Circular RNAs in cancer stem cells: Insights into their roles and mechanisms (Review)

LUNYU YANG, YULING YI, ZHU MEI, DONGMEI HUANG, SITIAN TANG, LIYI HU and LING LIU

Department of Medical Laboratory, Chongqing Liangjiang New Area People's Hospital, Chongqing 401121, P.R. China

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Abstract. Cancer stem cells (CSCs) represent a small, yet pivotal subpopulation of tumor cells that play significant roles in tumor initiation, progression and therapeutic resistance. Circular RNAs (circRNAs) are a distinct class of RNAs characterized by their closed-loop structures, lacking 5' to 3'ends. There is growing evidence that circRNAs are integral to the development and regulation of CSCs. Aberrant expression of circRNAs in CSCs can contribute to oncogenic properties and drug resistance. Specifically, oncogenic circRNAs modulate CSC behavior via key signaling pathways, thereby promoting CSC self-renewal and maintenance, as well as tumor progression. This review summarizes the latest research on the functional roles and regulatory mechanisms of circRNAs in CSC behavior and discusses potential applications and challenges of targeting circRNAs in CSCs. Understanding the intricate interactions between circRNAs and CSCs may lead to novel therapeutic strategies that effectively combat treatment resistance and improve patient outcomes.

Correspondence to: Dr Liyi Hu or Dr Ling Liu, Department of Medical Laboratory, Chongqing Liangjiang New Area People's Hospital, 199 Renhe Road, Chongqing 401121, P.R. China
E-mail: hlyhhy@163.com
E-mail: liuling0710dym@163.com

Abbreviations: circRNAs, circular RNA; ecircRNAs, exonic circRNAs; CSCs, cancer stem cells; TICs, tumor-initiating cells; ALDH1, aldehyde dehydrogenase 1; FACS, fluorescence-activated cell sorting; MACS, magnetic-activated cell sorting; SP, side population; RNA-seq, RNA sequencing; HCC, hepatocellular carcinoma; EpCAM, epithelial cell adhesion molecule; CRC, colorectal cancer; RBPs, RNA-binding proteins; GBM, glioblastoma; GSCs, glioma stem cells; HB, hepatoblastoma; FMRP, fragile X mental retardation protein; HCSCs, HCC stem cells; GLI1, GLI family zinc finger 1; Hh, Hedgehog; TOP1, topoisomerase 1; rt-circRNA, read-through circular RNA; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2; BCSCs, breast CSCs; NSCLC, non-small cell lung cancer; LUAD, lung adenocarcinoma; DDP, cisplatin; GC, gastric cancer; GCSCs, gastric CSCs; m6A, N6-methyladenosine; BLCA, bladder cancer; RCC, renal cell carcinoma; LGR5, leucine-rich repeat-containing G protein-coupled receptor 5; KIF4A, kinesin family member 4A; ECE1, endothelin converting enzyme 1; TNF-α, tumor necrosis factor α; NF-κB, nuclear factor κB; TGF-β, transforming growth factor β; VEGFA, vascular endothelial growth factor A; PAX5, paired box 5; JAK2, Janus kinase 2

Key words: circular RNA, cancer stem cells, isolation, self-renewal, function, mechanisms

Contents

1. Introduction

Circular RNAs (circRNAs), unlike their linear counterparts, are ring-shaped RNA molecules formed by back-splicing, wherein the 3' and 5'ends of linear RNA are joined. Although circRNAs were discovered as early as the 1970s (1,2), they were initially regarded merely as by-products of RNA splicing and garnered little attention. It was not until recent advancements in high-throughput sequencing technologies and bioinformatic tools that the widespread presence of circRNAs in eukaryotes was acknowledged (3,4). CircRNAs are produced through a process known as 'back splicing', which may include mechanisms such as exon skipping (5), circularization mediated by cis/trans elements (6), lariat-mediated circularization, circularization driven by intron pairing (4) or the splicing of pre-tRNAs (7). Based on their structural components, circRNAs are categorized into three primary types: Exonic circRNAs (ecircRNAs), which consist of one or multiple exon sequences; intronic circRNAs, composed solely of one or multiple intron sequences; and exon-intron circRNAs, which include both exons and introns (8). Among these, ecircRNAs have been the most extensively studied. CircRNAs exhibit several significant characteristics: i) Their unique circular structure confers resistance to degradation by exonucleases, thereby enhancing their stability and extending their half-life (9,10); ii) CircRNAs are ubiquitously expressed, as demonstrated by sequencing studies revealing their abundant presence across eukaryotic species (11,12); iii) circRNAs show

conservation across species, with studies indicating that certain circRNAs found in mouse tissues are homologous to those derived from humans (4,13); iv) the expression of circRNAs is both tissue- and cell-specific. Research by Memczak *et al* (3) and Salzman *et al* (14) has shown that, although thousands of circRNAs are expressed across the genome, their expression levels vary significantly among different cells, tissues and developmental stages. Accumulating evidence underscores the crucial roles of circRNAs in regulating a variety of cellular processes, including cell proliferation, differentiation and the maintenance of stemness (15).

Cancer stem cells (CSCs), also known as tumor-initiating cells (TICs), constitute a small subpopulation within tumors that have the capabilities of self-renewal and differentiation into various cell types (16). Initially identified in human acute myeloid leukemia, CSCs have subsequently been isolated from a range of solid tumors, including those of the breast, glioma, colon and liver (17,18). Two prevalent hypotheses propose different origins for these cells: The first suggests that CSCs arise from non-malignant stem cells that undergo transformation due to tumor gene mutations (19), while the second posits that CSCs develop from highly differentiated non-stem cells that acquire stem-like properties following transformation, a process often characterized by epithelial-mesenchymal transition (20). CSCs are distinguished by their robust self-renewal ability and differentiation capabilities, enabling them to produce progeny similar to themselves, as well as to differentiate into diverse cell types (21). Furthermore, CSCs display enhanced tumorigenicity, playing a critical role in tumor initiation, progression and treatment resistance (22). For instance, CSCs isolated from original tumor tissues and transplanted into severe combined immunodeficiency disease mice have been shown to form new tumors (23). Metastasis, the process through which tumor cells migrate from their primary site via the bloodstream or lymphatic system to establish new tumor foci in other parts of the body (24), is a principal characteristic of malignant tumors and a major contributor to advanced cancer and treatment failure (25). Research has demonstrated that CSCs are integral to the metastasis of various cancers, including pancreatic, breast and prostate cancers (26-28). In addition, angiogenesis, essential for tumor growth and metastasis, is facilitated by CSCs, which can differentiate into vascular endothelial cells to promote this process in tumors, such as glioblastoma, liver cancer and renal carcinoma (29-31). CSCs are also closely linked to treatment resistance, including resistance to chemotherapy and radiotherapy. Aldehyde dehydrogenase 1 (ALDH1), a detoxifying enzyme highly expressed in CSCs, helps mitigate the toxic effects of reactive oxygen species and regulates the cell cycle, allowing sufficient time for DNA repair and thus enabling CSCs to withstand therapeutic interventions (32-34). Therefore, elucidating the mechanisms underlying the unique characteristics and behaviors of CSCs may lead to more effective strategies to curb cancer progression and enhance therapeutic outcomes.

Recent research has highlighted the potential influence of circRNAs on the properties and behavior of CSCs, impacting tumor progression and therapeutic responses. This review aims to succinctly summarize current research on the roles and mechanisms of circRNAs in various CSCs and to discuss their potential applications in cancer research and treatment, thus offering new insights into CSC-related oncology.

2. Expression profiles of circRNAs in CSCs

Methods for isolating CSCs. CSCs, which typically account for as few as 1 in 100,000 to 1 in 1,000 cells within tumor tissues, present a considerable challenge for isolation and enrichment (35). The effective isolation of CSCs is crucial for advancing our understanding of tumor development and therapeutic resistance. Several prevalent methods are employed to enrich CSCs from tumor tissues or tumor cell populations, including fluorescence-activated cell sorting (FACS), magnetic-activated cell sorting (MACS), side population (SP) analysis and the sphere formation assay (refer to Fig. 1 showing a flow diagram of CSC isolation).

Both FACS and MACS techniques utilize cell surface labeling to sort cells (36,37). Key surface markers used to identify CSCs include CD44, CD133, ALDH and epithelial cell adhesion molecule (EpCAM). Over the years, these and other biomarkers have been identified to characterize CSCs across various tumor types (see Table I). Since the pioneering work by Bonnet and Dick (38), who first isolated CSCs from leukemia using FACS, this technology has become the predominant method for cell isolation. FACS enables the simultaneous sorting of cells based on multiple biomarkers, offering high purity and specificity. In addition, it allows for the analysis of intracellular pathways and protein interactions, thus addressing the challenges of CSCs' membrane antigen specificity (39). However, maintaining cell viability during FACS requires stringent experimental conditions and precise cell pretreatment, which can be challenging due to high equipment costs and complex operational requirements (40). By contrast, MACS employs magnetic beads coated with antibodies targeting specific cell surface markers on CSCs, with separation achieved using a magnetic field (41). Although MACS is less disruptive to cell viability, its dependence on a single antigen and the complexities associated with its operation, coupled with high costs, somewhat limit its widespread application (40).

SP cells, first identified by Goodell *et al* (42) in 1996, are characterized by their ability to efflux the Hoechst33342 dye during bone marrow cell culturing. These cells exhibit properties consistent with CSCs and have been identified in various tumor tissues and cell lines, including ovarian, colon, gastric and lung cancers (43-46). SP analysis is relatively straightforward, but it suffers from low separation efficiency and the cytotoxicity of the dye, which can compromise cell viability. However, for CSCs lacking known surface markers, SP analysis combined with flow cytometry remains a viable method for isolation. For instance, this approach has been utilized to study the impact of exosomes loaded with the circRNA of par-3 family cell polarity regulator on CSCs in nasopharyngeal carcinoma and to explore the metabolic mechanisms by which CSCs facilitate metastasis in pancreatic ductal carcinoma (47,48).

Another commonly utilized method for the isolation and identification of CSCs is the sphere formation assay (49). In this technique, tumor tissues are enzymatically dissociated into single cells, which are then cultured at low density in

Table I. Biomarkers of cancer stem cells in human cancers.

Cancer type	Markers	(Refs.)
Breast cancer	$CD44^+/CD24^-$, EpCAM, ALDH1, $CD29^+$, $CD133^+$, $ESA^+/CD44^+/CD24$, $CD90^+$	(139,202-207)
Gastric cancer	$CD44^+$, $ALDH^+$, $CD44V8\text{-}10^+$, $CD133^+$, $CD24^+$, $EpCAM^+$, LGR5,	(162,208-214)
Colorectal cancer	$CD200^+$, $CD133^+$, $EpCAM^+$, $CD44^+$, $ALDH1^+$, CXCR4, LGR5,	(215-221)
Glioma/glioblastoma	$CD133^+$, LGR5, $CD70^+$, CD49f, CXCR4, $CD44^+$, $CD87^+$, ALDH,	(93,94,222-227)
Hepatocellular cancer	EpCAM, LGR5, $CD24^+$, $CD133^+$, $CD24^+/CD133^+$, CD90, $CD44^+$	(228-234)
Cervical cancer	LGR5, $CD133^+$, $CD44^+/CD24^+$, $ALDH^+$	(235-238)
Pancreatic cancer	CXCR4, LGR5, $CD44^+/CD24^+$, $CD133^+$, CD90, AFP	(239-243)
Bladder cancer	$CD44v6^+$, $CD44^+$, ALDH, CD24	(244-247)
Ovarian cancer	$CD24^+$, ALDH, CD133+, $CD44^+/CD117^+$, $CD44^+/CD24^-$	(248-252)
Lung cancer	ALDH, $CD166^+$, $CD44^+$, $CD133^+$, CXCR4, CD87	(151,253-257)
AML	$CD133^+$, CD70/CD27, $CD25^+$, $CD123^+$, TIM-3, BMI-1	(258-263)

AML, acute myeloid leukemia; AFP, α fetoprotein; EpCAM, epithelial cell adhesion molecule; ALDH, aldehyde dehydrogenase; CXCR4, C-X-C chemokine receptor type 4; LGR5, leucine rich repeat containing G protein-coupled receptor 5; BMI-1, B lymphoma Mo-Mlv insertion region 1 homolog; TIM-3, hepatitis A virus cellular receptor 2.

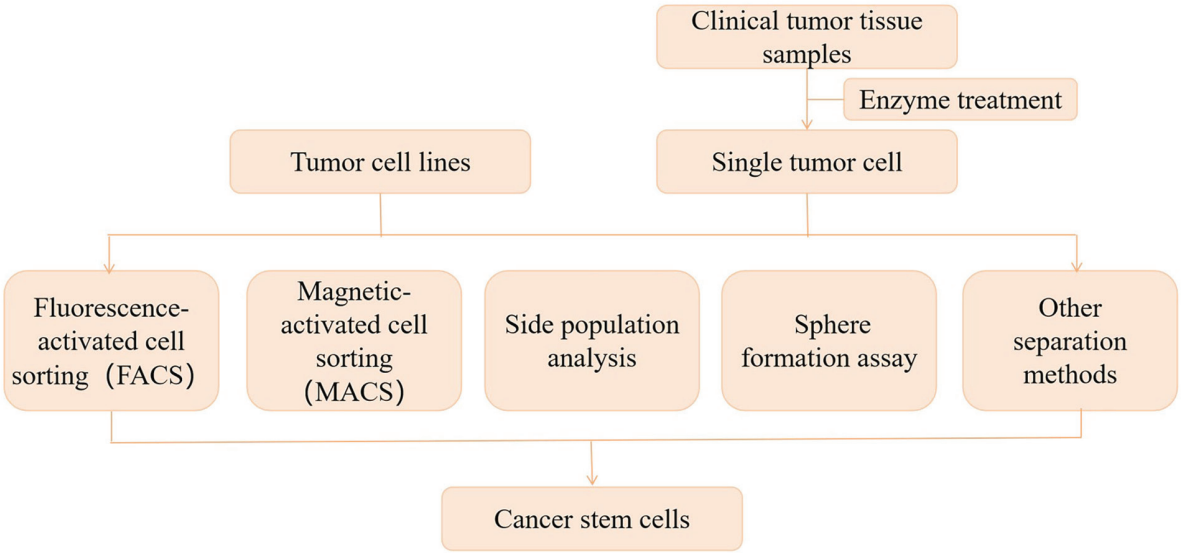

Figure 1. Flow diagram of cancer stem cell isolation.

serum-free medium supplemented with epithelial growth factor and basic fibroblast growth factor. Under these specific conditions, individual CSCs are capable of forming colonies or spheres, thereby facilitating their isolation and subsequent analysis (50,51). Although the purity and specificity of CSCs isolated by this method may not rival those achieved through FACS, the sphere formation assay remains popular in research laboratories due to its simplicity, cost-effectiveness and ease of implementation (52-55).

In addition to these traditional methods, CSCs can also be isolated based on their resistance to therapeutic agents. For instance, Calcagno *et al* (56) demonstrated that prolonged exposure of breast cancer cells to azithromycin not only selected drug-resistant cells but also enriched populations with a $CD44^+/CD24^-$ stem cell-like phenotype. Similarly, cancer stem-like cells have been isolated using cisplatin and paclitaxel selection from a human ovarian cancer cell line (57). Each of the aforementioned isolation methods has its own strengths and limitations and their combined application can lead to more effective isolation of CSCs with high purity.

Methods for screening target circRNAs. Screening for target circRNAs involves several methodologies, each with unique advantages and limitations:

RNA sequencing (RNA-seq). RNA-seq is a high-throughput method that is particularly powerful for discovering and profiling circRNAs (4,58,59). This technique provides comprehensive detection of both coding and non-coding RNAs, possesses high sensitivity for detecting low-expression circRNAs and enables quantitative comparisons of expression levels across samples. However, the high costs and the

complexity of data processing associated with RNA-seq are significant drawbacks (6). Challenges such as reverse transcription template-switching and ligation artifacts during circRNA-seq library construction can lead to the generation of inaccurately joined cDNA sequences, thus resulting in erroneous circRNA predictions (60). In addition, exon repeats and trans-splicing events in linear mRNA can further contribute to incorrect circRNA predictions (6).

Microarray analysis. As an alternative high-throughput technology to RNA-seq (61), microarray analysis is faster and requires less bioinformatics expertise but is limited to detecting known circRNAs (62). This method is advantageous for its speed and ease of use compared to RNA-seq.

Database screening. Various circRNA databases are available, covering aspects such as tissue and cell specificity [e.g., CircAtlas (63), CIRCpedia (64) and MiOncoCirc (65)], disease associations [e.g., circRNADb (66)], circRNA-miRNA interactions [e.g., MiRanda (67), TargetScan (68) and circBase (11)], circRNA-RNA-binding protein (RBP) interactions [e.g., CircInteractome (69), CSCD (70) and TSCD (12)] and circRNA protein-coding potential [e.g., circRNADb (66)]. Utilizing these databases facilitates the rapid identification and validation of known circRNAs. However, Vromman *et al* (71) have highlighted the limited content overlap between these databases, inconsistencies in circRNA naming and the frequent absence of complete sequences, which can complicate the identification process. It is crucial, therefore, to consider the specific molecular identity of circRNAs carefully, accounting for potential alternative splicing events.

Bioinformatics prediction. With the deepening research into circRNAs, numerous bioinformatics tools have been developed for their prediction, including find-circ (3), CIRI (72), CIRCexplore (73) and MapSplice (74), among others (75-77). However, these tools vary significantly in their algorithms, leading to substantial differences in their prediction outcomes. Hansen *et al* (78) analyzed results from several prediction tools and found only a 16.8% overlap in their predictions, with >40% of the predicted circRNAs identified by only one software tool. They also noted that certain circRNAs predicted by multiple tools were sensitive to RNase R, indicating that these might be artifacts (78). To minimize the risk of missing potential circRNAs and identifying false positives, it is recommended to use multiple prediction algorithms.

Expression profiles of circRNAs in CSCs. High-throughput sequencing technologies have led to the identification of numerous novel dysregulated circRNAs within cancer cells, including CSCs. These circRNAs exhibit differential expression patterns between CSCs and non-stem cancer cells, underscoring their potential roles in the biology of CSCs. The discovery of these novel circRNAs has primarily been facilitated by primary expression profiles obtained through RNA-seq following ribosomal RNA depletion and circRNA microarray analyses (9). For instance, Zhu *et al* (79) analyzed RNA-seq data from 10 hepatocellular carcinoma (HCC) samples along with paired para-cancerous tissues, identifying 3,198 liver-specific circRNAs. Among these, 120 circRNAs were found to be >2-fold downregulated in HCC tissues compared to paired non-cancerous tissues (79). Furthermore, in comparison to a high EpCAM expression group - a marker associated with CSC expansion in HCC (80) - 157 circRNAs were upregulated in the low EpCAM expression group (79). Chen *et al* (55) compared the circRNA transcripts in five matched pairs of HCC adherent cells and CSCs using RNA-seq. They discovered that 193 circRNAs were aberrantly expressed in HCC stem cells relative to the adherent cells. Similarly, Yan *et al* (81), through high-throughput sequencing of three pairs of breast CSCs and their non-stem counterparts, identified a total of 5,727 circRNA candidates, with 27 exhibiting differential expression, including 8 that were upregulated and 19 that were downregulated. Sphere culture, a commonly used method to enrich CSCs, has also been instrumental in identifying circRNA profiles. For instance, Rengganaten *et al* (82) conducted genome-wide sequencing analysis of CSC-enriched colorectal cancer (CRC) spheroid cells and identified 636 circRNAs specific to these cells. Sohn (83) utilized a circRNA-based microarray to examine two epithelial ovarian cancer cell lines and their spheroid-forming derivatives, finding 214 circRNAs with significant differential expression in the ovarian CSCs; 159 of these were upregulated, while 55 were downregulated. In a study by Tao *et al* (84), transcriptome microarray analysis of human bladder CSCs (BCMab1+CD44+) and non-stem bladder cancer (BLCA) cells (BCMab1-CD44-) isolated from three patients revealed 127 differentially expressed circRNAs, with 113 significantly upregulated and 14 downregulated. The findings of RNA-seq and microarray analyses that identify CSC-related circRNAs are summarized in Table II.

3. Function and mechanisms of circRNAs in CSCs

Initially regarded as mere byproducts of splicing errors, circRNAs have emerged as a significant class of regulatory molecules with diverse functions. Notably, they play a crucial role as microRNA (miRNA) sponges, effectively sequestering miRNAs and inhibiting their activity (85). Furthermore, circRNAs interact with RBPs, which significantly impacts gene regulation and the maintenance of cellular homeostasis (86-88). In addition, circRNAs are involved in regulating alternative splicing, transcriptional control and even protein translation (89-91). The role of circRNAs in these complex processes add an additional layer of regulatory complexity within cells. Investigating the functions and mechanisms of circRNAs in CSCs could illuminate key aspects of tumorigenesis and open new avenues for cancer diagnosis and therapeutic strategies (the functions and mechanisms of circRNAs in CSCs are detailed in Tables III-V).

Glioma stem cells (GSCs). Glioma, the most prevalent and aggressive form of tumor within the central nervous system, is associated with a poor prognosis for patients (92). Glioblastoma (GBM), a subtype of glioma, is notably characterized by the presence of GSCs, which exhibit properties akin to stem cells. These GSCs express markers typical of stem cells, such as CD133 and leucine-rich repeat-containing G protein-coupled receptor 5 (LGR5), and are capable of continuous proliferation and multilineage differentiation (93,94). There is growing evidence that a group of RNA molecules, including circRNAs, play significant roles in the

Table II. Overview of circRNAs identified by RNA-seq and microarrays in CSCs.

Samples	CSC separation methods	Special treatment	Detection method	Total circRNAs	Number of differently expressed circRNAs	CircRNAs validated by RT-qPCR	(Refs.)
5 pairs of HCC adherent cells and matched CSCs	Suspension culture	rRNA-depleted and RNase R	RNA-seq	/	193 circRNAs (fold change >2 or <0.5)	9	(55)
3 pairs of BCSCs and matched non-breast CSCs	Sphere culture	rRNA-depleted and RNase R	RNA-seq	5,727	27 circRNAs (8 upregulated circRNAs and 19 downregulated circRNAs, fold change ≥1.8)	6	(81)
3 pairs of GCSCs and MCs	Sphere culture	RNase R	RNA-seq	/	416 circRNAs (203 upregulated circRNAs and 213 downregulated circRNAs)	10	(168)
3 pairs of bladder CSCs and bladder cancer non-stem cell samples	FACS	/	transcriptome microarray	/	127 circRNAs (113 upregulated circRNAs and 14 downregulated circRNAs, fold change >2.0)	6	(84)
Colorectal-TICs and non-TICs (mice)	/	/	RNA-seq	39,258	10,863 circRNAs (fold change >2)	10	(187)
2 pairs of colorectal TICs and non-TICs	Sphere culture	RNase R	RNA-seq	~15,000	8,281 (1,503 upregulated and 636 downregulated)	8	(82)
2 pairs of ovarian CSCs and monolayer cells	Sphere culture	/	circRNA microarray	/	214 circRNAs (159 upregulated circRNAs and 55 downregulated circRNAs, fold change >1.5)	/	(83)

circRNAs, circular RNAs; CSCs, cancer stem cells; HCC, hepatocellular carcinoma; GCSCs, gastric cancer stem cells; MCs, monolayer cells; BCSCs, breast cancer stem cells; FACS, fluorescence-activated cell sorting; TICs, tumor-initiating cells; /, none or unknown; RT-qPCR, reverse transcription-quantitative PCR; RNA-seq, RNA sequencing.

Table III. CircRNAs act as miRNA sponges in CSCs.

CSC type	CSC separation method	CircRNA name	Expression levels in tumors and CSCs	Location	Target miRNAs	Downstream gene	Signaling pathway	Function	(Refs.)
GSCs	Sphere culture	circPTN	Upregulated	Cytoplasm	miR-145-5p	SOX9	/	Promoted cell self-renewal	(96)
GSCs	Sphere culture	circPTPRF	Upregulated	/	miR-1208	YY1	/	Promoted cell proliferation, invasion, self-renewal and tumorigenesis	(97)
GSCs	Sphere culture	circKIF4A	Upregulated	/	miR-139-3p	Wnt5a	Wnt/β-catenin ↑	Promoted cell self-renewal and proliferation	(99)
GSCs	Sphere culture and MACS	circCHAF1A	Upregulated	Cytoplasm	miR-211-5p	HOXC8	MDM2↑/P53 ↓	Promoted cell proliferation and tumorigenesis	(100)
GSCs	Sphere culture	circATP5B	Upregulated	Cytoplasm	miR-185-5p	HOXB5	IL6/JAK2/STAT3 ↑	Promoted cell proliferation, tumorigenesis	(101)
GSCs	Sphere culture	circNDC80	Upregulated	Cytoplasm	miR-139-5p	ECE1	/	Promoted cell growth, viability and self-renewal	(102)
GSCs	Sphere culture	circASPM	Upregulated	Cytoplasm	miR-130b-3p	E2F1	/	Promoted cell proliferation and tumorigenesis	(103)
GSCs	Sphere culture	circMELK	Upregulated	Cytoplasm	miR-593	EphB2	/	Promoted cell viability, growth and self-renewal	(200)
GSCs	Sphere culture	cARF1	Upregulated	Cytoplasm	miR-342-3p	ISL2	VEGFA/ERK ↑	Promoted cell proliferation, invasion and angiogenesis	(112)
GSCs	Sphere culture	circGNB1	Upregulated	Cytoplasm	miR-515-5p/miR-582-3p	XPR1	IL6/JAK2/STAT3 ↑	Promoted cell viability, proliferation, invasion, self-renewal and tumorigenesis	(201)
LCSCs	Sphere culture	CDR1as	Upregulated	Cytoplasm	miR-7-5p	KLF4	/	Promoted cell proliferation and self-renewal	(121)
LCSCs	Suspension culture	circ-MALAT1	Upregulated	Cytoplasm	miR-6887-3p	JAK2	JAK2/STAT3 ↑	Promoted cell self-renewal	(55)
Breast CSCs	Sphere culture	circVRK1	Downregulated	/	miR-153-5p	/	/	Inhibited cell self-renewal and expansion	(81)
Lung CSCs	Drug screening and sphere culture	hsa_circ_0003222	Upregulated	Cytoplasm	miR-527	PHF21B	Wnt/β-catenin ↑	Promoted cell proliferation, self-renewal, invasion and migration	(153)

Table III. Continued.

CSC type	CSC separation method	CircRNA name	Expression levels in tumors and CSCs	Location	Target miRNAs	Downstream gene	Signaling pathway	Function	(Refs.)
Gastric CSCs	MACS	hsa_circ_0051246	Upregulated	Cytoplasm and nucleus	miR-375	YAP1	/	Promoted cell proliferation, self-renewal, migration, invasion and tumorigenesis; inhibited cell apoptosis	(167)

CSCs, cancer stem cells; circRNAs, circular RNAs; miRNA, microRNA; GSCs, glioma stem cells; LCSCs, liver cancer stem cells; MACS, magnetic-activated cell sorting; circPTN, circRNA of pleiotrophin; circPTPRF, circRNA of protein tyrosine phosphatase receptor type F; circKIF4A, circRNA of kinesin family member 4A; circCHAF1A, circRNA of chromatin assembly factor 1 subunit A; circNDC80, circRNA of NDC80 kinetochore complex component; circASPM, circRNA of assembly factor for spindle microtubules; circMELK, circRNA of maternal embryonic leucine zipper kinase; cARF1, circRNA of ARF GTPase 1; circGNB1, circRNA of G protein subunit beta 1; CDR1as, cerebellar degeneration-related protein 1 antisense RNA; circ-MALAT1, circ-MALAT1, circRNA of metastasis associated lung adenocarcinoma transcript 1; circVRK1, circRNA of VRK serine/threonine kinase 1; SOX9, sry-box transcription factor 9; YY1, YY1 transcription factor; Wnt5a, Wnt family member 5A; HOXC8, homeobox C8; E2F1, E2F transcription factor 1; ECE1, endothelin-converting enzyme 1; EphB2, Eph receptor B2; ISL2, ISL LIM homeobox 2; XPR1, xenotropic and polytropic retrovirus receptor 1; KLF4, krüppel-like factor 4; JAK2, janus kinase 2; PHF21B, PHD finger protein 21B; YAP1, Yes1 associated transcriptional regulator; IL6, interleukin 6; VEGFA, vascular endothelial growth factor A; MDM2, MDM2 proto-oncogene; STAT3, signal transducer and activator of transcription 3; ↑, upregulation or activation; ↓, downregulation or inactivation; /, none or unknown.

progression of GBM and in the enhancement of aggressive traits in GSCs (95).

CircRNA of pleiotrophin (circPTN; hsa_circ_0003949), a cytoplasmic circRNA, functions as a molecular sponge for miR-145-5p, thereby facilitating the self-renewal of GSCs (96). CircRNA of protein tyrosine phosphatase receptor type F (circPTPRF; hsa_circ_0012077), has been found to support the self-renewal of GSCs and to foster tumorigenesis through the circPTPRF/miR-1208/YY1 signaling axis (97). CircKIF4A (hsa_circ_0090956), originating from the kinesin family member 4A (KIF4A) gene, is implicated in promoting cell proliferation across various tumors, including gliomas (98). Huo *et al* (99) have proposed that circKIF4A sustains the stemness of GSCs through the miR-139-3p/Wnt5a signaling pathway. CircCHAF1A (hsa_circ_0000876), which is formed by the back-splicing of chromatin assembly factor 1 subunit A (CHAF1A) transcript variant 1 exons 1 and 2, enhances GSC proliferation and tumorigenicity via the FMR1/circCHAF1A/miR-211-5p/HOXC8 feedback loop (100). CircATP5B (hsa_circ_0027068), produced from the *ATP5B* gene, augments cell proliferation by sequestering miR-185-5p, which in turn upregulates homeobox B5 expression in GSCs (101). CircNDC80 is generated by the circularization of exons 14 to 17 of the NDC80 kinetochore complex component (NDC80) gene. It acts as a sponge for miR-139-5p and supports the self-renewal and stemness of GSCs by inhibiting the expression of endothelin converting enzyme 1 (ECE1) (102). CircRNA of assembly factor for spindle microtubules (circASPM; hsa_circ_0015772), found to be upregulated in glioblastoma tissues, contributes to GSC proliferation and tumorigenesis via the CircASPM/miR-130b-3p/E2F1 pathway (103). Beyond their role as miRNA sponges, circRNAs also influence the malignant characteristics of GSCs through interactions with RBPs. Jiang *et al* (104) have demonstrated that circRNA of karyopherin subunit β1 (circKPNB1; hsa-circ_0004796) binds to the SPI1 protein, facilitating its nuclear translocation. As a transcription factor, SPI1 subsequently upregulates tumor necrosis factor α (TNF-α) and activates nuclear factor κB (NF-κB) signaling, which promotes the malignant phenotypes of GSCs (104). CircRNA of ribonuclease P RNA component H1 (circRPPH1; has_circ_0000512), which is upregulated in glioma cell spheres, enhances the stemness of glioma cells (105). Furthermore, Xu *et al* (54) have identified a crucial role for circRPPH1 in sustaining the self-renewal capabilities of GSCs through its interaction with the RBP ATF3, thereby activating the TGF-β1/Smad2 signaling pathway. In addition, Li *et al* (106) reported a feedback loop involving U2AF65, circRNA of non-SMC condensin I complex subunit G (circNCAPG; hsa_circ_0069280) and RREB1 that exacerbates the malignant phenotypes of GSCs by activating the transforming growth factor β (TGF-β) pathway.

In the realm of oncology, angiogenesis is pivotal for tumor growth, progression and metastasis (107). Gliomas, in particular, demonstrate increased angiogenesis, contributing significantly to their rapid proliferation and aggressive behavior (108). Vascular endothelial growth factor (VEGF), a key gene in angiogenesis, is essential for the induction of blood vessel formation during tumor growth and metastasis (109). VEGFA, highly upregulated under hypoxic conditions, is

Table IV. CircRNAs interact with RNA-binding proteins and RNA in CSCs.

CSC type	CSC separation method	CircRNA name	Expression levels in tumors and CSCs	Location	Target proteins (RNA)	Mechanism	Signaling pathway	Function	(Refs.)
GSCs	Sphere culture and MACS	circKPNB1	Upregulated	Cytoplasm	SPI1	Promoted SPI1 protein stability and nuclear translocation	TNF-α/NF-κB signaling ↑	Promoted cell viability, proliferation, invasion and self-renewal	(104)
GSCs	Sphere culture	circRPPH1	Upregulated	Cytoplasm	ATF3	Promoted ATF3 protein stability and nuclear translocation	TGF-β1/Smad2 ↑	Promoted cell proliferation, invasion and self-renewal	(54)
GSCs	Sphere culture	circNCAPG	Upregulated	Cytoplasm	RREB1	Promoted RREB1 protein stability and nuclear translocation	TGF-β1/Smad ↑	Promoted cell proliferation, invasion and self-renewal	(106)
GSCs	Sphere culture	circLRFN5	Downregulated	Cytoplasm	PRRX2	Promoted PRRX2 degradation	GCH1 ↓	Inhibited cell viability and proliferation and promoted cell ferroptosis	(114)
GSCs	Sphere culture	CircRNF10	Upregulated	Cytoplasm	ZBTB48 and MKRN3	Enhanced ZBTB48 stability	HSPB1/ IGF2BP3 ↑	Promoted cell stemness maintenance and proliferation; inhibited cell ferroptosis	(115)
LCSCs	suspension culture	Circ-MALAT1	Upregulated	Cytoplasm	Ribosomes and PAX5 mRNA	Inhibited PAX5 mRNA translation	/	Promoted cell self-renewal	(55)
LCSCs	sphere culture	CircIPO11	Upregulated	Nucleus	TOP1 and GLI1 promoter	Promoted GLI1 transcription	Hedgehog ↑	Promoted cell self-renewal and tumorigenesis	(128)
LCSCs	FACS	Cia-MAF	Upregulated	Nucleus	TIP60 and MAFF promoter	Promoted MAFF expression	/	Promoted cell self-renewal, metastasis and tumorigenesis	(129)
LCSCs	FACS	rtcisE2F	Upregulated	Cytoplasm	IGF2BP2, E2F6 and E2F3 mRNAs	Promoted E2F6/E2F3 expression	Wnt/β-catenin ↑	Promoted cell self-renewal and metastasis	(131)
LCSCs	FACS	mcPGK1	Upregulated	Cytoplasm	PGK1 and TOM40/ TOM70	Drove mitochondrial translocation of PGK1	Wnt/β-catenin ↑	Promoted cell self-renewal and metabolic reprogramming	(134)
GCSCs	Sphere culture	circSLC4A7	Upregulated	Nucleus	HSP90	/	Notch1 ↑	Promoted cell proliferation, migration and invasion	(168)

Table IV. Continued.

CSC type	CSC separation method	CircRNA name	Expression levels in tumors and CSCs	Location	Target proteins (RNA)	Mechanism	Signaling pathway	Function	(Refs.)
Colon TICs	FACS	circCTIC1	Upregulated	Nucleus	NURF complex and c-Myc promoter	Promoted c-Myc transcription	/	Promoted cell self-renewal	(186)
Colorectal-TICs (mice)	FACS and sphere culture	cis-HOX	Upregulated	Nucleus	HOXC10 mRNA	Inhibited KSRP-HOXC10 interaction and promoted HOXC10 stability	Wnt/β-catenin ↑	Promoted cell self-renewal, metastasis and tumorigenesis	(187)
LSCs	MACS	hsa-circ_0003420	Downregulated	/	IGF2BP1mRNA	Inhibited IGF2BP1 expression	/	Promoted cell apoptosis	(195)

CSCs, cancer stem cells; circRNAs, circular RNAs; GSCs, glioma stem cells; LCSCs, liver cancer stem cells; GCSCs, gastric cancer stem cells; FACS, fluorescence-activated cell sorting; MACS, magnetic-activated cell sorting; TICs, tumor-initiating cells; LSCs, leukemia stem cells; circKPNB1, circRNA of karyopherin subunit beta 1; circRPPH1, circRNA of ribonuclease P RNA component H1; circNCAPG, circRNA of non-SMC condensin I complex subunit G; circLRFN5, circRNA of leucine rich repeat and fibronectin type III domain containing 5; circRNF10, circRNA of ring finger protein 10; circ-MALAT1, circRNA of metastasis associated lung adenocarcinoma transcript 1; circIPO11, circRNA of importin 11; circSLC4A7, circRNA of solute carrier family 4 member 7; SPI1, Spi-1 proto-oncogene; ATF3, activating transcription factor 3; RREB1, ras responsive element binding protein 1; PRRX2, paired related homeobox 2; ZBTB48, zinc finger and BTB domain containing 48; MKRN3, makorin ring finger protein 3; PAX5, paired box 5; TOP1, DNA topoisomerase I; GLI1, GLI family zinc finger 1; TIP60, tat-interactive protein 60 kDa; MAFF, MAF BZIP transcription factor F; IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; E2F3, E2F transcription factor 3; PGK1, phosphoglycerate kinase 1; TOM40, translocase of outer mitochondrial membrane 40; HSP90, heat shock protein 90; NURF, nucleosome remodeling factor; c-Myc, cellular myelocytomatosis oncogene; HOXC10, homeobox C10; TNF-α, tumor necrosis factor α; NF-κB, nuclear factor κB; TGF-β1, transforming growth factor β1; Smad2, SMAD family member 2; GCH1, GTP cyclohydrolase 1; HSPB1, heat shock protein family B (small) member 1; IGF2BP3, insulin-like growth factor 2 mRNA binding protein 3; ↑, upregulation or activation; ↓, downregulation or inactivation; /, none or unknown.

Table V. CircRNAs translated into proteins in CSCs.

CSC type	CSC separation method	CircRNA name	Expression levels in tumors and CSCs	Location	Proteins (peptides)	Mechanism	Signaling pathway	Function	(Refs.)
LUAD-SCs	FACS	circ-FBXW7	Downregulated	/	circFBXW7-185AA	Promoted ubiquitination and inhibited stability of β-catenin	Wnt/β-catenin ↓	Inhibited cell renewal and promoted cell sensitivity to Osimertinib	(156)
Bladder CSCs	FACS	circGprc5a	Upregulated	Nucleus	circGprc5a-peptide	circGprc5a-peptide bound to Gprc5a	/	Promoted cell self-renewal and metastasis	(192)

CSCs, cancer stem cells; circRNA, circular RNA; LUAD-SCs, lung adenocarcinoma stem cells; FACS, fluorescence-activated cell sorting; circ-FBXW7, circRNA of F-box and WD repeat domain containing 7; ↑, upregulation or activation; /, none or unknown.

among the most potent inducers of angiogenesis (110). ISL LIM homeobox 2 (ISL2), a LIM/homeodomain-type transcription factor belonging to the Islet-1 family and primarily expressed in primary sensory and motor neurons (111), has been shown to regulate transcriptionally and promote the secretion of VEGFA in GSCs, thus enhancing cell proliferation, invasion and angiogenesis (112). However, the expression of ISL2 in GSCs is modulated by the circRNA of ARF GTPase 1 (cARF1; hsa_circ_0016767) /miR-342-3p/ISL2 axis, which plays a significant role in angiogenesis and tumorigenesis (112).

Emerging evidence suggests that circRNAs are implicated not only in the growth and development of GSCs but also in their metabolic processes. Distinct from apoptosis, necrosis and autophagy, ferroptosis is an iron-dependent regulated form of cell death (113). In ferroptosis, the accumulation of ferrous ions leads to the aggregation of peroxidized lipids in membranes, causing instability or rupture and ultimately resulting in cell death (113). Hsa_circ_0031751, also known as circLRFN5, is an exonic circRNA derived from the back-splicing of exon 13 to exon 19 of the leucine rich repeat and fibronectin type III domain containing 5 (LRFN5) transcript. It has been reported to bind to paired related homeobox 2, inhibiting GTP cyclohydrolase 1 expression, thus suppressing the viability and proliferation of GSCs and promoting their ferroptosis (114). CircRNA of ring finger protein 10 (circRNF10; hsa_circ_0028912), a circular RNA highly upregulated in glioblastoma, is associated with poor prognosis. It can bind to MKRN3, blocking the activity of E3 ubiquitin ligase and enhancing the expression of the transcriptional factor ZBTB48. In addition, by binding with ZBTB48, it upregulates heat shock protein family B (small) member 1 and insulin-like growth factor 2 mRNA binding protein 3 expression, thereby promoting iron metabolism and aiding GSCs in evading ferroptosis (115).

Liver CSCs. Liver cancer remains one of the deadliest malignancies globally, accounting for hundreds of thousands of deaths annually (116). In liver cancer, stem cells characterized by markers such as CD13, CD133, CD90 and EpCAM are implicated in cancer progression, drug resistance, metastasis and recurrence (117). Recent research has highlighted that circRNAs are abnormally expressed and play vital regulatory roles in both cancer cells and CSCs in liver cancer.

Hepatoblastoma (HB), the most common primary malignant hepatic tumor in infants and children, is composed of heterogeneous populations of stem/progenitor cells (118,119). Cerebellar degeneration-related protein 1 antisense RNA (CDR1as; hsa_circ_0001946), a prominent circRNA, has been identified to play a significant role in various diseases, particularly in tumors (120). Chen *et al* (121) demonstrated that CDR1as was highly expressed in CSCs derived from HB cell lines and, through the CDR1as/miR-7-5p/KLF4 axis, contributes to the proliferation and self-renewal capabilities of CSCs within these cells.

HCC is the most prevalent form of liver cancer, accounting for ~70-85% of liver cancer cases worldwide. HCC primarily arises from hepatocytes and is characterized by high invasiveness and a propensity for malignant metastasis (122). CircZKSCAN1, a circular RNA originating from the zinc finger with KRAB and SCAN domains 1 (ZKSCAN1) gene, has been demonstrated by Yao *et al* (123) to inhibit HCC proliferation, invasion and migration. Furthermore, Zhu *et al* (79) reported that circZKSCAN1 is downregulated in $EpCAM^{low}$ HCCs. It inhibits HCC stem cell stemness by competitively binding to fragile X mental retardation protein (FMRP), thereby blocking the interaction between FMRP and cell cycle and apoptosis regulator 1 mRNA, which leads to the suppression of the transcriptional activity of the Wnt signaling pathway (79). Telomerase activity plays a vital role in maintaining genomic stability and cellular longevity.

In liver cancer, the circular RNA of maternally expressed 3 (circMEG3) is expressed at low levels and negatively correlates with the expression of the telomerase-related gene Cbf5, a component of the telomere synthase H/ACA ribonucleoprotein. Jiang *et al* (124) demonstrated that, dependent on HULC, circMEG3 suppresses the expression of Cbf5 by inhibiting the N6-methyladenosine (m6A) methyltransferase METTL3, thereby impeding the growth of liver CSCs.

Significant activation of the JAK/STAT pathway has been observed in tumor stem cells (125). The transcription factor paired box 5 (PAX5), acting as a tumor suppressor, is involved in liver carcinogenesis (126). CircRNA of metastasis associated lung adenocarcinoma transcript 1 (circ-MALAT1; hsa_circ_0002082) is highly expressed in hepatocellular carcinoma stem cells (HCSCs) and functions as a sponge for miR-6887-3p, leading to the upregulation of Janus kinase 2 (JAK2) expression. In addition, it binds to ribosomes and PAX5 mRNA, inhibiting the translation of PAX5 mRNA and thus promoting the self-renewal of HCSCs (55). Unlike GLI family zinc finger 2 (GLI2) and GLI3, GLI1 functions solely as an activator within the Hedgehog (Hh) signaling pathway, which is crucial for tumor initiation and progression (127). Gu *et al* (128) discovered that circRNA of importin 11 (circIPO11) is highly expressed in liver tumor tissues and liver CSCs (CD13+CD133+). They revealed that circIPO11 interacts with topoisomerase 1 (TOP1) to initiate transcription of GLI1, thereby activating the Hh signaling pathway and sustaining the self-renewal of liver CSCs (128). Cia-MAF, another circular RNA robustly expressed in liver cancer and liver TICs, has been shown to contribute to the self-renewal and metastasis of TICs by binding to and activating the transcription factors MAFF promoter through the recruitment of the TIP60 complex to the promoter (129).

A read-through circular RNA (rt-circRNA) is a distinctive type of circRNA formed by coding exons from two adjacent and similarly oriented genes (130). Chen *et al* (131) discovered that a functional rt-circRNA, rtcisE2F, enhances the self-renewal and metastasis of liver TICs by facilitating the interaction between E2F transcription factor 6 (E2F6)/E2F3 mRNA and insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2, m6A reader that maintains mRNA stability), and inhibiting their association with YTH domain-containing family protein 2, a m6A reader that promotes mRNA decay. This interaction increases the stability of E2F6/E2F3 mRNA and prevents its degradation, which is vital for the self-renewal of liver TICs and the activation of the Wnt/β-catenin pathway (131). Traditionally, circRNAs were primarily understood to originate from the nuclear genome. However, recent studies have shown that the mitochondrial genome also encodes a small number of circRNAs, known as mecciRNAs (132,133). Chen *et al* (134) identified a mitochondria-encoded circular RNA, mitochondrial circRNA for translocating phosphoglycerate kinase 1, which inhibits mitochondrial oxidative phosphorylation and promotes glycolysis and the self-renewal of liver TICs by regulating the PGK1-PDK1-PDH pathway.

Breast CSCs (BCSCs). Breast cancer continues to be one of the most challenging malignancies in women, despite advances in targeted therapies, radiotherapy and immunotherapy (135,136). A significant contributor to treatment resistance and disease persistence in this context is the presence of BCSCs, a subset of cells within the tumor that exhibit stem cell-like characteristics (137). Ponti *et al* (138) reported the isolation and *in vitro* propagation of breast cancer-initiating cells, which possess stem/progenitor cell properties, providing a valuable model for studying BCSCs and developing therapeutic strategies. Wright *et al* (139) identified distinct populations of CD44+/CD24- and CD133+ cells with CSC characteristics in Brca1 breast tumors, emphasizing the heterogeneity of BCSCs.

Recent research has found that circRNAs play a significant role in regulating the biological functions of BCSCs. For instance, hsa_circ_002178, a circRNA found to be upregulated in breast cancer tissues and cells, was shown by Li *et al* (140) to support the maintenance of stem cell characteristics in breast cancer cells, as demonstrated by sphere-forming assays and stem cell surface marker analysis. CircRNA of nucleolar and coiled-body phosphoprotein 1 (circNOLC1) previously reported to promote tumorigenesis in prostate and ovarian cancers through sponging miR-647 and binding ESRP1 protein, respectively (141,142), has also been found by Liu *et al* (143) to be involved in BCSC activity and progression via the miR-365a-3p/STAT3 signaling pathway. Additionally, another circRNA, circRNA of VRK serine/threonine kinase 1 (circVRK1), has been identified as an inhibitor of the self-renewal and expansion of BCSCs (81). Circ-Foxo3, a circRNA that promotes apoptosis and inhibits cell proliferation and metastasis, is expressed at low levels in breast cancer spheroidal cells, which may facilitate these cells' evasion of apoptosis (144-146). It is well established that CSCs mediate the metastasis of tumor cells and are associated with a poor patient prognosis (147). Kamalabadi-Farahani *et al* (148) observed that metastatic breast cancer cells have a significantly higher capability of forming spheres, a method used to enrich CSCs, compared to primary breast cancer cells. Furthermore, the expression of cicBIRC6 was significantly upregulated in these metastatic tumor cells, suggesting that cicBIRC6 plays a crucial role in the dynamics of breast CSCs (148).

Lung CSCs. Lung cancer remains a prevalent malignant tumor and a leading cause of cancer-related mortality globally (135). CD133-positive CSCs have been identified in lung cancer, demonstrating both tumorigenic potential and stem-like features (149,150). ALDH1 has also been recognized as a marker for lung CSCs, offering a promising prognostic factor and therapeutic target for lung cancer treatment (151). Beyond traditional markers, studies have indicated that circRNAs play a role in influencing lung CSC properties and mediating lung cancer progression. For instance, circ_0044516 has been found to regulate the miR-136/MAT2A pathway, maintaining lung CSC properties and facilitating lung cancer development (152). Hsa_circ_0003222, highly expressed in lung CSCs, contributes to the progression of non-small cell lung cancer (NSCLC) and the maintenance of stemness via the miR-527/PHF21B/β-catenin axis (153). In addition to their self-renewal and differentiation capabilities, CSCs are implicated in drug resistance and recurrence of NSCLC (154,155). Hsa-circ-0001451, formed by the circularization of exon 3 and exon 4 of the F-box and WD repeat domain containing 7 (FBXW7) gene and termed circ-FBXW7, has been studied by Li *et al* (156). They identified that circ-FBXW7 can be

translated into a short polypeptide, circFBXW7-185AA, which inhibits CSC renewal and reverses resistance to osimertinib in drug-resistant lung adenocarcinoma cells and stem cells by modulating the Wnt pathway through the ubiquitination and inhibitory effects of circFBXW7-185AA on β-catenin. Long-term exposure of lung cancer cells to cisplatin (DDP) can effectively enrich tumor stem cells in NSCLC (157). Zhao *et al* (158) suggested that circRNA CDR1as modulates the enrichment of CSCs in DDP-resistant NSCLC cells by controlling the miR-641/HOXA9 axis, providing new insights into the enrichment of CSCs in DDP-resistant NSCLC cells.

Gastric CSCs (GCSCs). Gastric cancer is a major malignant tumor of the digestive system, ranking fifth in incidence and fourth in mortality among cancers worldwide (159). Previous studies have underscored that the acquisition of CSC-like properties is critical for the development and maintenance of gastric cancer malignancy (160,161). Various cell surface markers, such as CD44 and CD44CD24, which are linked to self-renewal and differentiation properties, have been identified in GCSCs (162,163). The study of circRNAs in relation to GCSCs has attracted significant attention recently. For instance, circ0007360, primarily expressed in the cytoplasm, inhibits the stemness of gastric cancer cells through the circ0007360/miR-762/IRF7 axis (164). Another circRNA, circ-0075305, indirectly disrupts the TCF4-β-catenin complex and downregulates sry-box transcription factor 9 (SOX9) through the miR-708-5p/RPRD1A axis, thereby suppressing the stem cell-like properties of gastric cancer (165). Conversely, Xia *et al* (166) proposed that circFAM73A enhances stem cell-like properties by sponging miR-490-3p to increase the expression of the stem cell factor high mobility group A2 in gastric cancer cells. In addition, hsa_circ_0051246 acts as a sponge for miR-375, promoting the progression of GCSCs via the hsa_circ_0051246/miR-375/YAP1 axis (167). Furthermore, circRNA of solute carrier family 4 member 7 (hsa_circ_0064618), mainly localized in the nucleus, interacts with HSP90 to activate the NOTCH1 signaling pathway, thereby enhancing CSC-like properties in gastric cancer (168).

Colorectal CSCs. CRC ranks as the third leading cause of cancer-related deaths, with ~1.85 million cases and 850,000 deaths annually (169). In CRC, CSCs are identified by specific surface markers such as CD44, CD133 and LGR5 (170-172). These markers are crucial in promoting the malignant behavior of colon cancer (173,174). In addition, emerging evidence indicates that circRNAs play a significant role in the development and progression of colorectal cancer by regulating the behavior and activity of CSCs.

One notable circRNA, circAGFG1, originates from the ArfGAP with FG repeats 1 (AGFG1) gene. It has been recognized as an oncogene in various cancers, including triple-negative breast cancer, NSCLC, ovarian cancer and osteosarcoma (175-178). In CRC, circAGFG1 is known to activate the WNT/β-catenin pathway by modulating the miR-4262 and miR-185-5p/YY1/CTNNB1 axis (179). The knockdown of circAGFG1 leads to a reduction in sphere-forming ability and a decrease in the population of CD133+ cells, underscoring its role in controlling CSCs in CRC (179). Similarly, hsa_circ_0001806 and hsa_circ_0082096 have been found to influence CSC properties and tumor growth in CRCs by sponging different miRNAs (180,181). Another circRNA, circRNA of receptor accessory protein 3 (circREEP3), which is upregulated in CRC tissues, was knocked out to result in suppressed CRC tumorigenesis, metastasis and stem cell-like phenotypes. The underlying mechanism involved circREEP3's recruitment of the chromatin remodeling protein CHD7 to the promoter of the FKBP prolyl isomerase 10 gene, thereby activating it (182). m6A, the most prevalent RNA modification in eukaryotic cells, plays a regulatory role in RNA transcription, splicing, degradation and translation (183). Both m6A modification and circRNAs are implicated in the pathogenesis of various diseases, particularly cancer (184). For instance, m6A-modified circRNA of fibronectin type III domain containing 3B curtails CRC stemness and metastasis via the degradation of ASB6, dependent on ring finger protein 41 (185). Another circRNA, circCTIC1, highly expressed in colon tumors and colon TICs, promotes the self-renewal of colon TICs by recruiting the nuclear remodeling factor complex to the c-Myc promoter, thereby enhancing c-Myc expression (186). Furthermore, Cis-HOX, a circular RNA, regulates the stability of homeobox C10 (HOXC10) mRNA by directly interacting with it, thus preventing KSRP-mediated degradation. This interaction leads to increased HOXC10 expression, which in turn supports the self-renewal, invasion and tumorigenesis of APC-wild type colorectal TICs (187).

Bladder CSCs. BLCA is a prevalent malignant urothelial cancer in men, posing a significant health burden. Recent statistics indicate there were ~549,000 new cases and 200,000 deaths in 2018, with the death rate being about four times higher in men compared to women (188). Advances in understanding bladder CSCs and the role of circRNAs have been pivotal.

C-Myc, a well-established oncogene, is known for its role in maintaining the pluripotency and self-renewal across various stem cell types, including CSCs. Chen *et al* (189) reported that hsa_circ_0068307 influences bladder CSC-like properties via the hsa_circ_0068307/miR-147/c-Myc axis. By contrast, circ_0030586 was found to inhibit cell proliferation and stemness in BLCA by deactivating the ERK signaling pathway through the circ_0030586/miR-665/NR4A3 axis (190). In addition, circSETD3 has been shown to curtail stem cell properties in BLCA via the circSETD3/miR-641/PTEN axis (191). In a transcriptome microarray analysis that compared bladder CSCs with non-stem cells, Tao *et al* (84) identified circRNA_103809 as the most highly expressed circRNA in bladder CSCs. They demonstrated that circRNA_103809 enhances self-renewal, migration and invasion capabilities in BLCA by acting as a sponge for miR-511 (84). Furthermore, Gu *et al* (192) discovered that circGprc5a, which is upregulated in BLCA and bladder CSCs, can encode peptides. CircGprc5a exerts its effects through a peptide-dependent mechanism via the circGprc5a-peptide-Gprc5a axis, promoting CSC self-renewal and metastasis.

Other CSCs. Beyond the regulatory roles of circRNAs in CSCs previously discussed, several studies have highlighted their involvement in other cancer types. For instance, Yang *et al* (193) discovered that cir-CCDC66

(hsa_circ_0001313) was upregulated in renal cell carcinoma (RCC) stem cells and demonstrated that overexpressed cir-CCDC66 promoted RCC stem cell growth and enhanced CSC enrichment. Similarly, Wang *et al* (194) identified that estrogen receptor-β augmented the CSC population by regulating the circPHACTR4/miR-34b-5p/c-Myc signaling pathway in clear cell RCC. In another study, Lin *et al* (195) found that hsa-circ_0003420 induced apoptosis in acute myeloid leukemia stem cells and impaired their stem cell properties by inhibiting insulin-like growth factor 2 mRNA-binding protein 1 levels. Furthermore, Shi *et al* (196) demonstrated that the knockdown of circRNA of phosphatidylinositol-4-phosphate 5-kinase type 1 α (circPIP5K1A) in osteosarcoma cells suppressed sphere formation abilities and reduced the population of CD133+CD44+ cells, indicating its role in controlling CSCs in osteosarcoma.

4. Potential applications of circRNAs in CSCs

As potential biomarkers for CSCs. Specific cell markers, including CD133, CD44, EpCAM and ALDH, have proven valuable for identifying CSCs (197). However, distinguishing true CSCs from non-CSC tumor cells remains challenging because these markers are not uniquely specific to the CSC subpopulation, and certain CSCs may lack these traditional markers (198). Therefore, the search for new markers is crucial for more accurate identification and isolation of CSCs.

CircRNAs exhibit specific expression patterns in CSCs, rendering them promising biomarkers for the identification and characterization of CSCs. For instance, in hepatocellular CSCs, 193 circRNA transcripts were found to be aberrantly expressed compared to adherent cells, with circ-MALAT1 showing significantly higher expression levels in CSCs than in matched adherent cells (55). Profiling circRNA expression in CSCs has led researchers to identify signature circRNA profiles that can distinguish CSCs from non-CSCs across various cancer types, including breast, bladder, colorectal, ovarian and gastric cancers (81-84,168). These circRNA signatures provide valuable insight into the presence, abundance and heterogeneity of CSCs within tumors. Furthermore, multiple circRNAs are highly expressed in both tumors and CSCs, influencing the proportion of CSCs. For instance, circPTN expression in GSCs was ~10-fold higher than in adherent cells, and overexpressed circPTN enhanced the sphere formation ability of these stem cells (96). CircPIP5K1A expression was significantly increased in clinical osteosarcoma tissues and its knockdown reduced the CD133+CD44+ cell population in osteosarcoma cells (196).

Furthermore, the inherent stability and resistance to degradation of circRNAs make them suitable for detection in various clinical samples, such as blood, urine or tissue biopsies. Utilizing circRNAs as biomarkers may enable non-invasive or minimally invasive approaches for detecting and monitoring CSCs, thereby facilitating personalized treatment strategies.

Regulation of CSC self-renewal. Self-renewal is a fundamental characteristic of CSCs, enabling them to maintain their population and contribute to tumor growth and progression. CSCs can self-renew through asymmetric division, which produces both identical stem cells and differentiated progenitor cells (199). Dysregulation of self-renewal processes in CSCs can lead to uncontrolled proliferation and therapy resistance.

Studies have highlighted circRNAs as critical regulators of self-renewal in CSCs by influencing key signaling pathways and molecular processes. These circRNAs function as miRNA sponges, sequestering miRNAs and preventing their interaction with target mRNAs, thus regulating the self-renewal of CSCs. For instance, circPTN, circMELK and CDR1as maintain self-renewal in GSCs and HB-CSCs, by sequestering miR-145-5p, miR-7-5p and miR-593, preventing their negative effects on the key transcription factors SOX9 and KLF4, and oncogenic gene Eph receptor B2 (96,121,200). Similarly, circPTPRF, circNDC80, and hsa_circ_0051246 support the self-renewal capacity of glioma and gastric CSCs by adsorbing various miRNAs, thus inhibiting their degradative impact on target genes such as YY1, ECE1, and YAP1 (97,102,167). Furthermore, abnormal activation of the Wnt/β-catenin and JAK-STAT signaling pathways is associated with enhanced proliferation, differentiation and self-renewal capabilities of CSCs (21). In glioma and lung CSCs, circKIF4A and hsa_circ_0003222 activate the Wnt/β-catenin signaling pathway by sequestering miR-139-3p and miR-527, respectively, thereby fostering CSC self-renewal (99,153). In addition, circ-MALAT1 and circRNA of G protein subunit β1 (circGNB1; hsa_circ_0009362) enhance the self-renewal of liver and glioma CSCs by activating the JAK2/STAT3 pathway through the sequestration of different miRNAs (55,201). This competitive interaction mitigates the inhibitory effect of miRNAs on self-renewal-associated genes, leading to an enhanced self-renewal capacity in CSCs.

CircRNAs can interact with RBPs, significantly influencing cell signaling pathways that govern the self-renewal processes. For instance, circKPNB1 promotes the self-renewal of GSCs by binding to the SPI1 protein and activating the TNF-α/NF-κB signaling pathway (104). Similarly, CircRPPH1 interacts with the ATF3 protein to activate the TGF-β1/Smad2 signaling pathway, supporting the ongoing self-renewal of GSCs (54). Certain circRNAs have been identified that regulate gene transcription or protein translation to enhance CSCs' self-renewal capabilities. CircIPO11 and circCTIC1, for instance, are involved in promoting the transcription of key oncogenes GLI1 and c-MYC by interacting with the proteins TOP1 and BPTF, respectively (128,186). In addition, Circ-MALAT1 has been shown to bind both ribosomes and PAX5 mRNA, inhibiting the translation of PAX5 mRNA and thereby promoting the self-renewal of CSCs (55). There is increasing evidence that certain circRNAs can be translated into functional peptides that contribute to CSC regulation. For instance, circGprc5a has been reported to translate into a peptide that supports the self-renewal of bladder CSCs (circRNAs involved in the regulation of CSC self-renewal are shown in Fig. 2).

In summary, self-renewal is a critical trait of CSCs. CircRNAs modulate this process by acting as miRNA sponges, interacting with RBPs, regulating transcription or translation, and even translating into proteins. Dysregulation of circRNA-mediated self-renewal regulation is implicated

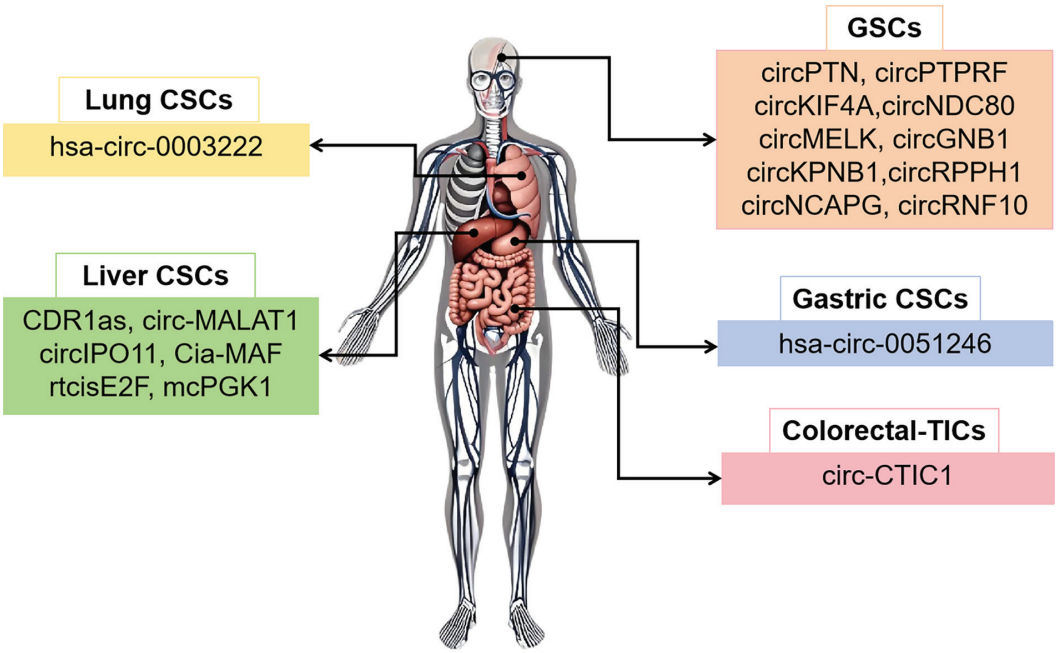

Figure 2. CircRNAs are involved in the regulation of CSC self-renewal. CSCs, cancer stem cells; circRNA, circular RNA; GSC, glioma stem cell; LCSC, liver CSC; TIC, tumor-initiating cell. CDR1as, cerebellar degeneration-related protein 1 antisense RNA; circ-MALAT1, circRNA of metastasis associated lung adenocarcinoma transcript 1; circIPO11, circRNA of importin 11; circPTN, circRNA of pleiotrophin; circPTPRF, circRNA of protein tyrosine phosphatase receptor type F; circKIF4A, circRNA of kinesin family member 4A; circNDC80, circRNA of NDC80 kinetochore complex component; circKPNB1, circRNA of karyopherin subunit beta 1; circRPPH1, circRNA of ribonuclease P RNA component H1; circNCAPG, circRNA of non-SMC condensin I complex subunit G; circRNF10, circRNA of ring finger protein 10.

in cancer progression and therapy resistance. Targeting circRNAs involved in self-renewal regulation could offer novel therapeutic approaches to disrupt CSC populations and enhance the efficacy of cancer treatments.

Potential therapeutic targets for CSC-directed therapies. Research has identified specific circRNAs that are differentially expressed in CSCs compared to non-CSC populations within tumors. These CSC-associated circRNAs are implicated in crucial functions such as tumor initiation, metastasis and therapy resistance. Modulating the expression of these circRNAs through RNA interference, lentiviral vector infection, plasmid transfection or CRISPR/Cas9 editing may prove to be an effective strategy for influencing tumor progression. For instance, administering small interfering RNAs targeting circPTPRF has been shown to inhibit tumor growth and prolong the median survival time in a tumor xenograft model, suggesting that circPTPRF may serve as a viable therapeutic target in GSCs (97). Hu *et al* (201) conducted an orthotopic xenograft study to verify the role of circGNB1 in GSC tumorigenesis. They observed that mice treated with circGNB1 knockdown exhibited significantly smaller tumor volumes and longer survival times compared to the control group. Similarly, Gu *et al* (128) used lentivirus-mediated short hairpin RNA to deplete circIPO11 in liver CSCs and found that this significantly suppressed tumor growth in xenografts. Using a CRISPR/Cas9 approach, Chen *et al* (129) created cia-MAF knockdown cells and discovered that this modification hindered tumor growth and initiation capacities in liver cancer. Of note, they also found that cia-MAF antisense oligonucleotide enhanced the efficacy of 5-fluorouracil by eliminating TICs. Furthermore, targeting circRNAs associated with therapy resistance in CSCs can increase the sensitivity of these cells to treatments and help overcome drug resistance. For instance, Li *et al* (156) demonstrated that circ-FBXW7 suppresses CSC renewal and drug resistance, and that overexpressing circ-FBXW7 could re-sensitize drug-resistant lung adenocarcinoma cells and CSCs to osimertinib, providing a potential therapeutic avenue for treating osimertinib-resistant lung adenocarcinoma.

In addition, circRNAs that influence signaling pathways known to affect CSC biology, such as Wnt (99), Notch (168), NF-κB (104), JAK/STAT (55), TGF/SMAD (106) and Hh signaling (128), can be modulated to alter CSC behavior and enhance their response to anticancer therapies (circRNA-associated signaling pathways in CSCs are shown in Fig. 3). However, research into the role of circRNAs in regulating CSCs is still nascent. Further studies are required to elucidate the precise mechanisms by which circRNAs influence CSC biology and to develop efficient, specific therapeutic interventions.

5. Conclusions

In conclusion, while existing studies emphasize the significant role of circRNAs in CSCs, a comprehensive exploration into the functions of circRNAs in tumor stem cells and the elucidation of their underlying mechanisms are paramount. These in-depth investigations are expected to unveil novel circRNAs that hold potential as promising therapeutic targets. To advance this field, it is essential to identify CSC-specific circRNAs across diverse cancer types using advanced

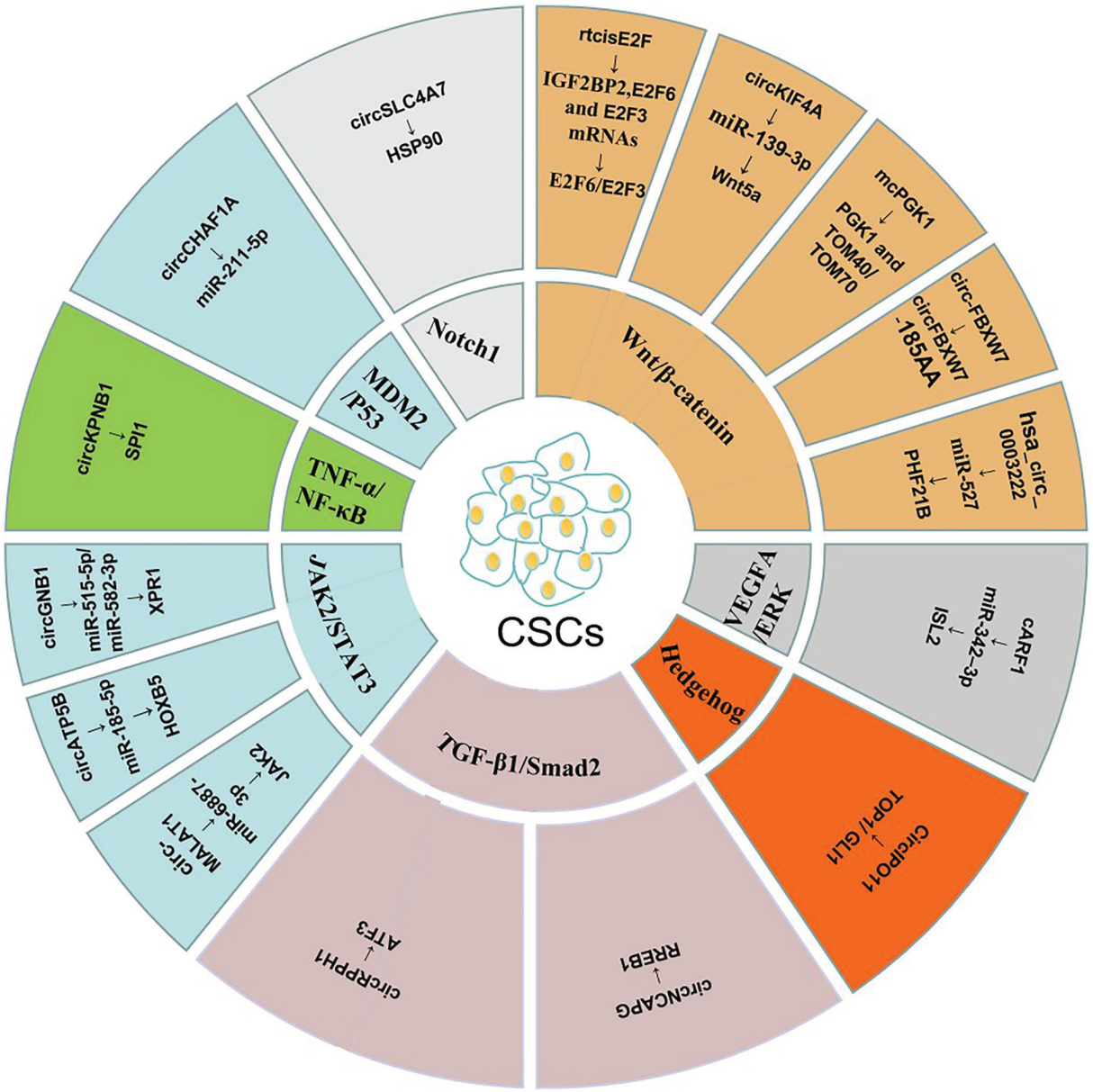

Figure 3. Signaling pathway-associated circRNAs in CSCs. Examples of circRNAs regulating signaling to modulate the biology (e.g., self-renewal, proliferation, invasion, angiogenesis and tumorigenesis) of the CSCs. CSCs, cancer stem cells; circRNA, circular RNA; circSLC4A7, circRNA of solute carrier family 4 member 7; circKIF4A, circRNA of kinesin family member 4A; circIPO11, circRNA of importin 11; circNCAPG, circRNA of non-SMC condensin I complex subunit G; circRPPH1, circRNA of ribonuclease P RNA component H1; circ-MALAT1, circRNA of metastasis associated lung adenocarcinoma transcript 1; circGNB1, circRNA of G protein subunit beta 1; circKPNB1, circRNA of karyopherin subunit beta 1; circCHAF1A, circRNA of chromatin assembly factor 1 subunit A; JAK2, Janus kinase 2; HSP90, heat shock protein 90; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2; E2F3, E2F transcription factor 3; Wnt5a, Wnt family member 5A; PGK1, phosphoglycerate kinase 1; PHF21B, PHD finger protein 21B; ISL2, ISL LIM homeobox 2; TOP1, topoisomerase 1; GLI1, GLI family zinc finger 1; RREB1, ras responsive element binding protein 1; ATF3, activating transcription factor 3; HOXB5, homeobox B5; XPR1, xenotropic and polytropic retrovirus receptor 1; SPI1, Spi-1 proto-oncogene.

technologies like high-throughput sequencing and bioinformatics tools. These efforts will facilitate the discovery of circRNAs specifically enriched or dysregulated in CSCs, shedding light on their unique regulatory roles. Furthermore, delving deeper into the functions of circRNAs in CSCs is crucial. While current knowledge highlights their involvement in self-renewal, proliferation, metastasis and drug resistance, additional research is needed to elucidate their impact on processes such as drug resistance, vascularization and cellular metabolism, including mechanisms like ferroptosis and glycolysis. In addition, gaining mechanistic insights into how circRNAs modulate signaling pathways, interact with miRNAs or proteins and influence gene expression in CSCs will provide a clearer understanding of the intricate regulatory networks governing CSC biology. Ultimately, exploring circRNAs as potential therapeutic targets offers a promising avenue for developing targeted therapies that could specifically disrupt CSC populations and surmount treatment resistance in cancer. By integrating these research endeavors, we can not only advance our understanding of CSC biology, but also pave the way for innovative approaches to combat cancer more effectively.

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Authors' contributions

LY and YY collected the related papers and drafted the manuscript. ZM and DH drafted all tables and figures. ST revised the manuscript. LH and LL participated in the design of the review and helped to draft and modify the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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