block metastasis remains unclear. As shown by Gavert *et al.*, IL-1 enhanced CRC cell motility and invasion, and promoted liver metastasis *in vivo*. This process is rarely dependent on changes in CSCs markers such as CD133, CD44, and EpCAM [113]. Furthermore, de Sousa and Melo *et al.* validated the distinct role of Lgr5⁺ CSCs in primary and metastatic CRC in a lineage-tracing GEM model. In liver metastases, where the TME is largely different from that in primary CRC, the ablation of Lgr5⁺ CSCs rarely affected tumor growth [19,114]. Metastasis

requires cancer cells to invade the surrounding niche, disseminate into the circulation, enter and exit quiescence, and colonize distant organs [115]. A better explanation is that CSCs are more proficient in counteracting the TME to survive the metastatic cascade. Todaro *et al.* showed that overexpression of CD44v6 in CSCs enhanced their ability to drive CRC metastasis through their capacity for migration [116]. In another study, Li *et al.* showed that overexpression of PTPRO and ASCL2 facilitated the interaction between CSCs, CAFs, and endothelial cells to promote metastasis [117]. In another study on breast cancer, PGC-1 α -mediated mitochondrial biogenesis enhanced the survival of circulating tumor cells (CTCs) [55]. This is consistent with our finding that overexpression of PGC-1 α in CRC-CSCs promoted their metastatic capacity *in vivo* [39]. Thus, a deeper understanding of how CSCs survive the metastatic cascade may benefit the development of anti-metastatic strategies.

3.2 The role of CSCs in therapy resistance

CSCs are well known for their ability to give rise to resistance against chemotherapy, radiotherapy, and immune and targeted therapies [118]. A typical explanation is the inherent overexpression of ATP-binding cassette (ABC) transporter family proteins in CSCs [119]. In CRC, the expression of the ABC transporter appears to be regulated by SOX2 and PGC1- α [120,121]. Targeting ABC protein-related signals impairs the efflux of anticancer drugs driven by CSCs [121]. Because of their specific transcription networks, CSCs may also develop other drug-resistance mechanisms. Mangiapane *et al.* showed that PI3K-driven overexpression of human epidermal growth factor receptor 2 (HER2) sustained the interaction of CSCs with cancer-associated fibroblasts to promote CRC resistance to anti-EGFR therapy. The blockade of this signal reduced the dissemination of CSCs in adjuvant therapy [122]. Yuan *et al.* showed that the CSC marker, CD133, directly interacted with ABCC1 protein through the AKT/NF- κ B signaling axis to augment chemotherapy resistance in CRC cells, providing a rationale for targeting the cooperation between two individual CSC-related molecules [123].

The use of scRNAseq technology has advanced our understanding of how the TME regulates therapy resistance. Li *et al.* employed scRNAseq to investigate the dynamics of immune and stromal cells in 19 patients with CRC receiving immune checkpoint inhibitor (ICI) therapy. They found that CRC resistance to PD-1 blockade was associated with the absence of CCL2⁺ fibroblasts and the presence of HLA-DRA⁺ endothelial cells [124]. It would be worthwhile investigating how TME affects therapeutic resistance by regulating the interactions of CSCs with these stromal cell populations.

Acquired drug resistance is another mechanism by which CSCs cause failure of clinical treatment. Using a panel of CRC PDOs, Solé *et al.* found that DNA-damaging agents induced a persistent quiescent-like phenotype by triggering the YAP-dependent acquisition of the fetal stem cell signature in P53 wild-type CRC cells [125]. These findings highlight the correlation between stem cell plasticity and chemotherapy resistance in patients with CRC. Consistent with this, Dong *et al.* established several 5-FU-resistant CRC cell lines and showed that HIF-1 α -mediated glucose metabolism reprogramming promoted the survival of CRC cells via activating the Wnt/ β -catenin signal [126]. Using an *in silico* model, Woolston *et al.* analyzed the genomic and transcriptomic landscapes of patients with cetuximab-resistant CRC. Consequently, most

biopsies with acquired resistance harbored no genetic resistance drivers; instead, interactions between fibroblasts and growth factors aggravated drug resistance in CRC cells [127]. (Table 1)

Table 1 Potential targets by which CSCs lead to CRC progression.

Clinical relevance	Protein name	Validating model	Functioning mechanism	Reference
Metastasis	PAR2	Cancer cell lines	ECM remodeling	[111]
	PGE2	GEM	Inflammatory regulation	[112]
	CD44v6	PDC/PDX	Enhancing cell motility	[116]
	ASCL2	Cancer cell lines	Triggering Notch pathway	[117]
	PGC-1α	PDX	Metabolism reprogramming	[39,51]
Drug resistance	ABC	Cancer cell lines	Triggering efflux of drugs	[119-121]
	HER2	PDC/PDX/GEM	Promoting CSC-CAF interplay	[122]
	CD133	Cancer cell lines	Interacting with ABCC1	[123]
	YAP	PDO	Sustaining quiescent-like phenotype	[125]
	PKCα	PDX	Promoting vesicle trafficking	[128]

Abbreviations: GEM, genetically-engineered mice; PDO, patient-derived organoid; PDC, patient-derived cancer cells, PDX, patient-derived xenograft; ECM, extracellular matrix; CAF, cancer-associated fibroblast.

4. Conclusions

Overall, the hypothesis that the CSC phenotype is plastic has been widely accepted and thoroughly validated in CRC. Self-renewal and differentiation of CSCs, as well as dedifferentiation of non-CSCs appears to be regulated by a series of factors, including key driver mutations of CRC, the inflammatory niche stromal cells, specific metabolites and intestinal microbiota (Figure 3). Development of multi-omics sequencing (omics approaches, including proteomics or epigenomics) and *in silico* analyses facilitated investigation of the above mechanisms, and elucidated the indispensable role of the TME in regulating the plasticity of CSCs. Construction of human organoid models provides a novel strategy to identify the key drivers of mutated ISCs, the central pathways of CSC plasticity, and the interplay of CSCs with the surrounding niche. Of note, TME regulation of CSCs in CRC may be further complicated by frequent exposure to chyme, metabolites, and bacteria, but how these exogenous factors affect CSC properties remains unclear. In addition, the targeting of CSCs in CRC still faces considerable challenges due to the lack of specific markers. In future, a combination of biotechnology, bioinformatics, and artificial intelligence technology should provide keen insights into the intimate relationships between CSCs and CRC, hopefully providing a new group of targets for therapeutic exploitation.

Declarations

Consent for Publication

Not applicable.

Availability of Data and Material

Not applicable.

Competing Interests

The authors declare that no competing interests exist.

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