

# World Journal of *Stem Cells*

*World J Stem Cells* 2023 April 26; 15(4): 105-280



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Editorial Board Member of *World Journal of Stem Cells*, Mariarosaria Miloso, PhD, Associate Professor, Experimental Neurology Unit, School of Medicine and Surgery, University of Milano-Bicocca, Via Cadore 48, Monza 20900, MB, Italy. mariarosaria.miloso@unimib.it

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The primary aim of *World Journal of Stem Cells (WJSC, World J Stem Cells)* is to provide scholars and readers from various fields of stem cells with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJSC* publishes articles reporting research results obtained in the field of stem cell biology and regenerative medicine, related to the wide range of stem cells including embryonic stem cells, germline stem cells, tissue-specific stem cells, adult stem cells, mesenchymal stromal cells, induced pluripotent stem cells, embryonal carcinoma stem cells, hemangioblasts, lymphoid progenitor cells, etc.

**INDEXING/ABSTRACTING**

The *WJSC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, PubMed, PubMed Central, Scopus, Biological Abstracts, BIOSIS Previews, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports cites the 2021 impact factor (IF) for *WJSC* as 5.247; IF without journal self cites: 5.028; 5-year IF: 4.964; Journal Citation Indicator: 0.56; Ranking: 12 among 29 journals in cell and tissue engineering; Quartile category: Q2; Ranking: 86 among 194 journals in cell biology; and Quartile category: Q2. The *WJSC*'s CiteScore for 2021 is 5.1 and Scopus CiteScore rank 2021: Histology is 17/61; Genetics is 145/335; Genetics (clinical) is 42/86; Molecular Biology is 221/386; Cell Biology is 164/274.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Xiang-Di Zhang; Production Department Director: Xu Guo; Editorial Office Director: Jia-Ru Fan.

**NAME OF JOURNAL**

*World Journal of Stem Cells*

**ISSN**

ISSN 1948-0210 (online)

**LAUNCH DATE**

December 31, 2009

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Shengwen Calvin Li, Carlo Ventura

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/1948-0210/editorialboard.htm>

**PUBLICATION DATE**

April 26, 2023

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**INSTRUCTIONS TO AUTHORS**

<https://www.wjgnet.com/bpg/gerinfo/204>

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**PUBLICATION ETHICS**

<https://www.wjgnet.com/bpg/GerInfo/288>

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<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Roles of cancer stem cells in gastrointestinal cancers

Shi-Hai Xuan, Meng-Lu Hua, Ze Xiang, Xiang-Lin He, Lan Huang, Chun Jiang, Peng Dong, Jian Wu

**Specialty type:** Oncology

**Provenance and peer review:**

Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): A, A, A

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Ikram D, Indonesia;

Tang ZP, China

**Received:** January 2, 2023

**Peer-review started:** January 2, 2023

**First decision:** February 7, 2023

**Revised:** February 25, 2023

**Accepted:** March 27, 2023

**Article in press:** March 27, 2023

**Published online:** April 26, 2023



**Shi-Hai Xuan**, Department of Laboratory Medicine, The People's Hospital of Dongtai City, Dongtai 224299, Jiangsu Province, China

**Meng-Lu Hua, Ze Xiang, Xiang-Lin He**, School of Medicine, Zhejiang University, Hangzhou 310009, Zhejiang Province, China

**Lan Huang, Chun Jiang, Jian Wu**, Department of Clinical Laboratory, Suzhou Municipal Hospital, Suzhou 215008, Jiangsu Province, China

**Peng Dong**, Hangzhou Institute of Cardiovascular Diseases, Hangzhou Normal University, Hangzhou 310015, Zhejiang Province, China

**Corresponding author:** Jian Wu, MD, PhD, Professor, Department of Clinical Laboratory, Suzhou Municipal Hospital, No. 242 Guangji Road, Suzhou 215008, Jiangsu Province, China. [wujianglinxing@163.com](mailto:wujianglinxing@163.com)

### Abstract

Cancer stem cells (CSCs) are the main cause of tumor growth, invasion, metastasis and recurrence. Recently, CSCs have been extensively studied to identify CSC-specific surface markers as well as signaling pathways that play key roles in CSCs self-renewal. The involvement of CSCs in the pathogenesis of gastrointestinal (GI) cancers also highlights these cells as a priority target for therapy. The diagnosis, prognosis and treatment of GI cancer have always been a focus of attention. Therefore, the potential application of CSCs in GI cancers is receiving increasing attention. This review summarizes the role of CSCs in GI cancers, focusing on esophageal cancer, gastric cancer, liver cancer, colorectal cancer, and pancreatic cancer. In addition, we propose CSCs as potential targets and therapeutic strategies for the effective treatment of GI cancers, which may provide better guidance for clinical treatment of GI cancers.

