**Name of Journal:** *World Journal of Gastrointestinal Oncology*

**Manuscript NO:** 64713

**Manuscript Type:** REVIEW

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

Chao HM *et al*. Regulatory RNAs in CRC stem cells

Hsiao-Mei Chao, Teh-Wei Wang, Edward Chern, Shan-hui Hsu

**Hsiao-Mei Chao,** Department of Pathology, Wan Fang Hospital, Taipei Medical University, Taipei 11696, Taiwan

**Hsiao-Mei Chao,** Department of Pathology, School of Medicine, College of Medicine, Taipei Medical University, Taipei 110, Taiwan

**Teh-Wei Wang, Edward Chern,** niChe Lab for Stem Cell and Regenerative Medicine, Department of Biochemical Science and Technology, National Taiwan University, Taipei 10617, Taiwan

**Shan-hui Hsu,** Institute of Polymer Science and Engineering, National Taiwan University, Taipei 10617, Taiwan

**Author contributions:** Chao HM, Wang TW, Chern E and Hsu Sh reviewed the papers and wrote the manuscript; and all authors have read and approve the final manuscript.

**Corresponding author: Shan-hui Hsu, PhD, Professor,** Institute of Polymer Science and Engineering, National Taiwan University, No. 1, Sec. 4, Roosevelt Rd., Taipei 10617, Taiwan. shhsu@ntu.edu.tw

**Received:** February 22, 2021

**Revised:** August 18, 2021

**Accepted:** March 25, 2022

**Published online:** April 15, 2022

**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

**©The** **Author(s) 2022.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Chao HM, Wang TW, Chern E, Hsu Sh. Regulatory RNAs, microRNA, long-non coding RNA and circular RNA roles in colorectal cancer stem cells. *World J Gastrointest Oncol* 2022; 14(4): 748-764

**URL:** https://www.wjgnet.com/1948-5204/full/v14/i4/748.htm

**DOI:** https://dx.doi.org/10.4251/wjgo.v14.i4.748

**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.

**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 tRNALeu 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-3β, 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-βR1 to prevent the activation of the TGF-β1/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/Smand 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].

***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 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, 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, eIcircRNA), 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/RARα 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 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, miravirsen (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.

**REFERENCES**

1 **American Cancer Society**.In: Siegel R, Miller K, Jemal A. Descriptive Epidemiology. New York: Wiley, 2017 [DOI: 10.1002/9781119468868.ch1]

2 **Reya T**, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. *Nature* 2001; **414**: 105-111 [PMID: 11689955 DOI: 10.1038/35102167]

3 **Nowell PC**. The clonal evolution of tumor cell populations. *Science* 1976; **194**: 23-28 [PMID: 959840 DOI: 10.1126/science.959840]

4 **Kreso A**, Dick JE. Evolution of the cancer stem cell model. *Cell Stem Cell* 2014; **14**: 275-291 [PMID: 24607403 DOI: 10.1016/j.stem.2014.02.006]

5 **Vlashi E**, Pajonk F. Cancer stem cells, cancer cell plasticity and radiation therapy. *Semin Cancer Biol* 2015; **31**: 28-35 [PMID: 25025713 DOI: 10.1016/j.semcancer.2014.07.001]

6 **Kelly PN**, Dakic A, Adams JM, Nutt SL, Strasser A. Tumor growth need not be driven by rare cancer stem cells. *Science* 2007; **317**: 337 [PMID: 17641192 DOI: 10.1126/science.1142596]

7 **Quintana E**, Shackleton M, Sabel MS, Fullen DR, Johnson TM, Morrison SJ. Efficient tumour formation by single human melanoma cells. *Nature* 2008; **456**: 593-598 [PMID: 19052619 DOI: 10.1038/nature07567]

8 **Dalerba P**, Dylla SJ, Park IK, Liu R, Wang X, Cho RW, Hoey T, Gurney A, Huang EH, Simeone DM, Shelton AA, Parmiani G, Castelli C, Clarke MF. Phenotypic characterization of human colorectal cancer stem cells. *Proc Natl Acad Sci U S A* 2007; **104**: 10158-10163 [PMID: 17548814 DOI: 10.1073/pnas.0703478104]

9 **Ricci-Vitiani L**, Lombardi DG, Pilozzi E, Biffoni M, Todaro M, Peschle C, De Maria R. Identification and expansion of human colon-cancer-initiating cells. *Nature* 2007; **445**: 111-115 [PMID: 17122771 DOI: 10.1038/nature05384]

