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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, etc.

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Regulatory RNAs, microRNA, long-non coding RNA and circular RNA roles in colorectal cancer stem cells

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Abstract

The properties of cancer stem cells (CSCs), such as self-renewal, drug resistance, and metastasis, have been indicated to be responsible for the poor prognosis of patients with colon cancers. The epigenetic regulatory network plays a crucial role in CSC properties. Regulatory non-coding RNA (ncRNA), including microRNAs, long noncoding RNAs, and circular RNAs, have an important influence on cell physiopathology. They modulate cells by regulating gene expression in different ways. This review discusses the basic characteristics and the physiological functions of colorectal cancer (CRC) stem cells. Elucidation of these ncRNAs will help us understand the pathological mechanism of CRC progression, and they could become a new target for cancer treatment.

Key Words: Regulatory RNAs; MicroRNA; Long-non coding RNA; Circular RNA; Colorectal cancer; Cancer stem cell; Stemness

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Core Tip: Cancer stemness is one of the key reasons to contribute to the tumor aggressiveness, disease progression and cancer recurrence. Some reports have suggested the essential roles of regulatory RNAs in the modulation of the colorectal cancer (CRC) stemness. Here, we focus on the findings of microRNAs, long noncoding RNAs, and circular RNAs in CRC stem cells. We not only introduce the basic concepts of these non-coding RNA but address their pathologic roles in the stemness related signals and molecules to realize their functions in CRC stem cells and CRC progression.

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INTRODUCTION

Colorectal adenocarcinoma is the most common colorectal cancer (CRC), resulting from the abnormal proliferation of colon epithelial cells. According to statistics from the American Cancer Society, the risk factors of CRC include obesity, physical inactivity, high consumption of red or processed meat, alcohol uptake, and very low intake of fruit and vegetables[1]. Other factors include inflammatory bowel diseases such as Crohn's disease and ulcerative colitis. Based on TNM classification for CRC, which includes the invasive depth of primary tumor, the status of lymph nodes, and distant metastasis, CRC can be categorized into four stages: I, II, III, and IV. Typical treatments for CRC are surgical resection, neoadjuvant/adjuvant radiation therapy, and chemotherapy. Advanced CRC has high potential for metastasis and recurrence. Therefore, clarifying the mechanisms of drug-resistance and the metastasis of cancer cells is an important issue in cancer treatment. According to previous research, RNA plays important roles in physiology and pathology. Non-coding RNA (ncRNA) such as microRNA (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA) have functional roles in physiopathological processes. These RNA molecules are involved in the pathobiology of cancer and have become targets for the diagnosis, prognosis, and treatment of various cancers. At present, in CRC, ncRNA regulates CRC metastasis, drug resistance, and stemness characteristics through various signal networks. Therefore, understanding the role of ncRNA in the CRC signaling pathway can help develop new strategies for the prognosis and treatment of CRC. In this review, we analyzed the latest findings about ncRNA, particularly miRNA and lncRNA, which are involved in the pathological mechanism of CRC.

CANCER STEM CELL

The existence of cancer stem cells (CSCs) is considered to account for cancer recurrence and metastasis. Tumor heterogeneity exists, which means that there are different cancer cell clones within tumors including different cancer cell clones, cancer progenitor cells, and CSCs[2]. Two competing theories have been proposed to explain the development of heterogeneous tumors: Clonal evolution theory and CSC theory[3,4]. The first postulates that each cell within a tumor is considered to have equal potential to promote tumorigenesis. In contrast to the clonal evolution theory, CSC theory claims that CSC is a small group of cancer cell population located at the highest level in the hierarchy of solid tumor tissues [5]. Only CSCs have the potential to form new tumors on serial transplantation. *In vivo* research studies also provide evidence to support this theory by the xenograft model[6,7]. On the other hand, CSCs have been reported to exist in many different types of cancer. For instance, many studies show that CSCs dominate the tumorigenic potential in CRC[8,9]. Based on CSC theory, eliminating the CSC population would be an efficient way to prevent tumor relapse and can be expected to achieve a complete clinical therapeutic response[10].

Self-renewal is the process by which a stem cell divides to generate daughter cells that have similar developmental potential to the mother cell[11]. In normal stem cells, self-renewal is essential for expanding their population pool during development. When tissue injury occurs, stem cells differentiate into somatic cells to restore damage. In hematopoietic stem cells, defects in self-renewal reduce the potential of repopulation capacity upon serial transplantation[12,13]. On the other hand, CSCs also possess the ability to self-renew and differentiate[14,15]. CSCs are injected into immunodeficient mice and only the CSCs with self-renewal and tumor-initiating potential could generate tumors successfully in xenograft models compared to non-CSC[16]. Due to self-renewal, stem cells can overcome anoikis (a kind of programmed cell death induced when cells detach from the surrounding extracellular matrix). Therefore, stem cells can form spheres in suspension culture[17]. As a result, the sphere-forming frequency can be used to estimate CSC frequency in cancers[18].

CSCs are believed to have higher drug resistance ability and could escape from chemotherapy, leading to tumor relapse. Most cytotoxic drugs used for cancer therapy damage DNA to induce the cell death of proliferative tumor cells. However, CSCs have three different pathways to avoid death. First, CSCs can repair DNA damage more efficiently than non-stem cancer cells through ataxia telangiectasia mutated and the activation of the checkpoint kinases Chk1 and Chk2[19]. This characteristic also helps CSCs overcome the effect of radiation therapy[20]. Second, CSCs could remain at a quiescent stage to slow the cell cycle[21], which would protect CSCs from most chemotherapeutic drugs that target rapidly proliferating cells[22]. The last is that the up-regulated expression of ATP-binding cassette transporters (ABC transporters) is observed in CSCs[23]. The ABC transporter is a membrane protein that could extrude toxins out of the cell[24].

Most cancer-related deaths are attributed to recurrence and metastasis. However, metastasis initiating cells (MICs) have not yet been well-defined to date. Evidence from many previous studies implies that a subpopulation of MICs is probably comprised of CSCs[25]. For example, in CRC patients, tumors with higher expressions of CSC markers CD133 and CD44 are correlated to metastasis[26]. In the “seed and soil” hypothesis[27], metastatic cancer cells have to float in the circulatory system as seeds and find appropriate organs as “soil” in which to settle down. Consequently, the self-renewal capacity that resists anoikis might explain why CSCs are related to metastasis. On the other hand, the beginning of metastasis includes two irreplaceable steps, invasion and migration[28]. As mentioned above, repressing self-renewal or migration abilities, or even restricting the CSC population directly may reduce cancer metastasis.

Regulatory signals of CRC stem cells

Many molecular networks are related to the stemness of CRC, and several have been found to be important and crucial in the growth and functional maintenance of CSCs, such as Wnt, bone morphogenetic protein (BMP), Hedgehog (Hh), and Notch signals. The Wnt signaling pathway has been recognized as a stemness-related pathway in CSCs[29,30]. Wnt is involved in the maintenance, proliferation, apoptosis, and differentiation of intestinal tract stem cells and CSCs. In the intestine, after Wnt signal activation, the downstream β -catenin translocates into the nucleus and turns on the transcriptional activity of important developmental-related genes such as c-Myc, Axin2, and Lgr5. These downstream factors are also involved in colorectal CSCs' characteristics[31-33]. In CRC cells, this is often accompanied by abnormal Wnt signals. For example, adenomatous polyposis coli (APC) mutation leading to the excessive activation of Wnt signals has been considered the first step in tumor formation with CRC. In addition, in the population of colorectal CSCs, it has been found to have a high degree of Wnt activity. All these suggest that Wnt signaling is closely related to the origin of CRC.

Notch signaling is also enhanced in colorectal CSCs; its interaction with Wnt signaling is also considered to be an important message affecting tumor proliferation[34]. In addition, if the Notch signal were inhibited by the deletion or inhibition of γ -secretase inhibitors, this will lead to an increase in the level of Math1 that promotes stem cell differentiation and undermines the maintenance of stem cell populations[35]. On the other hand, BMP and Hh signals are more present in differentiated intestinal cells. Studies have pointed out that the Hh signal also antagonizes the Wnt signal and helps Gli-dependent tumor cell differentiation[36].

The transforming growth factor (TGF)- β /BMP pathway has multiple roles in colorectal CSCs[30]. It inhibits Wnt messages to promote cancer stem cell differentiation and promotes Wnt messages to help tumor formation[37]. BMP signaling inhibits the stemness of Lgr5+ stem cells through Smad-mediated transcriptional repression[38]. In addition, it was found that knocking out GATA6- α zinc finger transcription factor that helps maintain Lgr5+ CSCs in adenomas - can up-regulate BMP signaling, thereby inhibiting the development of CRC. Knocking out GATA6 *in vivo* can up-regulate BMP signaling, thereby inhibiting the development of CRC[39]. Therefore, these signaling pathways are multiple mechanisms of stem cell regulation during the origin and development of CRC, which contributes to the development of therapeutic strategies required to treat CRC.

MIRNA

MiRNA is a small non-coding RNA molecule with 20-22 nucleotides (nt)[40]. After primary miRNA is initially transcribed, two splicing processes sequentially occur by Drosha and Dicer to generate precursor miRNA and mature miRNA. One of the two major functions of miRNA is translational repression, causing mRNA degradation through hybridization between the target mRNA and miRNA. In recent decades, numerous studies have reported that the expression of miRNA is dysregulated in malignancies as an oncogene or tumor-suppressor gene. For example, miR-21 as oncomir has been shown to be associated with poor prognosis and metastasis in patients with breast cancers[41,42]. In breast CSCs, diminished miRNA let-7 is required to maintain self-renewal ability and inhibit differentiation[43]. In pancreatic cancer, miR-34a suppresses the expression of BCL2, Notch1, and Notch2, which are implicated in anti-apoptosis to maintain the tumor-initiating cell population[44]. Furthermore, MRX34, a liposomal miR-34 mimic, has already been evaluated in phase I clinical trials

against liver cancer[45]. Most studies about miRNA have focused on the regulation of transcription factors or abnormal copy numbers. However, the epigenetic regulation of miRNA in cancers has attracted more attention in the last decade[46]. Unraveling the regulatory mechanisms of cancer-associated miRNA may provide a novel therapeutic strategy for cancers.

In the progression of CRC, regulatory miRNAs are also involved in the CRC stem cell population and many studies have also described the regulation of miRNA, which is involved in the network of the origin of CRC. Many current studies have found that certain miRNAs related to CRC stem cells mostly target certain important signaling pathways and molecules that maintain colorectal CSCs or cell surface markers, showing the cancer-inhibition function. Such miRNAs are often found in cancer. The amount of expression in the cells decreases. In contrast, some miRNAs that target tumor-suppressor genes will play an important role in the cancer process.

In previous studies, under the deficiency of Dicer - an important protein involved in the miRNA process - the expression of CD44 and Lgr5 will increase, as will the stem cell transcription factors Sox2 and Nanog. This shows that some miRNAs are inhibitory molecules for CRC. Meanwhile, it will also affect the stem cell population in CRC cells and enhance the ability to initiate tumors and metastasis [47]. At present, many studies have reported that miRNAs have been targeting stem cell genes or genes involved in the regulation of stem cell properties, which have led to the development of different CSC populations.

CRC stem cell surface markers

CRC stem cell markers such as CD44, CD133, and Lgr5 also participate in the physiological network regulation of many CSCs as the surface antigens of colorectal CSCs. For example, CD44 can participate in the Wnt/ β -catenin signal to induce stem cell properties whether in breast cancer or CRC[33]. Lgr5 belongs to the GPCR family and can identify stem cells in colonic epithelial cells. It is considered a negative modulator of the Wnt signal. A group found that miR-23b can distinguish malignant CRC from normal intestinal epithelium and the miR-23b added in CRC is expected to target the Lgr5 gene. In CRC, miR-23b promotes cell proliferation and the cell cycle and improves the self-renewal ability, thus affecting metastasis and drug resistance, which are closely related to the characteristics of CSCs. Furthermore, this also increased the aldehyde dehydrogenase (ALDH) + CSC population group[48]. CD24, a glycosylphosphatidylinositol-anchor protein, is considered a CRC stem cell marker and has been shown to increase cancer stem cell properties. Wang *et al*[49] reported that miR-1185-1 suppresses the expression of CD24 by targeting its 3' untranslated region (3'UTR) and could be inhibited by SIRT1 *via* histone deacetylation. Targeting SIRT1 by RNAi could increase the expression of miR-1185-1 and further repress CD24 translation and CRC stemness. Transmembrane-4-L-six-family-1 (TM4SF1), a cell surface antigen, is increased in various human epithelial carcinomas[50]. In CRC tumor tissues and cell lines, miR-30a is downregulated. Overexpression of miR-30a reduces migration and invasion in CRC cell lines. miR-30a could target TM4SF1, and it inhibits vascular endothelial-derived growth factor expression and enhances E-cadherin expression[51]. LRIG1, leucine-rich repeats and immunoglobulin-like domains protein 1, is a type I single-transmembrane protein and an intestinal stem cell marker that functions as a tumor suppressor[52]. Viswanathan *et al*[53] found that miR-92a can target LRIG1 and promote the proliferation of HT29 CRC cells. miR-92a also promotes the tumorigenesis of CRC.

CRC stemness-related intracellular regulatory and transcription factors

Some miRNAs regulate important stemness transcription factors in CRC progress. SOX2 plays an important role in embryonic development and the formation of induced pluripotent stem cells[54]. SOX2 is also necessary to maintain CSC. A study found that miR-450a-5p can target the 3'UTR region to inhibit SOX2 expression in CRC. Therefore, SOX2-induced CSC properties and angiogenesis are inhibited. On the contrary, overexpression of SOX2 can rescue the inhibition brought by miR-450a-5p *in vivo* and *in vitro*. Kruppel-like factor 5 (KLF5) is a zinc-finger transcription factor of the KLF family. KLF family proteins play various roles in homeostasis and stem cell regulation[55]. The transcription factor YAP1 affects multiple signaling pathways in CRC cells. Ou's[56] group has pointed out that miR-590-5p directly inhibits YAP1 in CRC cells and inhibits tumorigenesis. The miR-590-5p-YAP1 axis in CRC specimens is dysregulated and affects the survival of patients. GATA transcription factors comprise a family of zinc-finger proteins and play an essential role in embryo development[57]. In CRC cells, GATA6 is the direct target of miR-203. miR-203-overexpressing HCT-116 and HT-29 cells decrease self-renewal ability and cancer stemness[58]. Spalt-like (SALL) transcription factor is an important transcription factor for self-renewal and pluripotency. A study showed that miR-3622a-3p is downregulated in CRC tissues and cells. miR-3362a-3p inhibits the malignant biological characteristics of CRC. miR-3622a-3p also inhibits the stemness and epithelial to mesenchymal transition (EMT) of CRC cells through SALL4 targeting. In tumor xenograft models and *in vivo* metastasis models, miR-3622a-3p can also inhibit the tumorigenesis and metastasis of CRC cells *in vivo*[59].

EMT is related to tumor metastasis and is considered one of the properties of CSCs. The EMT-related ZEB2 gene was verified as the binding target of miR-377. The expression of miR-377 was downregulated in colon cancer tissues and cell lines. Knockdown of miR-377 increases the number of ALDH+ cells and promotes the ability to form cancer spheres. Overexpression of ZEB2 could prevent the inhibition of miR-377 in cancer stem cell phenotypes, EMT, migration, and invasion[60]. Regulation of cytoskeleton

remodeling is a crucial process in cellular migration. Recently, miR-210-3p has been shown to target stathmin1, a microtubule destabilization regulator, to reduce cell elasticity without affecting EMT and upregulate the invasion ability of CRC stem cells[61]. Quaking (QKI) is a member of the signal transduction and activation of RNA protein family. QKI is highly conserved over different species and is important for normal development[62]. Studies have pointed out that miR-221 has high expression in EpCAM+/(CD44 + CRC stem cells). When miR-221 is overexpressed, it can promote the tumorigenesis of CRC by targeting the most abundant splicing isoform of the human QKI gene, QKI-5, in the CRC patient-derived xenograft model. In addition, overexpression of QKI-5 in CRC could inhibit the formation of cancer[63].

Hypoxia

Rapid cell division and abnormal blood vessel formation can be observed in tumor hypoxic areas. Hypoxia-inducible factors are also activated due to hypoxia, and they stimulate many transcription factors that control stem cell self-renewal and pluripotency, such as CSCs, which are also considered to play an important role[64]. Under hypoxic conditions, miR-34a targets and reduces the expression of PPP1R11, E3 ubiquitin-protein ligase, which activates signal transducer and activator of transcription 3 (STAT3) by phosphorylation and inhibits metastasis to the liver[65]. Hypoxia can also upregulate miR-215. miR-215 can target Lgr5 and affect the stemness of CRC stem cells[66].

Notch signaling

Transfer RNA-derived RNA fragments (tRFs) belong to a family of short noncoding RNAs and can be produced by multiple RNA enzymes and ribonuclease to regulate translation, similar to miRNAs[67]. A study found that a fragment derived from tRF/miR-1280, a 17-bp fragment derived from tRNA^{Leu} and pre-miRNA, affects Notch signaling. tRF/miR-1280 targets Notch ligand JAG2, which reduces the stem cell properties of CRC and inhibits the transcription of Gata1/3 and miR-200b genes[68]. Moreover, some tumor suppressor miRNAs are inhibited and promote the tumorigenesis of CRC. Cullin 4B (CUL4B) is considered an oncogene that promotes the development of many solid tumors. CUL4B drives the development and metastasis of colon cancer by maintaining cancer stem-like characteristics. The CUL4B and PRC2 complex synergistically inhibits the expression of miR-34a, a tumor suppressor miR that targets oncogenic MYCN and NOTCH1, to promote stem cell properties[69].

Wnt/ β -catenin signaling

Wnt/ β -catenin signaling is involved in the regulation of stem cells and tumorigenesis in several kinds of cancers[29,70]. Some positive regulatory miRs of Wnt/ β -catenin signaling have also been addressed. The current study reported that miR-501-3p is overexpressed in colorectal tumor tissues. miR-501-3p targeted APC, a negative regulator of Wnt/ β -catenin signaling. The downregulation of miR-501-3p in CRC cells inhibited tumor proliferation and sphere formation and induced cell cycle arrest at the G1 phase. miR-501-3p promotes cancer stem cell properties through Wnt/ β -catenin[71]. Many studies have also found that inflammation is related to tumor formation. Interleukin (IL)-6/STAT3 signaling is one of the important pathways induced by inflammation. Zhang *et al*[72] found that the activation of IL-6/STAT3 can induce miR-92a expression in chemical-resistant CRC and tissues. miR-92a targets the negative factors KLF4, glycogen synthase kinase-3 β , and Dickkopf 3 to upregulate Wnt/ β -catenin signaling activity in CRC. Decreased levels of the miR-30-5p family have been reported in CRC patients and human CD133 + CRC cells. Overexpression of miR-30-5p inhibits the expression of stem cell markers CD133 and SOX2, spheroid formation, and cell proliferation by suppressing USP22/Wnt/ β -catenin signals[73]. CD133+ and Lgr5+ stem cells in the colon cancer cell lines HCT-116 and SW-480 show high levels of miR-3120-5p. Overexpression of miR-3120-5p increases the CSC population and promotes the stemness and invasiveness of colon cancer cells by directly targeting Axin2[74]. Inhibition of the RCN2/Wnt/ β -catenin pathway by miR-183-5p also inhibits the proliferation and invasion of CRC [75]. On the other hand, negative regulator miRs of Wnt/ β -catenin signaling play tumor suppressor roles in CRC. In SW1116 and SW480 CRC cells, overexpression of miR-302c weakens the proliferation, invasion, and migration capabilities of CRC stem cells. miR-302c binds to CARF and inhibits its expression. CARF has been shown to maintain the stemness of CSCs of CRC and to be a positive regulator of Wnt/ β -catenin signaling[76,77].

TGF- β /Smad signaling

TGF- β /Smad signaling is involved in the regulation of many physiological processes in the body, including the regulation of CSCs. Through bioinformatics analysis and research, it was also found that miR-4666-3p and miR-329 target TGF- β R1 to prevent the activation of the TGF- β 1/Smad pathway and act as tumor suppressor genes in quiescent CSCs, identified as a subgroup of colon cancer cells that are in a dormant state and have strong stem cell-like properties[78]. Recently, decreased levels of miR-147 were found in colon cancer. Overexpressed miR-147 decreases the CRC stem cell markers such as OCT4, SOX2, and NANOG and inhibits EMT and the TGF- β /Smad pathway in HCT116 and SW480 colon cancer cells. Moreover, miR-147 downregulates the expression of β -catenin, c-myc, and survivin related to Wnt/ β -catenin signaling[79].

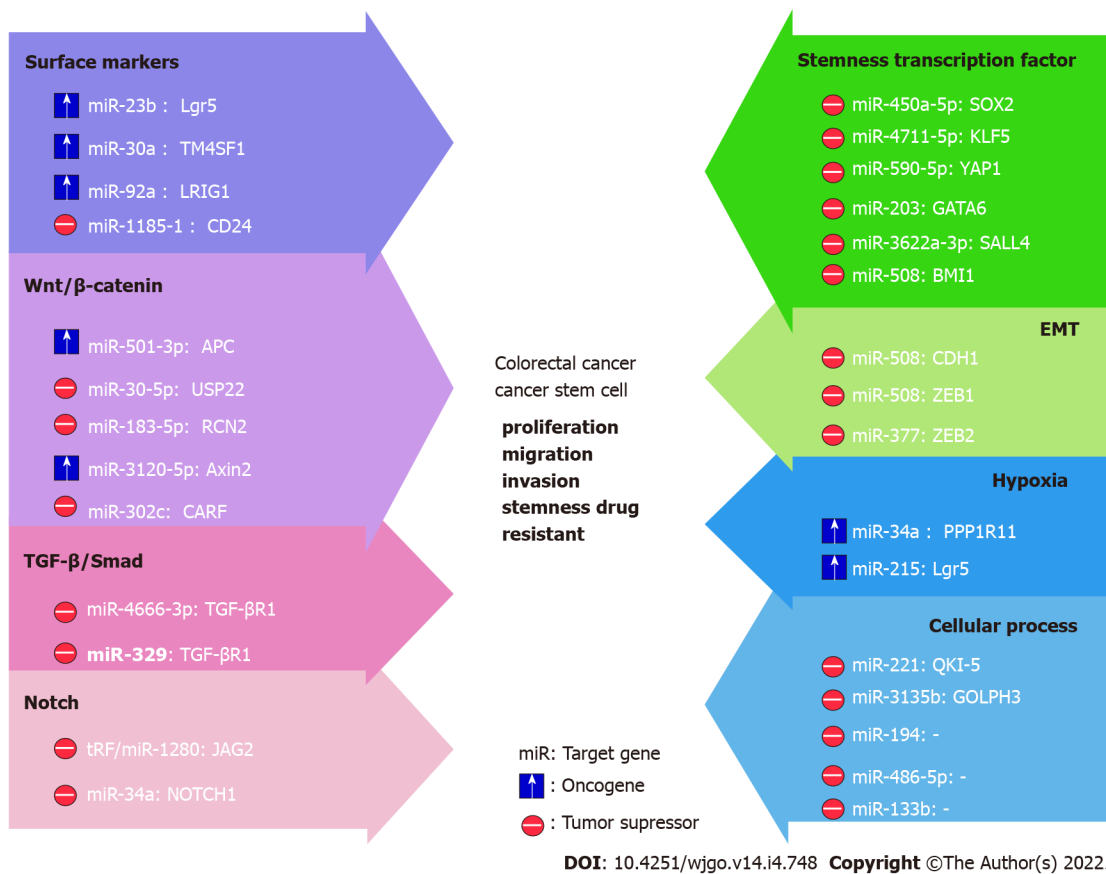


Figure 1 The role of regulatory micro RNAs of colorectal cancer stem cells in this article. TGF: Transforming growth factor; QKI: Quaking; EMT: Epithelial to mesenchymal transition; KLF: Kruppel-like factor; SALL: Spalt-like; tRF: Transfer RNA-derived RNA fragments.

Cellular response and process

Golgi fragmentation of cancer cells is one of the new chemotherapy strategies. This phenomenon is affected by the Golgi phosphoprotein-3 (GOLPH3)/Myo18A/F-actin axis. Núñez-Olvera *et al*[80] found that miR-3135b overexpression attenuates Golgi fragmentation induced by chemotherapy drugs in CRC cells and that miR-3135b targets the 3'UTR of the GOLPH3 proto-oncogene. Moreover, they noted that overexpression of miR-3135b in HCT-15 cancer cells can significantly inhibit cell proliferation, increase sensitivity to 5-fluorouracil lysis, and promote late cell degradation and necrosis. They also indicated that miR-3135b reduces the phosphorylation level of p-AKT1 (Ser473) and p-mTOR (Ser2448) and activates the autophagy and stemness of CRC. Many studies have indicated that the expression of some miRs in CSCs decreases, and the forced expression of these miRs can inhibit the characteristics of CSCs. For example, the expression of miR-194 in CRC stem cells decreases. Overexpression of miR-194 can cause G1/S transition, induce cell apoptosis, and inhibit the malignant behavior of CRC stem cells[81]. Pisano *et al*[82] found that miR-486-5p was downregulated in CRC stem cells. Overexpression of miR-486-5p can also inhibit stem cell characteristics: miR-133b was found to be downregulated in the colorectal spheroids, a model to enrich CSCs. Overexpression of miR-133b inhibits the stemness and chemoresistance of CRC. This study also found that miR-133b affected the DOT1L-mediated modification of H3K79me2 and the transcription of stem cell-related genes (Figure 1)[83].

Many miRs are involved in the regulation of the fate of CRC stem cells and affect the prognosis of CRC. At present, high-throughput next-generation sequencing is used to screen these miRs. In addition, it can also be predicted by miR-targeting sequences of genes that regulate CSC-related genes and signaling pathways. The information of the tumor suppressor miR may be used to develop a nucleic acid biosimilar drug for the treatment of CRC. These findings are quite helpful for the development of new drugs.

LNCRNAS

LncRNAs comprise various RNA species longer than 200 nt, lack protein-coding ability, and are involved in regulation of genes expression and regulate diverse functions. There are many different structure forms of lncRNA, such as mRNA-like gene transcripts (lincRNA), covalently closed circular

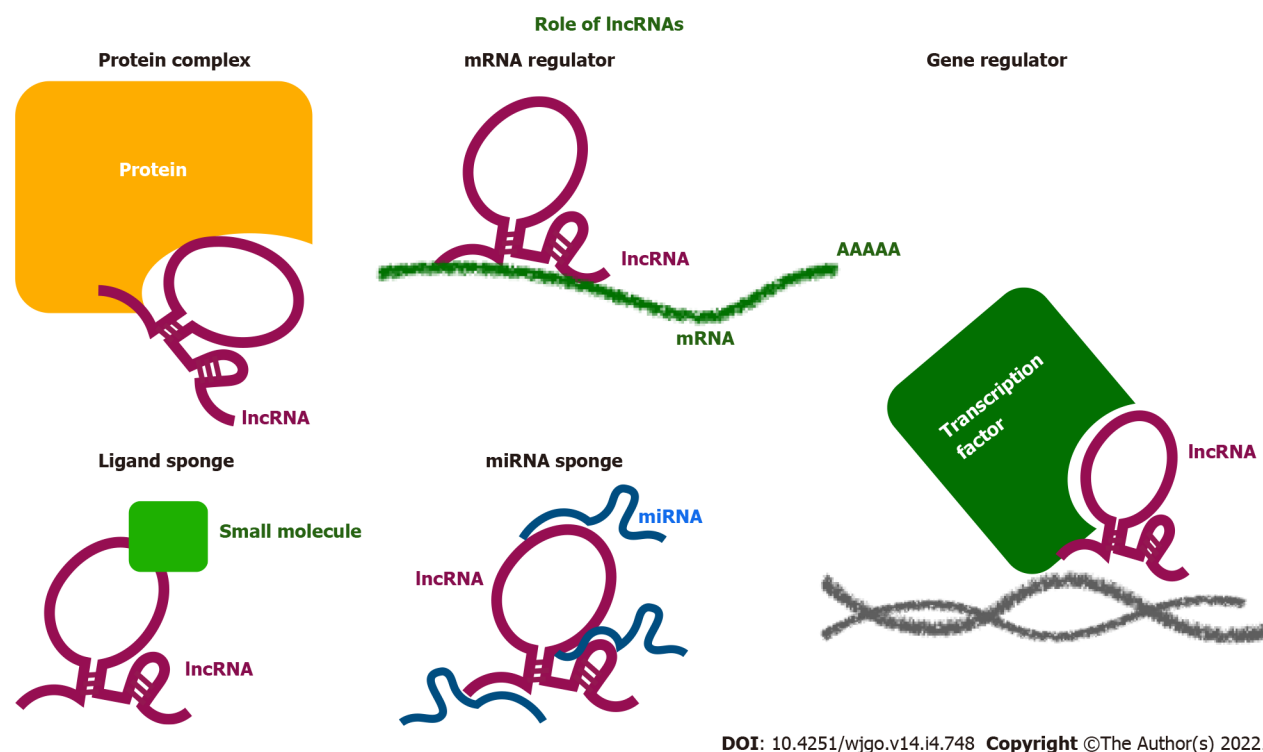


Figure 2 The functions of long non-coding RNAs. lncRNAs: Long-non coding RNAs; miRNA: MicroRNA.

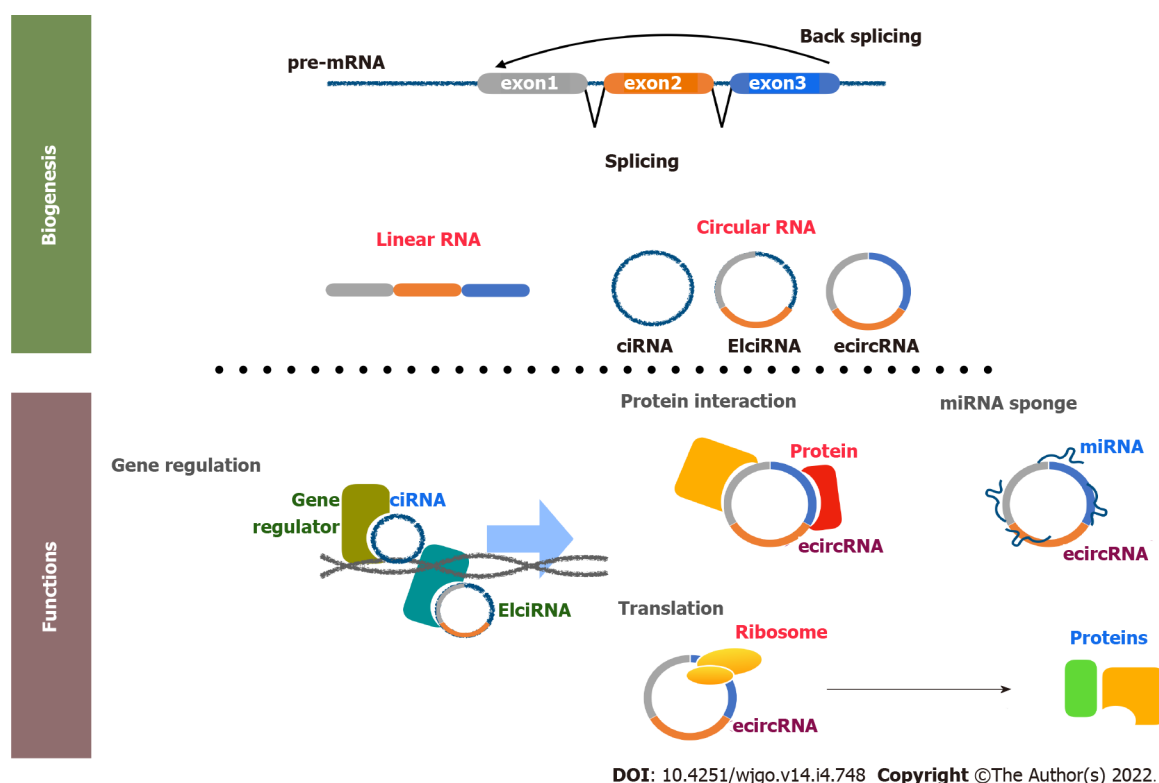


Figure 3 The functions of circular RNAs. miRNA: MicroRNA; ciRNA: Circular intronic RNA; ElciRNA: Exon-intron circular RNA; ecircRNA: Exonic circular RNA.

structures, antisense transcripts that inhibit gene expression, and A-U triple-helix structure of unconventional lincRNA modified by RNase P[84], which participate in global cellular behavior through different modifications and complexes with different molecules to control cell death and cell growth. LncRNAs control nuclear architecture and transcription in the nucleus. On the other hand, cytoplasmic lncRNAs regulate mRNA stability, affect translation, and act as miRNA sponges,

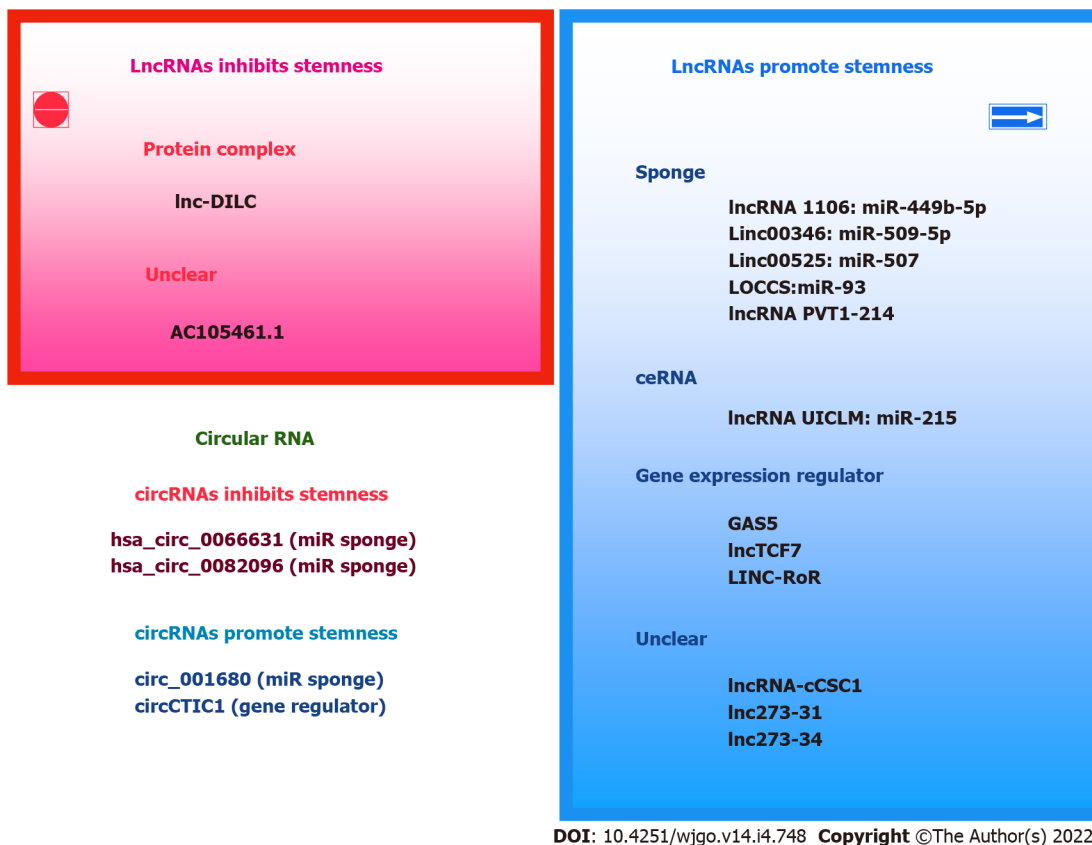


Figure 4 The role of regulatory long-non coding RNAs and circular RNAs of colorectal cancer stem cells in this article. IncRNA: Long-non coding RNAs; circRNA: Circular RNA; Inc-DILC: LncRNA downregulation in liver cancer stem cells; CSC: Cancer stem cell.

translation, and post-translational modifications[85]. Nowadays, over 170000 human lncRNA transcripts have already been identified; however, the mechanisms and the functions of most lncRNA are still unclear[86].

In nuclei, lncRNAs can regulate chromosome architecture and regulate genome organization at different statuses, such as imprinting. In females, X-chromosome inactivation (XCI) occurs to silence an X chromosome during embryonic development. XCI-induced gene silencing is initiated by the Xist lncRNA[87]. lncRNAs play an important role in gene regulation. They regulate gene expression in *cis* proximal transcription sites or *trans* distant transcription sites. lncRNA can form an R loop structure with transcription factors to form a complex and regulate transcription at the target gene locus[88]. Some lncRNAs serve as scaffold-like structure of RNA-protein interaction in nuclear bodies[89].

In cytoplasm, lncRNAs can control the stability of mRNA by regulating miRNA through competitive endogenous RNA that functions like a miRNA sponge. In addition, it has recently been reported that lncRNAs related to ribosomes can regulate translation. For example, MALAT1 interacts with ribosomes to regulate translation[90]. lncRNA also regulates post-translational modifications, such as regulating the phosphorylation of STAT3 and controlling the differentiation of human dendritic cells[91]. At present, many lncRNAs have been reported to be involved in tumor formation or to play a role in tumor suppression. C9orf139 is highly expressed in pancreatic cancer and serves as a prognostic marker for pancreatic cancer[92], HOXD-AS2 and LINC00511 promote gastric cancer[93,94]. In addition, LINC02532 promotes gastric cancer progression, migration, and invasion in Figure 2[95].

LncRNAs in CRC

Recent studies have pointed out that in CRC stem cells, lncRNA is also involved in many regulatory functions in transcription, translation, and signaling transductions. lncRNAs can play positive or negative roles for stem cell properties in CRC. Therefore, the lncRNA in CRC stem cells has the potential to become a target for CRC diagnosis and treatment.

Positive regulator of stem cell properties in CRC

Recently, many studies have found many lncRNAs that promote CSCs properties. These lncRNAs also relate to CRC prognosis. Guo *et al*[96] found that lncRNA1106 is highly expressed in colon adenocarcinoma and induces the proliferation, migration, and stem cell properties of CRC cells. Cytoplasmic lncRNA1106 can be used as miR-449b-5p sponge. The gene lncRNA1106 positively regulates Gli4 in CRC cells. In addition, Gli2 also induces lncRNA1106 expression up-regulation. The lncRNA1106-Gli

network plays an important role in CRC stem cells. LINC-RoR can induce many stem cell properties in many tumors. Li *et al*[97] found that LINC-RoR was up-regulated in CRC cell lines. Overexpression of LINC-RoR promotes cell proliferation, and its inhibition can reverse this effect *in vitro*. Fuortes *et al*[98] reported that GAS5 was associated with malignant features in HCT116-derived CSCs. Knockdown GAS5 significantly suppressed CSC self-renewal capacity, proliferation, drug resistant, stemness, and migration. Methyltransferase WBSCR22 is considered as a tumor promoter in CRC. WBSCR22 was negatively regulated by miR-509-5p. Zhao *et al*[99] reported that Linc00346 promotes the expression of WBSCR22 by adsorbing miR-509-5p, a WBSCR22 negative regulator. The Linc00346/miR-509-5p/WBSCR22 signal axis promotes the stemness of colon cancer.

Using bioinformatic analysis, Zhou *et al*[100] identified a novel lncRNA (lncRNA-cCSC1) that is highly expressed in CRC and colorectal CSCs. LncRNA-cCSC1 promotes the self-renewal capacity of the CRCSCs. Their study indicates that lncRNA-cCSC1 may regulate CSC-like properties *via* the Hh signaling pathway. Besides, lnc273-31 or lnc273-34 depletion inhibits CRC migration, invasion, cancer stem cell self-renewal and chemoresistance in p53-R273H mutation cells[101]. In addition, high expressions of LINC00525 are observed in CRC patients with poor prognosis. Wang *et al*[102] found that LINC00525 knockdown decreased stemness properties and tumorigenesis *via* miR-507, which is the direct target of LINC00525. LncRNA portal vein thrombosis (PVT)1-214 is a key regulator of CRC development and progression. Overexpression of PVT1-214 can upregulate Lin28 protein in CRC cells and serves as a critical role of CRC pathogenesis[103]. LncTCF7 can activate the Wnt/ β -catenin signaling pathway. Knocking down lncTCF7 in CRC cells decreased cancer cell progression[104]. Chen *et al*[105]'s study shows that lncRNA up-regulated in CRC liver metastasis (UICLM) was significantly up-regulated in liver metastasis-CRC. UICLM acted as a ceRNA for miR-215 to regulate ZEB2 expression and promote metastasis. Yu *et al*[106] also found an lncRNA: LOCCS was obviously upregulated in colon CD133+/CD166+/CD44+ CSCs. Knockdown of LOCCS reduced cell proliferation, invasion, migration, and tumorigenesis *in vivo*. Recently, lncRNA KLK8 has been reported that was upregulated and positively correlated with the stemness gene in CRC[107]. Wu *et al*[108] found that lncRNA SLCO4A1-AS1 could bind with miR-150-3p to elevate the expression of SLCO4A1 and the stemness of CRC.

Negative regulator of stem cell properties in CRC

Some lncRNAs that inhibit the properties of stem cells tend to have lower expression in CRC than normal colorectal cells. Overexpression of these lncRNAs can also inhibit tumor progression. LncRNA downregulation in liver CSCs (lnc-DILC) is a tumor suppressor in CRC. Li *et al*[109] found that lnc-DILC expression was downregulated in CRC tissues of human patients. Down-regulation of lnc-DILC increase aggressive of clinical characteristics. According their clinical study, lnc-DILC could be a diagnostic and prognostic marker in CRC. Besides, Liu *et al*[110] found an lncRNA (AC105461.1) is related to cancer stem cell properties. AC105461.1 overexpression reduced the percentage of CD133+CD44+ CRC stem cells, whereas its knockdown increased the population of CD133+CD44+ CRC stem cells (Figure 2).

CIRCRNAS

CircRNAs are circular noncoding RNAs (ncRNAs). This type of ncRNA was discovered in early 1990. Recently, using RNA-sequencing technology, researchers have found a large number of novel circRNAs in mammalian cells; however, the function of circRNAs is still unclear. Regarding the biogenesis, circRNA can be formed in the following ways: Exon reverse splicing into loops (exonic circRNA, ecircRNA), intron-preserving transcript reverse splicing (exon-intron circRNA, elcircRNA), and intron reverse complementary pairing (circular intronic RNA, ciRNA). According to a report, the precursor tRNA can be cut into a ring to form tricRNA (tRNA intronic circRNA)[111]. CircRNA can regulate many biological functions. CircRNA can act as an antagonist of miRNA sponge to regulate miRNA. Therefore, it is possible to control gene expression by competing miRNA. CircRNA has also been found to form complexes with proteins to regulate physiological functions together. Although circRNA is considered to be ncRNA, a previous study found that ribosome binding to the stop codon of circMBL was identified in the brain tissue of *Drosophila*, and the circRNA translation protein products were obtained by protein profiling. This result also confirms that circRNA may be like mRNA, which can translate protein functions[112]. (Figure 3)

In a study of PML/RAR α in leukemia, two fusion circRNAs (f-circRNA) were found in its chromosomal translocation. Further *in vivo* experiments showed that the f-circRNA can promote tumor growth. Several recent studies have shown that abnormal expression of circRNA occurs in almost all types of cancer. CircRNA can be an oncogene or a tumor suppressor gene, and it is involved in tumorigenesis of cancer[113].

CircRNAs in CRC stem cells

Currently, many scientists are interested in circRNAs involved in CRC stem cells. Understanding the

Table 1 Non-coding RNAs in colorectal cancer

Gene	Molecular mechanism in CRC	Molecular targets and interacts in CRC	Ref.
MicroRNAs			
CRC stemness-related intracellular regulatory and transcription factors			
MiR-1185-1	Inhibits tumor suppressor	CD24	[49]
MiR-30a	Reduces migration and invasion	Transmembrane-4-L-six-family-1	[51]
MiR-92a	Promotes the proliferation	Leucine-rich repeats and immunoglobulin-like domains protein 1	[53]
MiR-450a-5p	Inhibits CSC properties and angiogenesis	SOX2	[55]
MiR-590-5p	Inhibits tumorigenesis	YAP1	[56]
MiR-203	Inhibits self-renewal ability and cancer stemness	GATA6	[58]
MiR-3622a-3p	Inhibits the stemness and epithelial to mesenchymal transition	SALL4	[59]
MiR-210-3p	Upregulates the invasion ability	Stathmin1	[61]
MiR-221	Promotes the tumorigenesis	Quaking	[63]
Hypoxia signaling			
MiR-34a	Promotes metastasis	PPP1R11	[65]
MiR-215	Inhibit stemness	Lgr-5	[66]
Notch signaling			
MiR-1280	Reduces stemness	JAG2	[68]
Wnt/β-catenin signaling			
MiR-501-3p	Promotes tumor proliferation and stemness	APC	[71]
MiR-92a	Increases chPPemical-resistant	KLF4, GSK3 β , and DKK3	[72]
MiR-30-5p	Reduces stemness	CD133 and SOX2	[73]
MiR-3120-5p	Increases the CSC population and promotes the stemness and invasiveness	Axin2	[74]
MiR-302c	Reduces stemness	CARF	[77]
TGF-β/Smad pathway			
MiR-4666-3p	Tumor suppressor genes in quiescent CSCs	TGF- β R1	[78]
MiR-329	Tumor suppressor genes in quiescent CSCs	TGF- β R1	[78]
Cellular response and process			
MiR-3135b	Inhibits cell proliferation, increase sensitivity to 5-fluorouracil lysis, and promote late cell degradation and necrosis	GOLPH3	[80]
MiR-194	Induces cell apoptosis	NA	[81]
MiR-486-5p	Inhibits stem cell characteristics	NA	[82]
MiR-133b	Inhibits the stemness and chemoresistance of CRC	NA	[83]
Long noncoding RNAs			
Positive regulator			
LncRNA1106	Induces the proliferation, migration, and stem cell properties	MiR-449b-5p sponge, Gli4	[96]
LINC-RoR	Induces stem cell properties	NA	[97]
GAS5	Promotes CSC self-renewal capacity, proliferation, drug resistant, stemness, and migration	NA	[98]
Linc00346	Promotes the stemness	MiR-509-5p sponge, WBSCR22	[99]
LncRNA-cCSC1	Promotes the self-renewal capacity	Hh signaling pathway	[100]

Lnc273-31	Promotes migration, invasion, cancer stem cell self-renewal and chemoresistance	NA	[101]
Lnc273-34	Promotes migration, invasion, cancer stem cell self-renewal and chemoresistance	NA	[101]
LINC00525	Increase stemness properties and tumorigenesis	MiR-507	[102]
LncRNA PVT1-214	Promotes CRC progression	Lin28	[103]
LncTCF7	Promotes CRC progression	Wnt signaling	[104]
LncRNA UICLM	Promotes metastasis	ceRNA for miR-215	[105]
LncRNA: LOCCS	Promotes cell proliferation, invasion, migration, and tumorigenesis	NA	[106]
LncRNA KLK8	Increases stemness	NA	[107]
LncRNA SLCO4A1-AS1	Promote stemness	MiR-150-3p sponge	[108]
Negative regulator			
Lnc-DILC	Reduces aggressive of clinical characteristics	NA	[109]
LncRNA (AC105461.1)	Reduces stemness	NA	[110]
Circular RNAs			
Hsa_circ_0066631	High expression in CRC spheroid cells, associated with the stemness-associated signaling pathway network	MiRNA sponge: MiR-140-3p, miR-224, miR-382, miR-548c-3p, and miR-579	[114]
Hsa_circ_0082096	High expression in CRC spheroid cells, associated with the stemness-associated signaling pathway network	MiRNA sponge: MiR-140-3p, miR-224, miR-382, miR-548c-3p, and miR-579	[114]
Circ_001680	Enhances the proliferation and migration capacity	MiR-340	[115]
Circular RNA (circCTIC1)	Promotes stemness and triggers the transcriptional initiation of c-Myc	Nuclear remodeling factor complex	[116]

TGF: Transforming growth factor; KLF: Kruppel-like factor; SALL: Spalt-like; Lnc-DILC: LncRNA downregulation in liver cancer stem cells; CRC: Colorectal cancer; miRNA: MicroRNA; LncRNA: Long-non coding RNA; CSC: Cancer stem cell; UICLM: Up-regulated in colorectal cancer liver metastasis; PVT: Portal vein thrombosis; Hh: Hedgehog; GSK: Glycogen synthase kinase; TGF: Transforming growth factor; APC: Adenomatous polyposis coli; KLF: Kruppel-like factor; DKK: Dickkopf.

roles of these circRNAs can help to elucidate CRC tumorigenesis. High-throughput next-generation sequencing and bioinformatics methods can be good tools to find novel circRNAs. Recently, Rengganaten *et al* [114] used genome-wide sequencing to identify 1503 and 636 circRNAs specific to the CRC parental and spheroid cells (enriched CSCs), respectively. They found that the expression levels of circRNAs, has_circ_0066631 and hsa_circ_0082096, in a circRNA-miRNA-mRNA axis associated with the stemness-associated signaling pathway network, were significantly upregulated in the spheroid cells. The two circRNAs, as miRNA sponge, were found to target and downregulate CRC stemness miRs, miR-140-3p, miR-224, miR-382, miR-548c-3p, and miR-579. Moreover, circ_001680 was observed to enhance the proliferation and migration capacity of CRC cells. Bioinformatics analysis data from Jian *et al* [115] also reveals that circ_001680 affects the expression of stemness gene BMI1 by targeting miR-340. From the results of *in vivo* and *in vitro* experiments, circ_001680 could promote the CSC population in CRC.

CircRNA also affects CRC stemness *via* circRNA-mediated genome modeling to regulate gene transcription. Zhan *et al* [116] found that circular RNA (circCTIC1) was highly expressed in colon tumor and CRC stem cells and promoted the self-renewal of CRC stem cells. CircCTIC1 interacted with the nuclear remodeling factor complex on the c-Myc promoter and triggered the transcriptional initiation of c-Myc (Figure 4).

CLINICAL CHALLENGES AND PROSPECTION

CSCs are considered to be the origin of cancer and are also related to cancer progression. Recently, CSCs have become the therapeutic target cells for cancer. According to the clinicaltrials.gov database, CRC stem cells were also clinically evaluated (NCT01577511) to identify their invasive capacity in CRC. Reducing the stemness of cancer to increase the sensitivity of chemotherapy could be a useful strategy for cancer treatment. For example, inducing CSCs to differentiate and then combining treatment with

traditional chemotherapeutics will also help eliminate cancer tissues. Therefore, elucidating the molecular mechanisms that regulate cell stemness in CSCs is an important issue. In recent years, many reports have shown that ncRNA plays various roles in CRC stem cells and affects the fate of CSCs. These ncRNAs affect the functions of CRC stem cells and further affect the progress of CRC. Thus, characterizing the regulatory mechanism of ncRNA will provide new strategies for cancer treatment. Among ncRNAs, miRNA is the most widely used clinically. MiRNA profiles of different cancer types may be used as diagnostic biomarkers. Tumor suppressor miRNAs have the potential to become RNA biosimilar drugs. So far, in the clinicaltrials.gov database, clinical research has begun on a number of miRNA biomarkers. Some of this research focuses on assessing the progress of diseases, including diabetes, breast cancer, *etc.* In the case of NCT03362684, the performance of miRNA's miR-31-3p and miR-31-5p was used for the diagnosis and prognosis evaluation of anti-EGFR therapy in stage III Colon Cancer.

For treatment using RNA, the first small interfering RNA (siRNA), patisiran, was approved by the Food and Drug Administration (FDA) in 2018. This drug is used for rare polyneuropathy mediated by hereditary transthyretin (hATTR) caused by amyloidosis. Later, givosiran and lumasiran were approved by the FDA as siRNA drugs to treat hATTR-mediated amyloidosis and primary hyperoxaluria type 1, respectively. However, there are no approved drugs for miRNA.

Nevertheless, in different cancers, there are still many pharmaceutical companies that are developing miRNA mimics or anti-miRNA drugs and starting clinical testing. For example, miRagen Therapeutics Inc. developed MRG-106 (an inhibitor of miRNA-155), MRG-201 (a synthetic miRNA mimic to miRNA-29b), and MRG-110 (a synthetic miRNA inhibitor of miRNA-92). The MRX34 developed by Mirna Therapeutics Inc. for liver cancer has entered a phase 1 clinical trial. SantarisPharma's inhibitor, miravirsin (SPC3649), which was developed for miR-122, has also entered clinical testing. These tests all show that miRNA has the opportunity to become a potential drug for cancer treatment. In addition, in the current clinical trials' cases, lncRNA and circRNA still only serve as biomarkers of diseases. For example, in the report of clinical test NCT042697462, lncRNA CCAT1 was also used as a biomarker for the diagnosis and stage determination of CRC.

At present, ncRNAs are used as a biomarker for diagnosing diseases in most clinical trials. ncRNAs have multi-target genes and widely regulate cellular function, which are their advantages as a therapeutic drug. However, these complex and unclear functions also become challenges in the drug development. For carcinogenic ncRNA, the delivery of anti-ncRNA or siRNA may be a good strategy for cancer treatment, but the side effect issues of off-targeting and the effects on the expression of other genes must also be considered. In addition, a safe, high efficiency and highly specific gene delivery system of tumor suppressor ncRNA to target cancer cells is also a challenge for ncRNA drug applications. Despite these challenges, the understanding of the function of ncRNA in the cancer could provide new treatment targets and strategies for cancer treatment.

CONCLUSION

CRC is a common disease with high morbidity and fatality rates worldwide. Cancer targeted therapies have become an emerging and urgent topic in cancer research. CSCs are considered the new targets of cancer therapies. CRC stem cells are involved in the malignancy of CRC, such as proliferation, drug resistance, and metastasis; ncRNA research on CRC stem cells is also a current focus. With the advancement of bioinformatics and high-throughput RNA-sequencing technology, the role of ncRNAs in CRC stem cells has been revealed. These ncRNAs are involved in the fate of CSCs and affect tumor development (Table 1). Understanding the role of ncRNAs in oncogenes or tumor suppressors in CRC stem cells will improve CRC diagnosis, treatment, and new drug development.

FOOTNOTES

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