**Key Words:** Cancer stem cells; Gastrointestinal cancers; Promotion; Inhibition; Treatment

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**Core Tip:** This review summarizes the role of cancer stem cells (CSCs) in gastrointestinal (GI) cancers, focusing on esophageal cancer, gastric cancer, liver cancer, colorectal cancer, and pancreatic cancer. In addition, we propose CSCs as potential targets and therapeutic strategies for the effective treatment of GI cancers, which may provide better guidance for clinical treatment of GI cancers.

**Citation:** Xuan SH, Hua ML, Xiang Z, He XL, Huang L, Jiang C, Dong P, Wu J. Roles of cancer stem cells in gastrointestinal cancers. *World J Stem Cells* 2023; 15(4): 209-220

**URL:** <https://www.wjgnet.com/1948-0210/full/v15/i4/209.htm>

**DOI:** <https://dx.doi.org/10.4252/wjsc.v15.i4.209>

## INTRODUCTION

Cancer stem cells (CSCs) are small subgroups of undifferentiated cancer cells. CSCs possess an infinite self-renewal capability and a set of unique surface biomarkers[1]. Gastrointestinal (GI) cancer is the most common major malignancy, and includes esophageal cancer (EC), gastric cancer (GC), liver cancer (LC), colorectal cancer (CRC), pancreatic cancer and other related diseases[2]. The incidence of GI cancers is high. Recently, a growing number of studies have been conducted on the important role of CSCs in GI cancers. Research shows that CSCs are mainly involved in the growth, initiation, maintenance, survival, metastasis and recurrence of GI cancer. There are certain limitations in the methods of treatment for currently accepted GI cancers, often leading to treatment failure. This is due to CSCs resistance to chemotherapy and radiation therapy. In current treatment, CSCs cannot be erased, causing metastasis and recurrence of the tumor. Recently, studies have been conducted to clarify the signaling pathway which plays a critical role in the specific surface markers of CSCs and the self-renewal of CSCs. These cell surface markers as well as signaling pathways are potential targets for the treatment of GI cancer that provide the environment necessary for tumor growth[3-5]. Thus, certain therapies for CSCs will potentially help to eliminate the tumor.

This review aims to summarize the mechanism and treatment of CSCs in GI cancer, and to propose a potential target and therapeutic strategy for the treatment of GI cancer.

## ROLES OF CSCS IN EC

EC, a common tumor of the digestive tract, causes a majority of cancer deaths[6]. EC includes esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). EAC may be associated with obesity and ESCC may be associated with drinking and narcotics. Approximately 300000 people die of EC worldwide every year. The incidence and mortality rates of EC vary from country to country[7]. Recently, the relationship between CSCs and the occurrence and development of EC has attracted more and more attention. Chen *et al*[8] discovered that esophageal CSCs activate matrix metalloproteinase 9 in EC cells and promotes cancer metastasis by the expression of placental growth factor. Moreover, CSCs expressing placental growth factor can promote[9] or suppress tumor angiogenesis by stimulating vascular endothelial growth factor[10]. Wang *et al*[11] found that by acting on ATG7-dependent  $\beta$ -catenin, OV6 CSCs can stably promote the progression of ESCC. In addition, studies have shown that exosomal O-GlcNAc transferase derived from esophageal CSCs can promote the suppression of cancer immunity by increasing programmed death-1 (PD-1) in CD8 T cells[12].

CSCs play a critical role in the treatment of EC. CSCs markers could help to identify the functions of CSCs in EC and can be used as targets for the treatment of EC. It was found that CD44, a CSC surface marker, can isolate and detect ESCC[13]. In addition, Lu *et al*[14] found CD133 and CXCR4 markers on the surface of ESCC, and the high expression of CD133-CXCR4 may become a marker for forecasting poor prognosis in patients with ESCC. Liu *et al*[15] found that Cripto-1 is a functional marker of CSC-like cells (CSLCs) and can predict the prognosis of patients with ESCC. In addition, studies have shown that MYH9 is a novel esophageal CSC marker and prognostic indicator, which promotes tumorigenesis through the PI3K/AKT/mTOR axis[16]. Studies have demonstrated that esophageal CSLCs can resist ferroptosis induced cell death through the active HSP27-GPX4 pathway. Hence, targeting HSP27 or GPX4 blockade is a promising therapeutic strategy to eradicate CSCs in ESCC[17]. Li *et al*[18] found that exosomal FMR1-AS1 can promote CSLCs homeostasis through TLR7-NF $\kappa$ B-Myc signaling in female EC. Song *et al*[19] analyzed clinical specimens and found that BCL-2 inhibitor AT101 could overcome drug resistance by targeting the CSC pathway and had good antitumor activity. In addition, Zarei *et al*[20] found that salinomycin could destabilize the low-pathway sensor TAZ in CSLCs and reduce the viability of esophageal CSLCs. Studies have shown that TRPV2 can maintain the growth of CSCs, and its specific inhibitor trnilast may be used as a targeted therapeutic agent for ESCC[21]. STAT3 and miR-181b activate each other *via* the CYLD pathway, thereby regulating the proliferation of esophageal

CSLCs[22]. Metformin can inhibit EC cell growth and sensitize EC cells to the cytotoxic effects of 5-FU by targeting components of CSCs and mTOR[23].

CSCs play an important role in the development, progress and future treatment of EC, but the associated research is inadequate, and the underlying mechanisms have not been fully explored. Therefore, more studies are needed to determine the mechanism and support the corresponding conclusions.

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## ROLES OF CSCS IN GC

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GC is a malignant tumor derived from gastric mucosal epithelium. Most GCs are early adenocarcinomas with no apparent symptoms and are easily overlooked[24]. GC is the main cause of global cancer deaths. The treatment of GC involves surgery in combination with chemotherapy and radiotherapy, but the prognosis of terminal GC is still poor[25]. Over the past decade there is increasing evidence to show that CSCs have a significant role in GC development.

The concept that CSCs cause GC and may lead to invasion, metastasis, and treatment resistance has profound implications for anticancer therapy. Takaishi *et al*[26] implanted gastric CSCs (GCSCs) in the skin of immunodeficient mice, and a few weeks later observed that these GCSCs showed strong tumorigenic ability. Yang screened out GCSCs with serum-free medium, and found that these GCSCs had high tumorigenesis ability in nude mice, and high expression of GCSCs surface markers OCT4 and SOX2[27]. E-cadherin is a vital adhesion molecule, and its expression is closely related to the degree of cell adhesion[28]. Studies have found that the expression of E-cadherin in GCSCs is down-regulated, resulting in a decrease in the adhesion of tumor cells; thus, GCSCs are highly aggressive and easily metastasize to local lymph nodes or distant metastasis[29]. CSC Lgr5+ can promote the growth and proliferation potential of GC[30]. In addition, CSCs may maintain their viability through autophagy[31].

Identifying and targeting CSCs play a vital role in the treatment of GC. Chemotoxicity-induced exosomal lncFERO can regulate ferroptosis and stemness in GCSCs. Therefore, chemotherapy targeting the lncFERO/hnRNPA1/SCD1 axis could be an implicit strategy for CSCs-based GC therapy[32]. In addition, microRNA (miR)-375 can trigger ferroptosis by targeting SLC7A11, thereby attenuating the stemness of GCSCs[33]. CBX7 was found to positively regulate the stem-like characteristics of GC cells by inhibiting p16 and activating the AKT-NF- $\kappa$ B-miR-21 pathway[34]. Sezer *et al*[35] found that lymphatic metastasis-associated TBL1XR1 promotes the metastasis of gastric CSLCs by sensitizing ERK1/2-SOX2 signaling. Huang *et al*[36] found that SIRT1 inhibits both chemoresistance and cancer stemness in GC by launching a positive feedback loop of AMPK/FOXO3. The m6A methyltransferase METTL3 was found to promote oxaliplatin resistance in CD133+ GCSCs by improving PARP1 mRNA stability to increase base excision repair pathway activity[37]. *Celastrus orbiculatus* ethyl acetate extract can prevent GC growth by limiting the stemness of GCSCs by changing PDCD4 and EIF3H expression [38]. Methionine has been found to inhibit autophagy in GCSCs by promoting RAB37 methylation and phosphorylation. Therefore, supplementation with methionine  $\gamma$ -lyase can induce autophagy in GCSCs and inhibit tumor growth[36].

The role of CSCs in growth, metastasis, treatment and prognosis of GC is increasingly important. In the past few years, an increasing number of studies have been conducted on the mechanism of action of CSCs against GC and to offer promising targets and therapeutic tactics for GC treatment. Many treatments targeting CSCs have been developed, but there are limits to CSCs targeting therapy. It affects normal stem cells and causes tissue renewal problems. For example, Lgr5 is a marker associated with common stem cells in gastric tissue. mTORC1 can maintain self-renewal of the Lgr5 population, preventing cell differentiation and causing gastric tumorigenesis. However, the use of mTORC1 inhibitors may cause gastric glandular atrophy due to tissue malfunction, limiting its therapeutic use [39]. Therefore, more efforts are needed to treat GC based on CSCs.

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## ROLES OF CSCS IN LC

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LC is the third most common cause of cancer associated deaths worldwide. This is due to its high recurrence rate, which after normal treatment, can reach 70%. Hepatocellular carcinoma (HCC) is the main pathology and causes approximately 80% of LC cases[40]. Liver CSCs (LCSCs) are now known to be responsible for HCC growth, metastasis and recurrence, in addition to failure of chemotherapy and radiation therapy[41]. These findings indicate that LC therapy kills most of the tumor cells, but cannot eliminate LCSCs and treatment can eventually fail as LCSCs survive and generate new tumors. Therefore, CSCs theory has provided new findings in the diagnosis, treatment and prevention of LC (Table 1).

LCSCs play a vital role in the development, progression, recurrence and drug tolerance of HCC. Studies have shown that LCSCs can accelerate tumor growth in primary cancer cells and metastasis of secondary tumors, causing the recurrence of HCC[42]. Studies have found that EpCAM-high HCC stem cells can promote tumor growth by upregulating CEACAM1 to weaken the capacity of natural killer

**Table 1** Methods for targeting liver cancer stem cells in the treatment of liver cancer

Ref.	Genes/transcription factors/protein	Inducing way	Role
Park <i>et al</i> [43]	EpCAM-high HCC stem cells	Upregulating CEACAM1	Promoting the growth of LC
Deng <i>et al</i> [44]	Histone demethylase JMJD2D	Enhancing Sox9 expression	Promoting the growth of LC
Yang <i>et al</i> [45]	lncARSR	Targeting STAT3 signaling	Promoting LCSCs expansion
Chen <i>et al</i> [47]	4-PBA	Activating $\beta$ -catenin signaling pathway	Promoting the growth of LC
Galizia <i>et al</i> [49]	CD133	-	Indicator of tumor recurrence
Haraguchi <i>et al</i> [51]	CD13	-	Causing drug resistance of LCSCs
Yang <i>et al</i> [52]	OV6	-	Causing drug resistance of LCSCs
Wei <i>et al</i> [53]	CD44	Regulating PES1	Promoting the growth of LC
Chen <i>et al</i> [55]	FOXM1	Reducing the expression of ALDH2	Inducing the apoptosis of LCSCs
Dou <i>et al</i> [56]	BC-02	Inhibiting CD13	Eradicate LCSCs
Zhou <i>et al</i> [57]	CD133-apt-Dox	Targeting CD133-expressing cells	Inhibiting the growth of LC
Feng <i>et al</i> [58]	MiR-124	-	Inhibiting LCSCs self-renewal
Jiang <i>et al</i> [59]	MiR-365	Regulating RAC1 pathway	Inhibiting the proliferation and invasion of HCC cells
Li <i>et al</i> [60]	MicroRNA-21	-	Inhibiting highly invade LCSCs
Si <i>et al</i> [61]	MiR-219	E-cadherin pathway	regulates the expansion of LCSCs
Dou <i>et al</i> [62]	MicroRNA-6838-5p	Down-regulating CBX4 expression and Inactivating ERK signaling	Inhibiting self-renewal and metastasis of Human LCSCs
Zhang <i>et al</i> [63]	MiR-589-5p	Inhibiting MAP3K8	Inhibiting the growth of LC
Wang <i>et al</i> [64]	HAND2-AS1	-	Promoting the growth of LC
Li <i>et al</i> [66]	Neuropilin1	The loss of neuropilin1	Inhibiting LCSCs
Wang <i>et al</i> [67]	ZBP-89	Inhibiting Notch1 signaling pathway	Regulating self-renewal of LCSCs

HCC: Hepatocellular carcinoma; LC: Liver cancer; LCSCs: Liver cancer stem cells.

cells to recognize and kill cancer cells[43]. Histone demethylase JMJD2D can enhance EpCAM and Sox9 expression to promote the self-renewal of liver CSLCs, promoting tumor growth[44]. Yang *et al*[45] found that lncARSR promoted HCC cell dedifferentiation and LCSCs expansion by targeting STAT3 signaling. Moreover, LCSCs release exosomes in a RAB27A-dependent manner which can lead to resistance to regorafenib in LC cells[46]. Chen *et al*[47] found that activating the  $\beta$ -catenin signaling pathway leads to upregulation of PPAR- $\alpha$  by 4-PBA, which in turn initiates LCSCs and promotes early HCC. Cao *et al*[48] found that RACK1 advances self-renewal and chemoresistance of CSCs in HCC by stabilizing nanoparticles.