10 **Lee G**, Hall RR 3rd, Ahmed AU. Cancer Stem Cells: Cellular Plasticity, Niche, and its Clinical Relevance. *J Stem Cell Res Ther* 2016; **6** [PMID: 27891292 DOI: 10.4172/2157-7633.1000363]

11 **He S**, Nakada D, Morrison SJ. Mechanisms of stem cell self-renewal. *Annu Rev Cell Dev Biol* 2009; **25**: 377-406 [PMID: 19575646 DOI: 10.1146/annurev.cellbio.042308.113248]

12 **Allsopp RC**, Morin GB, DePinho R, Harley CB, Weissman IL. Telomerase is required to slow telomere shortening and extend replicative lifespan of HSCs during serial transplantation. *Blood* 2003; **102**: 517-520 [PMID: 12663456 DOI: 10.1182/blood-2002-07-2334]

13 **Yuan Y**, Shen H, Franklin DS, Scadden DT, Cheng T. In vivo self-renewing divisions of haematopoietic stem cells are increased in the absence of the early G1-phase inhibitor, p18INK4C. *Nat Cell Biol* 2004; **6**: 436-442 [PMID: 15122268 DOI: 10.1038/ncb1126]

14 **Tan BT**, Park CY, Ailles LE, Weissman IL. The cancer stem cell hypothesis: a work in progress. *Lab Invest* 2006; **86**: 1203-1207 [PMID: 17075578 DOI: 10.1038/Labinvest.3700488]

15 **Clevers H**. The cancer stem cell: premises, promises and challenges. *Nat Med* 2011; **17**: 313-319 [PMID: 21386835 DOI: 10.1038/nm.2304]

16 **O'Brien CA**, Kreso A, Jamieson CH. Cancer stem cells and self-renewal. *Clin Cancer Res* 2010; **16**: 3113-3120 [PMID: 20530701 DOI: 10.1158/1078-0432.CCR-09-2824]

17 **Reynolds BA**, Tetzlaff W, Weiss S. A multipotent EGF-responsive striatal embryonic progenitor cell produces neurons and astrocytes. *J Neurosci* 1992; **12**: 4565-4574 [PMID: 1432110 DOI: 10.1523/JNEUROSCI.12-11-04565.1992]

18 **Pastrana E**, Silva-Vargas V, Doetsch F. Eyes wide open: a critical review of sphere-formation as an assay for stem cells. *Cell Stem Cell* 2011; **8**: 486-498 [PMID: 21549325 DOI: 10.1016/j.stem.2011.04.007]

19 **Eyler CE**, Rich JN. Survival of the fittest: cancer stem cells in therapeutic resistance and angiogenesis. *J Clin Oncol* 2008; **26**: 2839-2845 [PMID: 18539962 DOI: 10.1200/JCO.2007.15.1829]

20 **Bao S**, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, Dewhirst MW, Bigner DD, Rich JN. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. *Nature* 2006; **444**: 756-760 [PMID: 17051156 DOI: 10.1038/nature05236]

21 **Holyoake T**, Jiang X, Eaves C, Eaves A. Isolation of a highly quiescent subpopulation of primitive leukemic cells in chronic myeloid leukemia. *Blood* 1999; **94**: 2056-2064 [PMID: 10477735]

22 **Chen W**, Dong J, Haiech J, Kilhoffer MC, Zeniou M. Cancer Stem Cell Quiescence and Plasticity as Major Challenges in Cancer Therapy. *Stem Cells Int* 2016; **2016**: 1740936 [PMID: 27418931 DOI: 10.1155/2016/1740936]

23 **Dean M**, Fojo T, Bates S. Tumour stem cells and drug resistance. *Nat Rev Cancer* 2005; **5**: 275-284 [PMID: 15803154 DOI: 10.1038/nrc1590]

24 **Shi GM**, Xu Y, Fan J, Zhou J, Yang XR, Qiu SJ, Liao Y, Wu WZ, Ji Y, Ke AW, Ding ZB, He YZ, Wu B, Yang GH, Qin WZ, Zhang W, Zhu J, Min ZH, Wu ZQ. Identification of side population cells in human hepatocellular carcinoma cell lines with stepwise metastatic potentials. *J Cancer Res Clin Oncol* 2008; **134**: 1155-1163 [PMID: 18470535 DOI: 10.1007/s00432-008-0407-1]

25 **Baccelli I**, Trumpp A. The evolving concept of cancer and metastasis stem cells. *J Cell Biol* 2012; **198**: 281-293 [PMID: 22869594 DOI: 10.1083/jcb.201202014]

26 **Pitule P**, Cedikova M, Daum O, Vojtisek J, Vycital O, