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Review

Mechanistic Role of circRNAs in Malignant Characterizations of Cancer Stem Cells

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Abstract

Cancer stem cells (CSCs) are a type of cancer cells in tumor tissues with highly malignant characterizations, including self-renewal, migration, invasion, metastasis and drug/radio therapy resistance. Numerous regulatory RNAs such as circular RNAs (circRNAs) are deregulated in CSCs and involved in stemness properties of these types of cancer cells. Due to the high stability and the half-life, circRNAs provide a significant clinical benefit for their use as diagnostic and therapeutic biomarkers. CircRNAs interact with specific miRNAs, proteins, and DNA regions, and thus can regulate various cellular functions and signaling pathways involved in the diverse biological, physiological, cellular, and pathophysiological processes. This review introduces CSCs and their associated markers. Also, it provides an overview of the biogenesis of circRNAs and emphasizes on the oncogenic and suppressive roles of circRNAs in different types of CSCs. Also, it highlights the mechanistic roles of circRNAs as miRNA sponger or/and protein decoy in this type of cancer cells. Understanding how circRNAs affect cellular processes at a molecular level holds significant potential for both diagnostic and therapeutic approaches in cancer treatment.

1. Introduction

Cancer is the second most common cause of mortality globally, characterized by unregulated cell proliferation [1]. Globally, it was estimated that nearly 10 million people died from cancer, and around 20 million new cases were detected in 2022. A significant increase has been observed in cancer incidence, reaching an estimated 35 million cases by the year 2050 [2]. Tumor development and malignancy are driven by genetic and epigenetic alterations arising from genomic instability. A large number of oncogenes and tumor suppressor genes (TSGs) promote the malignant characterizations of cancer through dysregulation of recognized molecular mechanisms of signaling pathways, including MAPK, PI3K, Notch, Hedgehog and Wnt/β-catenin signaling pathways [3-5].

While traditional cancer treatments, including surgery, hormone therapy, radiotherapy and chemotherapy are effective for some patients, cancer recurrence and unpredictable side effects are observed in most cases [4,6]. CSCs are one of the major contributors to cancer recurrence [7]. Even the use of radiation therapy can convert differentiated breast cancer cells back into cancer stem cells due to the expression of specific stemness genes such as Oct4, Sox2 and KLF4 induced by radiation [8]. This cellular heterogeneity highlights the need for targeted therapies that address the specific properties of CSCs [2]. Numerous regulatory RNAs such as noncoding RNAs have aberrant expression in CSCs and involved in stemness properties of these types of malignant cells. Recently, it has been explored that a newly discovered category of non-coding RNA (ncRNA) molecules known as circular RNAs (circRNAs), exhibit abnormal activity in CSCs and contribute to the aggressive nature of the cancer [9]. Researchers are developing novel therapeutic strategies according to personalized medicine. These approaches include immunotherapy and therapies that target specific biomarkers. In addition, they are designing and decorating nanostructures in combination with nanomaterials to specifically deliver therapeutic agents into cancer cells and CSCs [2,10-15]. However, cancer remains ongoing global health concern, offering continuous research and development of new treatments.

This review discusses the CSCs and their markers. Also, it summarizes the biogenesis of circRNAs and the oncogenic and suppressive roles of circRNAs in different types of CSCs. Also, the following highlights the regulator roles of circRNAs as miRNA sponger or/and protein decoy in the expression of genes related to stemness phenotypes of CSCs. Understanding the molecular mechanistic roles of circRNAs in cellular pathways and malignancy provides significant potential tools for both diagnostic and therapeutic approaches in cancer treatment.

2. Cancer Stem Cells (CSCs)

In the last ten years, a series of cancer cells with stem cell-like characteristics have been identified and studied, playing an important role in cancer progression, chemotherapy resistance, radiation therapy, and disease relapse. These cells, which constitute less than two

percent of cancer cells, emerge when tissue homeostasis breaks down, with the potential for unregulated survival and growth and a tendency to differentiate into various cell types. This small population of cancer cells causes the growth and metastasis of cancer cells and are also referred to as tumor-initiating cells (TICs) [16,17]. CSCs exhibit highly malignant characterizations such as self-renewal, migration, invasion, metastasis, angiogenesis, epithelial-mesenchymal transition (EMT) and chemo/radiotherapy resistance abilities [7]. Unlike normal stem cells, cancer stem cells have dysregulated signaling pathways that drive their uncontrolled proliferation and tumor formation. Malignant characterization of CSCs are mediated by activation of several signaling pathways such as MAPK, PI3K/Akt/NFκB, TGF-β, Wnt/β-catenin, Hedgehog and Hippo signaling pathways [7].

One of the key characteristics of CSCs is their ability to express specific markers. These markers can be proteins, genes, or surface molecules that are unique to CSCs and help researchers identify and target these cells for more effective therapy. By understanding the markers that are expressed on CSCs, scientists can develop targeted therapies that specifically eliminate these types of cancer cells without effecting on normal cells [18].

2.1 CSC Markers

Several markers have been identified on CSCs based on the different types of cancer, including CD44, CD133, ALDH1, and EpCAM. CD44, a cell surface receptor, interacts with hyaluronic acid (HA) and extracellular matrix proteins like osteopontin (OPN) and matrix metalloproteinases (MMPs). Research suggests that CD44 collaborates with receptor tyrosine kinases (RTKs) to regulate crucial processes in CSCs, including proliferation, cell adhesion, and migration [7]. Furthermore, CD44 plays a role in several signaling pathways, such as Rho GTPases, Ras-MAPK, and PI3K/AKT. These pathways are implicated in regulating cell adhesion, migration, invasion, and EMT, highlighting the multifunctional role of CD44 in cancer progression [7]. The ALDH enzyme plays a crucial part in the development of stem cells by facilitating the conversion of aldehydes within cells [19]. EpCAM is a surface protein crucial for the adhesive, proliferative, migratory, and invasive properties of CSCs. This functionality is mediated through the Wnt signaling pathway. A regulated process known as intramembrane proteolysis, involving ADAM17 and Presenilin-2 (PSEN2) enzymes, cleaves EpCAM into its intracellular domain (EpICD). Upon interaction with Four and a half LIM domains protein 2 (FHL2) and β-catenin, EPICD forms a complex that translocates into the nucleus. This complex subsequently activates genes linked to the stem cell-like properties [7]. CD133, also recognized as prominin-1, plays a significant role in CSCs. CD133 is involved in signaling pathways, such as the Wnt/β-catenin and PI3K-Akt pathways, which are known as critical signaling pathways for cell growth and survival. It also has influence in processes relating to apoptosis, and angiogenesis [20]. These markers are used to isolate and characterize CSCs in vitro and in vivo studies as well as clinical trials, allowing researchers to investigate their role in tumor initiation and progression. By targeting these markers, researchers hope to overcome therapy resistance and develop more effective treatments that can eradicate CSCs and prevent tumor recurrence [21].

2.2 Monoclonal Antibodies and Emerging Therapies

Recent advances have led to develop novel therapies that specifically target these cells. For example, monoclonal antibodies, targeting specific markers on CSCs have shown promising preclinical results [18]. Recent research has demonstrated that monoclonal antibodies against IGF receptor I, EpCAM, CD44, CD47, CD123, CD133, and engineered antibody constructs targeting these CSC-specific proteins show effectiveness against CSCs in preclinical models. Furthermore, some of these antibodies have exhibited antitumor activity in clinical trials, providing a promising new therapeutic approach for cancer treatment [18]. However, challenges remain in developing effective therapies that target CSCs.

2.3 Challenges in CSC Targeting

One major challenge is the heterogeneity of CSCs within tumors, which can vary in their marker expression and response to therapy [22]. Furthermore, the plasticity of CSCs allows them to adapt and evade cancer treatment, leading to therapy resistance and cancer progression [23]. It is imperative to further investigate the molecular mechanisms that promote CSCs behavior and the development of new therapeutic strategies in order to address these challenges. While challenges remain in developing targeted therapies for CSCs, continued research in this field holds great promise for improving outcomes of treatment. Therefore, CSCs and their markers play a crucial role in tumor initiation, migration, invasion, EMT, angiogenesis and chemo/radiotherapy resistance.

In addition to surface markers, CSC behavior is tightly regulated at the molecular level by ncRNAs, which orchestrate gene expression programs involved in stemness and malignancy [24].

3. Non-coding RNAs

While only a small percentage (3%) of the human genome is transcribed into protein-coding mRNA, approximately 75% is transcribed into various types of ncRNA. These ncRNAs are categorized based on their length, structure, and location. Three major classes of ncRNA play significant roles in cancer development: miRNA, long non-coding RNA (lncRNA) and circRNA.

3.1 MiRNAs

MiRNAs are small non-coding RNA molecules playing a crucial role in negative regulation of gene expression. MiRNAs were discovered initially in C. elegans, and then have been found in various organisms, including mammals, plants, and viruses [3]. These tiny molecules bind to the 3' UTR of target mRNAs, leading to either translational suppression or mRNA degradation,

depending on partial and complete complementary, respectively [25]. One miRNA can regulate a large number of mRNAs, and one mRNA can be targeted by various miRNAs, creating a complexity in the miRNA mediated regulatory networks. Furthermore, dysregulation of miRNA expression is correlated with various diseases, particularly cancer. MiRNAs are implicated in essential biological processes such as cell proliferation, differentiation, angiogenesis, drug resistance, invasion, metastasis and apoptosis [3]. Research analyzing patterns of miRNA expression in healthy tissues against cancerous tissues have revealed significant differences in the expression levels of miRNAs in these types of tissues. These aberrant miRNA expression levels are implicated in driving key characteristics of tumor cells as well as CSCs [26]. By targeting both oncogenes and tumor suppressor genes, miRNAs affect stemness processes such as self-renewal, angiogenesis, proliferation, apoptosis, cell cycle regulation, EMT, metastasis, and drug resistance [27]. Due to their abilities to target multiple genes as either tumor suppressor or oncogenic miRNAs, they present a potential therapeutic approach for cancer treatment and targeted therapies through influencing a wide range of biological processes [28].

3.2 LncRNAs

LncRNAs are considered as a class of RNA molecules exceeding 200 nucleotides in length that are not encoded into proteins. Their complex structure enable them to interact with DNA, RNA, and proteins [2]. In CSCs, lncRNAs support stemness features through competing endogenous RNA (ceRNA) mechanism by binding to miRNAs, preventing them from interacting with their target mRNA molecules [29]. Also, lncRNAs are implicated in modulation of protein activity and localization, participation in genomic imprinting, modification of chromatin structure, thereby impacting various biological processes such as cell proliferation, differentiation, metastasis, invasion, angiogenesis, EMT and drug/radiotherapy resistant through regulation of stemness-related transcription factors such as OCT4, SOX2 and NANOG in CSCs [29,30].

Both lncRNAs and circRNAs exceed 200 nucleotides in length. While lncRNAs are linear, circRNAs form circular structures. Both originate from different parts of gene, including exons, introns, intergenic regions, and untranslated regions. They have special and complex structure that allow these RNAs to interact with DNA, RNA, and proteins. These RNAs can regulate the pattern of genes expression in different physiological and pathological conditions. These RNAs regulate gene expression through multiple mechanisms. They can act as decoys for miRNAs, preventing the degradation of target mRNAs. They can also modulate transcription factors, influencing gene expression by controlling promoter binding. Furthermore, they can function as scaffolds, enabling interactions between proteins to initiate signaling pathways downstream. Recent studies suggest that circRNAs may also contribute to epigenetic regulation of chromatin, thereby impacting gene expression.

NcRNAs are widely acknowledged for their critical role in regulating gene expression across different biological activities, including epigenetic modification, transcription, post-transcriptional processing, and translation. Mechanistic function of ncRNAs is detected in both normal physiological processes and disease [31-33]. The evidence demonstrates that ncRNAs, such as miRNAs, lncRNAs and circRNAs implicated in stemness properties and the maintenance of CSC populations. A newly recognized group of endogenous RNAs, circRNAs are being studied extensively and have recently drawn a lot of attention from researchers [34].

3.3 CircRNAs

CircRNAs represent single-stranded RNAs, containing covalently closed 3′ and 5′ ends. They display a varied range of sizes, from 100 nt to several kb. However, the majority of circRNAs are shorter than 1000 nt, with a median length of around 530 nt. This structure provides greater stability than linear RNA. Due to the high stability and the half-life, circRNAs provide a significant clinical benefit for their use as diagnostic and therapeutic biomarkers. CircRNAs have been found to bind specific RNAs, proteins as well as specific DNA regions. This interaction ability allows circRNAs to affect a wide range of cellular processes, encompassing translation, transcription, splicing, and other fundamental biological functions. They also modulate various signaling pathways and participate in diverse biological, physiological, cellular, and pathophysiological processes. Research has shown that circRNAs have a critical role in disease development, tissue homeostasis, and cell differentiation [33]. Furthermore, the expression of circRNAs typically does not correlate with their parental genes. This suggests that they are either a product of the regulated alternative splicing or a byproduct generated during the process of mRNA splicing [34]. CircRNAs show distinct expression profiles in CSCs and play key roles in their malignant behavior. Consequently, they may be suggested as a promising diagnostic biomarkers and therapeutic targets.

3.3.1 Biogenesis of circRNAs

CircRNAs are produced through pre-mRNA splicing, with the spliceosomal machinery. One of the steps in the synthesis of circRNAs is back-splicing that is catalyzed by spliceosomes. This occurs when a splice donor site located later in the RNA sequence connects directly to a splice acceptor site positioned earlier in the sequence, resulting in a closed circular structure. Spliceosomal machinery creates canonical splice signals that aid in the elimination of intronic sequences to produce circRNAs [35,36]. This model referred to the "lariat-driven circularization", suggests that circRNAs originate from lariat intermediates generated during the splicing process. Subsequent internal splicing or debranching of these lariats can give rise to various types of circular transcripts [37]. Furthermore, certain enzymes, such as ribozymes I and II, may be implicated in catalyzing back-splicing [38].

On the other hand, complementary flanking elements play a role in circRNA production. This complementary material is likely located within an intron and facilitates the formation of a circular structure by drawing the splice sites closer together. This mechanism, referred to as the intron-pairing model, facilitates circularization, proposes that the hybridization of nearby introns brings the splice sites together. The ALU element frequently plays a role in this process due to its complementary nature [37].

Based on their source, circRNAs can be divided into three distinct groups: exonic circRNAs (EcircRNAs), intronic ciRNAs (IciRNAs), and exon-intron circRNAs (EIcircRNAs). EcircRNAs arise from a process called exon skipping, where an exon is looped back upon itself, forming a structure known as a lariat. This exon facilitates the elimination of intervening intron sequences through internal splicing [39]. IciRNAs are generated from intron lariats that evade degradation by debranching enzymes [22,38]. EIcircRNAs share a similar formation mechanism with EcircRNAs but incorporate intron retention. Consequently, these circRNAs encompass both exonic and intronic sequences [37].

3.3.2 Molecular Functions of circRNAs

MiRNAs have been exhibited to regulate negatively the expression of genes in many disorders, including cancer [40]. MiRNAs inhibit the expression of genes by suppressing translation or promoting degradation of mRNA based on the complete or incomplete base pairing with the 3'UTR of a specific target mRNA in cancer cells and CSCs [3,32,41]. CircRNAs have a number of microRNA response elements (MREs), enabling them to inhibit miRNA activity through making complementary base pairing and subsequently enhance the expression of genes regulated by these miRNAs (Figure 1). Furthermore, circRNAs possess the capability to temporarily sequester miRNAs, thereby influencing the expression patterns of miRNA-target genes involved in the development and malignant properties of cancer cells [42]. In recent years, the concept of miRNA sponges has emerged as a prominent model for understanding circRNA function, demonstrating their capacity to regulate miRNA activity. Notably, the intricate interplay between circRNAs, miRNAs, and mRNAs forms complex networks that play a crucial role in the development of cancer [43]. MiRNA sponger role of circRNAs can be confirmed by bioinformatics analysis and prediction of binding sites between circRNAs and miRNAs at the first stage of data analysis. Then, experimentally, treatment with a miRNA mimic resulted in decreased luciferase activity associated with circRNAs in CSCs, demonstrating the miRNA sponger role of circRNAs in these types of cancer cells. Furthermore, RNA pull down assays verify the direct interaction between circRNAs and miRNAs in CSCs [44,45].

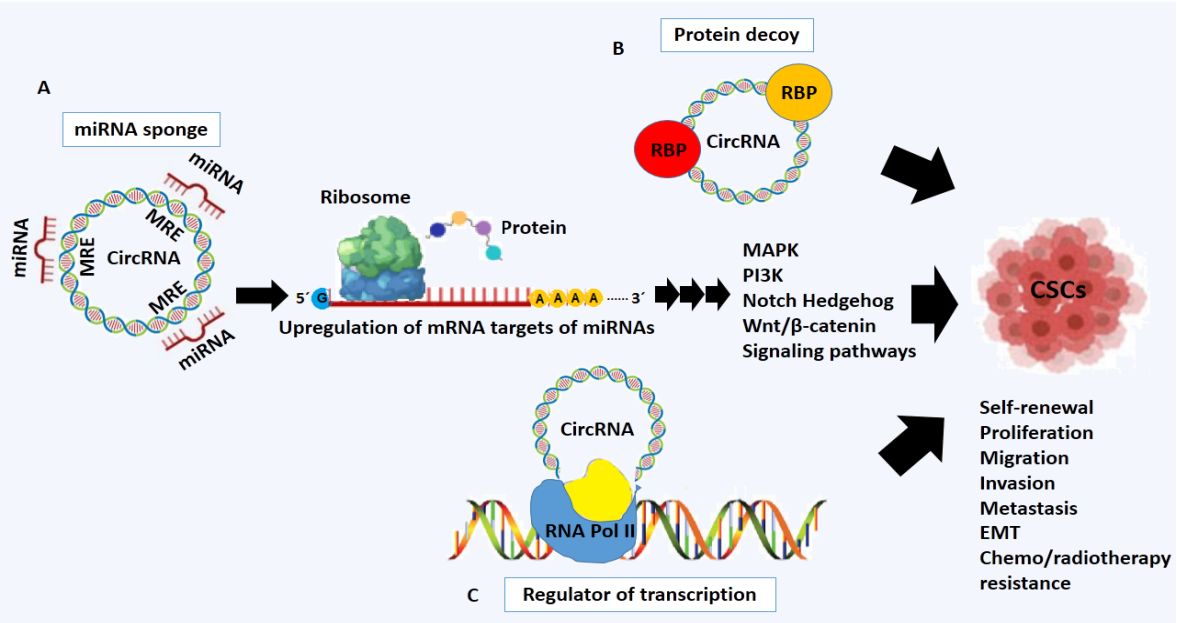

Figure 1. Biological role of circRNAs in CSCs. A) As a miRNA sponge, B) As a protein decoy, C) As a regulator of transcription

On the other hand, circRNAs have the ability to be translated, despite their deficiency in key components for cap-independent translation, including a 5′ cap and poly(A) tail. Adding m^{6}A RNA modification to the 5′UTR of circRNAs may lead to translation [46].

New studies have shown that a group of circRNAs can act as decoys, scaffolds, and recruiters for proteins and regulators of transcription in different physiological and pathological conditions [47-49] (Figure 1). CircRNAs exhibit specific interactions with RNA-binding proteins (RBPs), contributing to various biological processes. RBPs, characterized by the presence of one or more RNA-binding domains, are crucial regulators of gene expression at every stage, from transcription and pre-mRNA splicing to RNA modification. Understanding the functions of these RBPs is essential for comprehending complex post-transcriptional gene regulatory networks [42] (Figure 1). circRNAs have some secondary structures, suggesting that they may associate with some specific proteins to perform their biological functions. RNA pull down assay followed by Mass spectrometry can be used to investigate possible associated proteins of

circRNA in cancer cells and CSCs. The interaction of circRNAs with proteins is further confirmed by Western blot. RNA Composer to create the 3D structure and NPDock is also applied to calculate the molecular docking between circRNAs and proteins. Co-localization of circRNAs with proteins is more verified by immunofluorescence staining in cancer cells and CSCs [50]. When circRNAs interact with proteins, they can change the interaction patterns of proteins with each other, inhibit proteins from interacting with DNA or RNA, bring transcription factors to chromatin, recruit modifying enzymes to chromatin, bring chromatin remodelers, modulate RNA stability and translation as well as translocating proteins into the nucleus [47-49]. In addition, the interactions between different proteins and the same circRNA can occur in diverse ways, while distinct circRNAs may interact similarly or differently with the same proteins, ultimately playing critical roles in a various biological processes and disease development [51].

3.3.3 Oncogenic Role of circRNA in CSCs as a miRNA Sponger

There have been multiple studies investigating the oncogenic roles of various circRNAs as a miRNA sponger in different types of CSCs [44,52,53]. It has been verified that circular RNA nucleolar and coiled-body phosphoprotein 1 (circNOLC1) is overexpressed in breast cancer tissues and promotes CSC properties, such as proliferation, invasion, migration, and mammosphere formation. CSC promoting role of circNOLC1 is mediated by overexpression of vimentin, ATP-binding cassette G2 (ABCG2), c-Myc, B cell-specific Moloney murine leukemia virus integration site 1 (Bmi1), and SRY-box transcription factor 2 (Sox2) [44]. Mechanistically, CircNOLC1 promotes CSC self-renewal and migration by sponging *miR-365a-3p*, which depresses signal transducer and activator of transcription 3 (STAT3), a key transcription factor in the JAK/STAT pathway known to regulate stemness. This *miR-365a-3p*/*STAT3* axis is crucial for circNOLC1's function in promoting CSC activity [44]. STAT3 can induce the expression of genes such as CD133 involved in cell cycle progression and inhibit apoptosis, thereby promoting CSC proliferation, survival, metastasis and drug resistance [54,55]. In addition, it has been reported that propofol, an anesthetic agent has an inhibitory effect on the expression of STAT3 and circNOLC1. Propofol inhibits circNOLC1 expression through suppressing the expression of STAT3 in a feedback mechanism, thereby, attenuating breast cancer stem cell (BCSC) properties (Figure 2). These findings suggest that propofol may have therapeutic potential in breast cancer treatment by targeting the circNOLC1/*miR-365a-3p*/*STAT3* pathway [44].

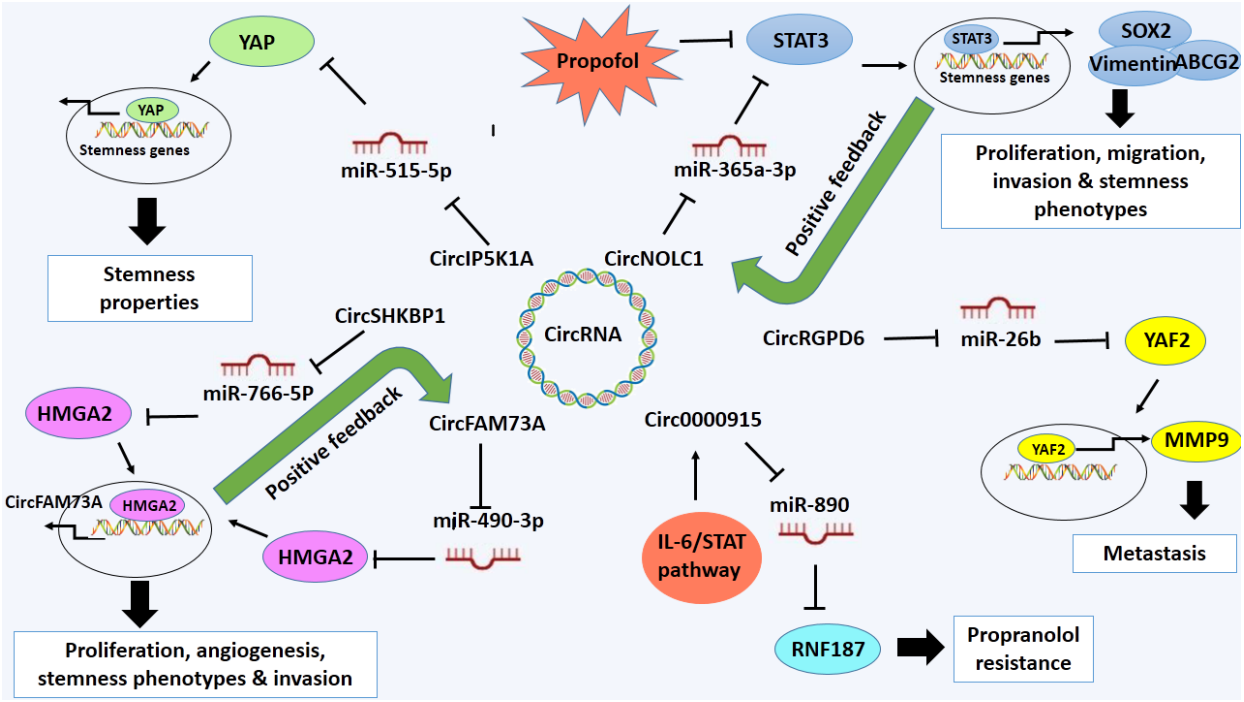

Figure 2. Oncogenic role of circRNAs as miRNA spongers in CSCs.

One of the other circRNAs overexpressed in breast cancer and BCSCs is circRGPD6 [53]. CircRGPD6 plays a role in maintaining the stem cell-like characteristics of BCSCs. A nanoparticle delivery system, TV-circRGPD6, has developed to specifically increase circRGPD6 expression in BCSCs. This approach successfully inhibits markers of stemness both alone and in combination with the chemotherapy drug, docetaxel. Oncogenic role of circRGPD6 is attributed by regulating the *miR-26b*/ YY1 Associated Factor 2 (YAF2) pathway, which is involved in metastasis [53]. YAF2 is a transcription factor involved in the expression of metastasis-related genes, including MMP9 [56] (Figure 2). High expression of circRGPD6 and *YAF2* are correlated with better prognosis in breast cancer patients. It suggests that targeted delivery of circRGPD6 using the TV-circRGPD6 nanoparticle could be a potential new approach for treating metastatic breast cancer [53].

Moreover, circPIP5K1A is highly expressed in osteosarcoma tissues and promotes CSC properties, contributing to tumor growth, invasion, and metastasis [52]. Oncogenic role of circPIP5K1A in mediated by suppressing *miR-515-5p*, which leads to increased expression of the *YAP*, a *miR-515-5p* target gene and a well-known driver of CSC characteristics [52] (Figure 2). Yes-associated protein (YAP) is a crucial downstream effector and transcriptional co-activator, phosphorylated by the regulatory kinases, LATS1/2 and MOB1A/B in the Hippo signaling pathway. When the Hippo pathway is "off" due to signals promoting cell growth and proliferation, LATS1/2 and MOB1A/B kinases are not active, and YAP remains unphosphorylated. Unphosphorylated YAP can then translocate into the nucleus and express genes involved in proliferation, migration, angiogenesis and chemotherapy resistance [7]. It proposes that targeting circPIP5K1A could be a promising therapeutic strategy for osteosarcoma treatment by inhibiting cancer stemness and tumor growth.

In addition, oncogenic role of circular RNA SHKBP1 (circSHKBP1) has been investigated in laryngeal squamous cell carcinoma (LSCC) [57]. The researchers have found that circSHKBP1 is overexpressed in LSCC cells and CSCs. They have demonstrated that circSHKBP1 acts as a competing endogenous RNA, sponging *miR-766-5p* and subsequently upregulating High-mobility group AT-hook 2 (*HMGA2*), a target gene of *miR-766-5p*. HMGA2 is implicated in the regulation of gene expression. In CSCs, HMGA2 is involved in regulating the stemness properties of cells such as self-renewal, migration, invasion, and metastasis [58] (Figure 2). Silencing circSHKBP1 inhibits LSCC cell proliferation, invasion, angiogenesis, and stemness. Furthermore, the study confirms that *miR-766-5p* suppression or *HMGA2* overexpression can converse the tumor-suppressive effects of circSHKBP1 knockdown. Therefore, it establishes circSHKBP1 as a potential oncogenic driver in LSCC by regulating the *miR-766-5p*/*HMGA2* axis and suggests it as a promising therapeutic target for this malignancy [57].

Moreover, the highly expression of circRNAs has been observed in gastric cancer stem cells [59]. Elevated circFAM73A expression has been found in gastric cancer tissues and CSCs. The experiments have been demonstrated that CircFAM73A is associated with increased proliferation, migration, and drug resistance in CSCs. CircFAM73A acts through a positive feedback loop involving *miR-490-3p*/*HMGA2* regulation [59] (Figure 2).

CircRNAs can also play a critical role in drug resistance of CSCs. Circ0000915 is overexpressed in propranolol resistant CSCs derived from infantile hemangiomas (IH) [60]. The researchers have found that depleting circ0000915 enhances the sensitivity of IH-derived stem cells to propranolol. Mechanistically, circ0000915, induced by the IL-6/STAT3 pathway, acts as a sponger of *miR-890*, leading to increased expression of *RNF187*, a target gene of *miR-890* [60]. RNF187 acts as an E3 ubiquitin ligase and ultimately promote signaling pathways involved in cell growth and survival, EMT, angiogenesis and drug resistance in cancer [61] (Figure 2). These findings suggest that targeting the IL-6/STAT3/Circ_0000915/*miR-890*/*RNF187* axis could be a possible therapeutic strategy for patients with propranolol resistant IH [60].

3.3.4 Oncogenic Role of circRNA in CSCs as a Protein Decoy

In addition to miRNA sponger, circRNA can also act as protein decoy in CSCs [50,59,62]. The research demonstrates that circIPO11 is overexpressed in hepatocellular carcinoma tissues and liver cancer stem cells, contributing to their self-renewal and tumor initiation [50]. Mechanistically, circIPO11, as a protein decoy, interacts with topoisomerase I (TOP1), leading to increased recruitment of TOP1 on GLI1 promoter, thereby, increases the expression of GLI1. Domain mapping analysis has been verified that the NTD domain of TOP1 is required for binding to segment 31–94 nt of circIPO11, suggesting direct interaction of circIPO11 with TOP1. GLI1 is an important molecule of the Hedgehog signaling pathway, which is known to promote cancer development (Figure 3). The study confirms that targeting circIPO11 with antisense oligonucleotides, in combination with a TOP1 inhibitor, camptothecin (CPT), effectively suppresses HCC growth, suggesting a potential therapeutic strategy for this type of cancer [50].

One of the other circRNAs overexpressed in liver cancer stem cells is cia-MAF [62]. It promotes cell growth, self-renewal, and metastasis of liver cancer stem cells. Cia-MAF is able to interact with v-maf musculoaponeurotic fibrosarcoma oncogene homolog F (*MAFF*) gene promoter and recruit a protein complex, TIP60, promoting the expression of MAFF [62]. MAFF is a transcription factor implicated in the development and progression of several types of cancer through regulating the expression of genes related to self-renewal, differentiation, and chemotherapy resistance [63] (Figure 3). Inhibition of cia-MAF reduces the stemness properties of liver cancer stem cells and development of tumor. Therefore, it highlights the importance of cia-MAF in regulating liver cancer stem cells and suggests it as a potential therapeutic target for liver cancer treatment [62].

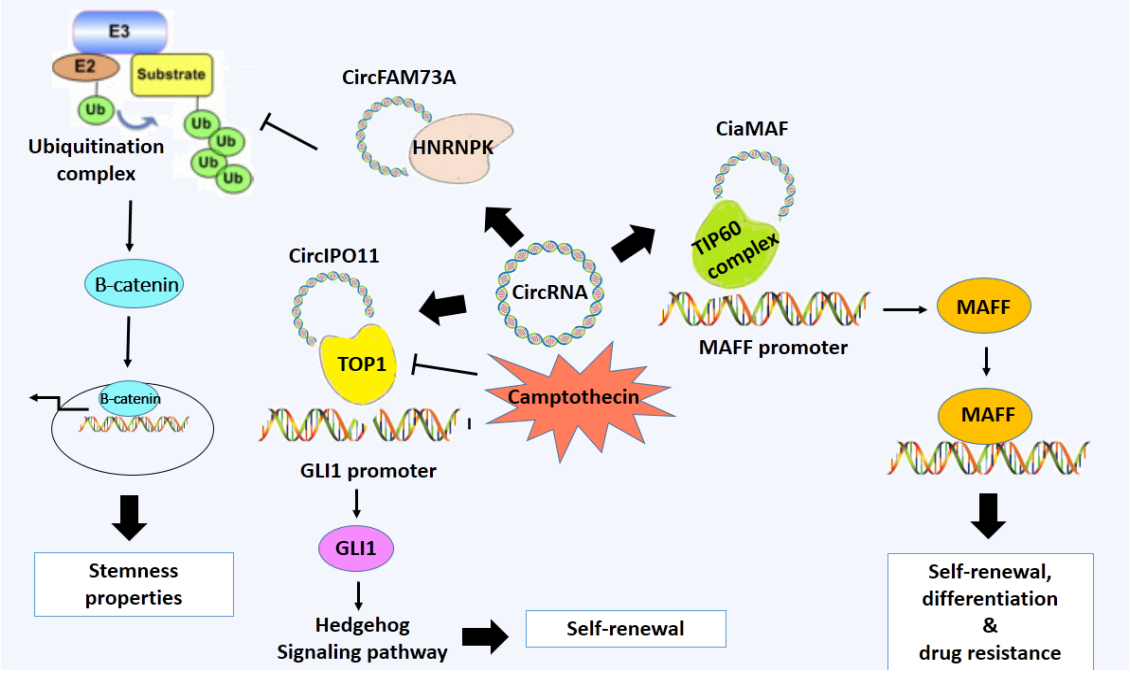

Figure 3. Oncogenic role of circRNAs as protein decoy in CSCs.

In addition to miRNA sponger, circFAM73A acts as a protein decoy [59]. The oncogenic role of circFAM73A is mediated by recruitment of Heterogeneous Nuclear Ribonucleoprotein K (HNRNPK) protein, leading to β-catenin stabilization through inhibiting proteasome-mediated degradation [59] (Figure 3). HNRNPK can also interact with other proteins that stabilize Beta-catenin, such as Axin or Adenomatosis Polyposis Coli Protein (APC). This can indirectly contribute to increased Beta-catenin protein levels [64]. It research highlights the importance of circFAM73A in gastric cancer progression and suggests its potential as a therapeutic target [59].

3.3.5 Tumor Suppressive Role of circRNAs in CSCs

On the other hand, several circRNAs show tumor suppressor roles in different types of CSCs [65]. It has been reported that circSETD3 show a significant decreased expression in bladder cancer. Lower expression levels of circSETD3 is correlated with more aggressive tumor characteristics, including larger size, advanced stage, lymph node metastasis, and poorer prognosis [65]. The experiments have demonstrated that enhanced expression of circSETD3 suppresses malignant properties of bladder cancer, such as proliferation, migration, EMT, and stemness. Mechanistically, circSETD3 acts as a sponger for *miR-641*, thereby preventing it from inhibiting PTEN expression. PTEN acts as a phosphatase and inhibitor of PI3K/AKT signaling pathway. This results in increased PTEN activity, which ultimately suppress progression and development of bladder cancer, suggesting circSETD3 as a tumor suppressor lncRNA a potential therapeutic target in bladder cancer [65].

3.3.6 Potential for circRNAs in Treatment of CSCs

Some research suggests that circRNAs show promise for treatment of cancer [66,67]. Recent research indicates that extracellular vesicles (EVs) and exosomes hold promise as delivery vectors for therapeutic interventions. CircRNAs are enriched in EVs and can be transported between CSCs [68]. Recent studies demonstrate the potential of charge-matched Y-shaped block catiomers for delivering small nucleic acid drugs to target cells. These engineered catiomers can selectively bind to nucleic acid drugs in the bloodstream, forming dynamic polyion complexes (uPICs) capable of penetrating tumor tissues, exhibiting significant antitumor activity [67]. Anti-sense oligonucleotides (ASOs) can also be designed to target intron sequences, binding sites for transacting splicing factors, or flanking intronic Alu repeats within circRNAs. Compared to RNAi, ASOs offer a wider range of targeted sites and reduced off-target effects [67,69]. Moreover, the CRISPR/Cas9 system presents a highly efficient tool for knocking out circRNAs. Early studies suggest that flanking intronic complementary sequences are crucial for circRNA production. Therefore, CRISPR/Cas9-mediated removal of these sequences can partially or completely suppress circRNA expression without impacting linear mRNA [39,67]. However, significant challenges remain in circRNA research, proposing further investigation [67]. While some studies present a therapeutic application for circRNAs in CSCs, the lack of direct clinical trials focusing on CSC-specific circRNA treatment hinders ultimate outcome. On the other hand, effectively delivering circRNAs to CSCs with long-term effects without immune rejection provides a substantial challenge. The long size and low hydrophobicity of circRNAs make passive diffusion difficult across cell membranes. Although RNAi techniques like siRNA and shRNA have been employed to silence circRNA expression, off-target effects are an unavoidable and concerns remain regarding their specificity. These molecules target the back splice site of circRNAs, but partial complementarity to the parental linear RNA may inadvertently influence the expression

of the parent gene. Consequently, further research is needed, such as establishing a database of circRNA expression in cancer stem cells and conducting relevant clinical trials [67].

4. Conclusion

CSCs are a minor population of tumor tissues with highly malignant characterizations, including self-renewal, migration, invasion, metastasis and drug/radio therapy resistance. CircRNAs are a class of non-coding RNAs that are often dysregulated in CSCs such as breast, hepatocellular, osteosarcoma, laryngeal squamous cell, gastric CSCs. Mechanistically, circRNAs contribute to CSC malignancy via two primary pathways: (1) acting as miRNA sponges that derepress oncogenic signaling, and (2) serving as protein decoys to activate transcription factors and stabilize stemness-promoting proteins. Tumorigenesis ability of the oncogenic circRNAs is mediated by suppressing several tumor suppressive miRNAs, resulting in overexpressing several target genes related to proliferation, self-renewal, migration, invasion, metastasis and drug/radiotherapy resistance in CSCs. Also, a circRNA, circSETD3, shows tumor suppressive role in suppressing stemness properties of CSCs in bladder cancer. In addition to miRNA sponger role, some circRNAs, including circIPO11 and circFAM73A act as a protein decoy in promoting stemness characterization of CSCs. Therefore, it is proposed that targeting these circRNAs represents a promising avenue for therapeutic development in cancer treatment for various types of cancer. In addition, these circRNAs may be suggested as a potential diagnostic biomarkers as well as therapeutic targets.

Abbreviations

APC, Adenomatosis Polyposis Coli Protein; ASOs, Anti-sense oligonucleotides; ABCG2, ATP-binding cassette G2; Bmi1, B cell-specific Moloney murine leukemia virus integration site 1; BCSC, Breast cancer stem cell; CPT, Camptothecin; CSCs, Cancer stem cells; CeRNAs, Competing endogenous RNAs; CircRNAs, Circular RNAs; CircNOLC1, Circular RNA nucleolar and coiled-body phosphoprotein 1; CircSHKBP1, Circular RNA SHKBP1; EpICD, EpCAM intracellular domain; EMT, Epithelial-mesenchymal transition; EcircRNA, Exonic circRNAs; EIciRNAs, Exon-intron circRNAs; EVs, Extracellular vesicles; FHL2, Four and a half LIM domains protein 2; HNRNPK, Heterogeneous Nuclear Ribonucleoprotein K; HMGA2, High-mobility group AT-hook 2; IciRNA, Intronic ciRNAs; IH, Infantile hemangiomas; LSCC, Laryngeal squamous cell carcinoma; LncRNA, Long non-coding RNA; MAFF, v-maf musculoaponeurotic fibrosarcoma oncogene homolog F; MMPs, Matrix metalloproteinases; MREs, microRNA response elements; NcRNA, Non-coding RNA; OPN, Osteopontin; uPICs, Polyion complexes; PSEN2, Presenilin-2; RTKs, Receptor tyrosine kinases; STAT3, Signal transducer and activator of transcription 3; Sox2, SRY-box transcription factor 2; TOP1, Topoisomerase I; TSGs; Tumor suppressor genes; TICs, Tumor-initiating cells; YAP, Yes-associated protein; YAF2, YY1 Associated Factor 2.

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Disclosure of Potential Conflicts of Interest

The author has not any conflict of interest to disclose.

Availability of Data and Materials

Not applicable.

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The manuscript is a review that does not require ethics committee approval.

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