The biomarkers of LCSCs are important targets in the treatment of LC. CD133 is one of the common surface markers of LCSCs, and studies have found that CD133 isolated from HCC cell lines has high proliferative and tumorigenic potential; thus, enhanced CD133 expression can also serve as a prognostic indicator for survival and tumor recurrence in patients with LC[49]. Yin *et al*[50] found that aldehyde dehydrogenase was expressed in LCSCs and was positively correlated with CD133 expression. CD13 is a marker of LCSCs, which has the function of dormancy and slow growth, and is the main reason for drug resistance of LCSCs[51]. The LCSCs marker OV6 was found to be chemoresistant, but this was reversed when lentivirus-delivered miRNAs targeting  $\beta$ -catenin were stably expressed. Therefore, targeting Wnt/ $\beta$ -catenin signaling could be a potential strategy to reverse the drug resistance properties of OV6 LCSCs[52]. Wei *et al*[53] found that CD44 regulated PES1 in LCSCs through miR-105-5p to promote tumor growth. Twist2 advances self-renewal of liver CSLCs by changing CD24[54].

LCSCs play a vital role in the treatment of LC. It was found that the transcription factor FOXM1 inhibits the dryness of LCSCs by reducing the expression of ALDH2, and inhibits proliferation, migration, invasion and tumorigenesis, while inducing apoptosis of LCSCs[55]. The CD13 inhibitor BC-02 can target CD13 and upregulate intracellular reactive oxygen species (ROS) and ROS-induced DNA damage to damage LCSCs. Therefore, BC-02 may be a potential therapeutic strategy to eradicate LCSCs and overcome chemoresistance in LC[56]. Studies have found that aptamer-based drug delivery agents

(CD133-apt-Dox) targeting CD133-expressing cells can impair the self-renewal ability of liver CSLCs and inhibit the growth of LC[57]. MiRNAs are important regulators of CSCs therapy in LC. Feng *et al* [58] found that forced expression of miR-124 can inhibit LCSCs self-renewal and tumorigenesis. It was shown that miR-365 regulated LCSCs through the RAC1 pathway and prevented the proliferation and invasion of HCC cells[59]. In addition, miR-21 downregulation can inhibit cell proliferation and highly invade LCSCs[60]. Si *et al*[61] found that miR-219 regulates the expansion of LCSCs through the E-cadherin pathway. Dou *et al*[62] showed that miR-6838-5p inhibited self-renewal and metastasis of LCSCs by down-regulating CBX4 expression and inhibiting ERK signaling. In addition, miR-589-5p inhibited MAP3K8 in HCC and inhibited CD90 CSCs[63]. It was shown that HAND2-AS1 can promote self-renewal of LCSCs and drive liver tumorigenesis, providing a potential new target for HCC treatment[64]. In addition, tumor-associated macrophages produce interleukin-6 and signal through STAT3 to improve the expansion of LCSCs[65]. Li *et al*[66] found that the loss of neuropilin 1 inhibits the LCSC population and blocks metastasis in HCC through epithelial-mesenchymal transition. Wang *et al* [67] found that ZBP-89 negatively regulated self-renewal of LCSCs by inhibiting the Notch1 signaling pathway.

Traditional HCC treatment mainly targets fast growing and differentiated HCC cells. However, a part of the emerging CSCs concept explains the failure of these therapies. The research progress of LCSCs has provided a new viewpoint on the possible adhibition in the clinical treatment of LCSCs. Detection of LCSCs is useful for predicting postoperative survival of patients. The development of treatment strategies for LCSCs may greatly improve the treatment of LC[68].

## ROLES OF CSCS IN CRC

CRC is one of the most common cancers and the fourth most frequent cause of cancer death worldwide [69]. Despite the great progress in surgery and chemotherapy over the past decade, the five year survival rate of CRC patients is 50%-65%[70]. In the past few years, an increasing number of studies have shown that CSCs are closely associated with the occurrence and development of CRC, which provides promising directions for the diagnosis and treatment of CRC (Table 2).

CSCs are the major cause of drug resistance and disease recurrence in CRC. Studies have found that Lgr5 CSCs have a vital role in primary and metastatic colon cancer, and can promote tumor growth and metastasis[71]. In addition, most colorectal CSCs (CCSCs) express Lgr5 and form distant metastasis, which is a major factor driving CRC metastasis[72]. Recent studies have found that human CCSCs can give rise to vascular endothelial cells and constitute the vasculature in cancer tissue, which provides a new mechanism for tumor angiogenesis in cancer[73]. CD26 CCSCs can lead to CRC metastasis[74]. Razi *et al*[75] found that DCLK1 is a promising CCSC marker that changes tumor progression and invasion in a miR-137- and miR-15a-dependent manner. The JAK2/STAT3/CCND2 axis promotes the persistence and radioresistance of CRCs, which is the drug resistance mechanism for the continuous growth of CSCs after radiotherapy[76]. Liu *et al*[77] found that Sec62 promotes stemness and chemoresistance in human CRC by sensitizing the Wnt/ $\beta$ -catenin pathway. Studies have shown that CCSCs acquire chemoresistance by the upregulation of F-Box/WD repeat-containing protein 7 and the consequent degradation of c-Myc[78]. In addition, PD-L1 can maintain CSCs self-renewal by activating the HMGA1-dependent signaling pathway[79]. 5-FU improves the stemness of CRC through p53-mediated WNT/ $\beta$ -catenin pathway activation[80].

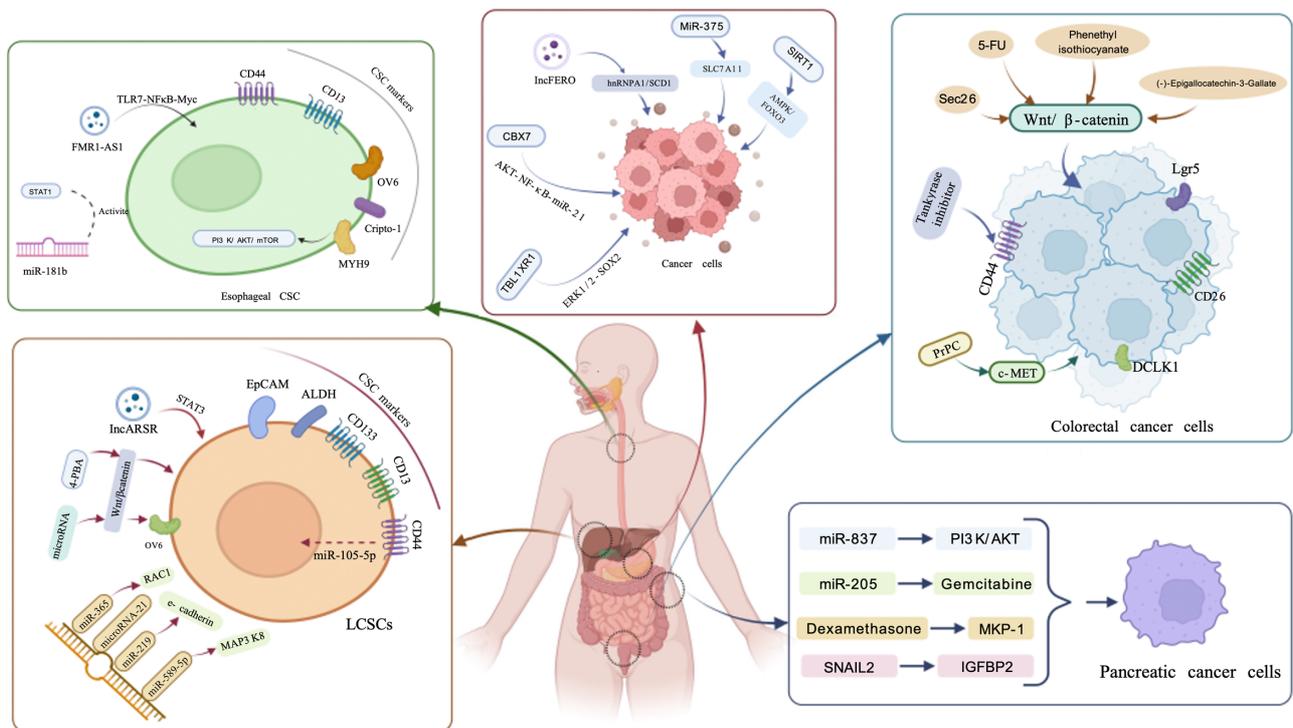
Whereas conventional therapies target proliferating and mature cancer cells, CSCs are mostly quiescent and poorly differentiated, so they could easily survive the chemotherapy attack. Therefore, novel therapies targeting CSCs are necessary. Chen *et al*[81] found that phenethyl isothiocyanate inhibits CCSCs by suppressing the Wnt/ $\beta$ -catenin pathway. In addition, (-)-Epigallocatechin-3-Gallate can also inhibit CCSCs by suppressing the Wnt/ $\beta$ -catenin pathway[82]. Studies have shown that AGR2 is a new stem cell marker that is changed by the canonical Wnt/ $\beta$ -catenin pathway in CCSCs and is important for stemness maintenance of CCSCs[83]. Jang *et al*[84] reported that tankyrase inhibitors downregulated c-KIT tyrosine kinase and prevented the growth of CD44-positive CCSCs. Liu *et al*[85] found that PTK6 interacts with JAK2 and phosphorylates to activate JAK2/STAT3 signaling, which can improve stemness and chemoresistance of CRC cells and reverse chemoresistance in CRC. Studies have shown that mithramycin A inhibits CRC growth by targeting CSCs[86]. Studies have also found that disruption of endolysosome RAB5/7 effectively eliminates CCSCs[87]. PrPC inhibits CSCs properties by interacting with c-MET in CRC cells[88].

According to the data accumulated during cancer research, CSCs have become a fundamental cause of cancer progression and resistance to treatment. Therefore, it is important to understand the biological, functional and clinical significance of CSCs in CRC tolerance in order to develop an effective treatment model for CRC patients. However, the practical clinical application of CSCs in CRC is still limited, and further studies and efforts are needed for clinical applications.

**Table 2** Methods for targeting colorectal cancer stem cells in the treatment of colorectal cancer

Ref.	Genes/transcription factors/protein	Inducing way	Role
Fumagalli <i>et al</i> [72]	Lgr5	-	Promoting the growth of CRC
Cheung <i>et al</i> [74]	CD16	-	Promoting the growth of CRC
Razi <i>et al</i> [75]	DCLK1	MiR-137 and Mir-15a-dependent manner	Promoting the growth of CRC
Park <i>et al</i> [76]	JAK2/STAT3/CCND2 axis	-	Causing drug resistance of CCSCs
Liu <i>et al</i> [77]	Sec62	Activating the Wnt/ $\beta$ -catenin pathway	Causing drug resistance of CCSCs
Izumi <i>et al</i> [78]	F-Box/WD repeat-containing protein 7	-	Causing drug resistance of CCSCs
Wei <i>et al</i> [79]	PD-L1	Activating HMGA1-dependent Signaling pathway	Maintaining CSCs self-renewal
Cho <i>et al</i> [80]	5-FU	Activating p53-mediated WNT/ $\beta$ -catenin pathway	Promoting the stemness of CRC
Chen <i>et al</i> [81]	Phenethyl isothiocyanate	Suppressing Wnt/ $\beta$ -catenin pathway	Inhibiting CCSCs
Chen <i>et al</i> [82]	(-)-Epigallocatechin-3-Gallate	Suppressing Wnt/ $\beta$ -catenin pathway	Inhibiting CCSCs
Dahal <i>et al</i> [83]	AGR2	Regulating Wnt/ $\beta$ -catenin pathway	Regulating the stemness maintenance of CCSCs
Jang <i>et al</i> [84]	Tankyrase inhibitors	Downregulating c-KIT tyrosine kinase	Inhibiting the growth of CD44-positive CCSCs
Liu <i>et al</i> [85]	PTK6 interacts with JAK2	Activating JAK2/STAT3 signaling	Reversing chemoresistance in CRC
Quarni <i>et al</i> [86]	Mitramycin A	-	Inhibiting CCSCs
Lim <i>et al</i> [88]	PrPC	Interacting with c-MET	Inhibiting CCSCs

CCSC: Colorectal cancer stem cells; CRC: Colorectal cancer; CSCs: Cancer stem cells.



**Figure 1** The roles of cancer stem cells in gastrointestinal cancers. CSC: Cancer stem cells; LCSC: Liver cancer stem cells.

## ROLES OF CSCS IN PANCREATIC CANCER

Pancreatic cancer is one of the most deadly human malignancies, the survival rate is 8% and the prognosis is the worst of all GI tumors[89-91]. It is now the fourth most common cause of cancer associated deaths worldwide. The tumorigenesis capacity of pancreatic cancer cells is different, and the proliferation and growth of pancreatic cancer are highly dependent on the presence of a limited subgroup of pancreatic cancer cells, called pancreatic CSCs (PCSCs)[92]. The concept of CSCs is recognized and some of the identified molecules and signaling pathways are associated with cancer diagnosis and treatment.

PCSCs contribute to the development and invasion of pancreatic cancer. It has been found that PCSC CD9 can promote the plasma membrane localization of glutamine transporter ASCT2, improving glutamine uptake in pancreatic cancer cells and promoting tumor growth[93]. Leng *et al*[94] found that SIRT1 coordinating with CRL4B can regulate PCSCs to promote tumorigenesis. In PCSCs, PAF1 interacts with DDX3 and PHF5A to regulate the expression of NANOG and other genes that regulate stemness. Therefore, knockdown of PAF1 reduced the development and progression ability of *in situ* pancreatic cancer in mice and its CSCs[95]. Bao *et al*[96] found that pancreatic CSLCs can promote tumor formation and rapid tumor growth by activating FoxQ1. Masuo *et al*[97] demonstrated that SNAIL2 can promote the tumorigenicity and chemotherapy resistance of PCSCs by regulating IGF2BP2.

PCSCs have an important role in pancreatic cancer therapy. Studies have shown that PCSCs have longer telomeres and higher telomerase activity than tumor cells, which is associated with the expression of pluripotent genes (Nanog, Sox2, Oct3/4). Therefore, telomerase inhibition can lead to apoptosis of PCSCs, which is a suitable therapeutic approach against CSCs, especially in pancreatic cancer[98]. Yang *et al*[99] found that miR-873 could inhibit self-renewal and proliferation of PCSCs by blocking the PLEK2-dependent PI3K/AKT pathway. In addition, miR-205 can resensitize gemcitabine-resistant pancreatic cancer cells to gemcitabine and act as a tumor suppressor miRNA[100]. JNK is required for PCSCs self-renewal and tumor initiation, as well as its survivin expression. Dexamethasone was found to induce the expression of MKP-1 through glucocorticoid receptor activation, thereby inactivating JNK and inhibiting tumor growth[101]. Urtasun *et al*[102] showed that simultaneous blockade of IGF-IR and EGFR/Her-2 using NVP-AEW541 and lapatinib could inhibit drug resistance in pancreatic cancer.

The role of CSCs in pancreatic cancer metastasis, recurrence and treatment has become very important. A large number of studies have allowed tumor stem cell markers to achieve metastasis, progression and resistance of pancreatic cancer cells, which provide potential targets and therapeutic directions for the treatment of pancreatic cancer. Nevertheless, there are still few practical clinical applications of PCSCs, and further studies are needed for clinical applications.

Recently, many studies have shown that CSCs are closely related to tumor recurrence, metastasis and drug resistance, especially in EC, GC, LC, CRC and pancreatic cancer (Figure 1). CSCs can be identified by a series of surface markers, including OV6, EpCAM, CD13, CD133 and CD44. Surface markers of CSCs are useful for cancer diagnosis and prognosis prediction. In addition, CSCs regulate tumor progression and therapeutic resistance through multiple mechanisms, including Notch, Wnt/ $\beta$ -catenin and other signaling pathways. There are many other elements that make CSC impressions, such as the tumor microenvironment and non-coding RNAs, including miRNAs and long non-coding RNAs.

## CONCLUSION

Currently, we have developed a combination of chemotherapeutic agents and small molecule inhibitors to reduce CSCs and effectively treat GI cancer. As CSCs have many similar features to stem cells, the molecular signal pathway or mechanism that distinguishes the two cell subgroups is still unknown. Therefore, stem cell therapy is limited, and it is necessary to further study the biological difference between normal stem cells and LCSCs. Research on the therapy of GI cancer with regard to CSCs is still at the *in vitro* and animal experimental stage, and the precise molecular mechanism of CSCs in GI cancer requires further study. Therefore, more research is needed to promote the application of CSCs in clinical practice.

## FOOTNOTES

**Author contributions:** Wu J and Dong P designed study and revised the manuscript. Xuan SH, Hua ML and Xiang Z analyzed data and performed manuscript drafting; He XL, Huang L and Jiang C searched the literature and collected data; Dong P and Wu J reviewed the results and made critical comments on the manuscript; all authors reviewed and approved the final version; Xuan SH and Hua ML contributed equally to this work; Wu J and Dong P contributed equally to this work.

**Supported by** the Youth Medical Talent of Jiangsu Province, No. QNRC2016475.

**Conflict-of-interest statement:** The authors declare that there are no competing interests associated with this manuscript.

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**Country/Territory of origin:** China

**ORCID number:** Jian Wu 0000-0003-0087-3744.

**S-Editor:** Yan JP

**L-Editor:** A

**P-Editor:** Zhang XD

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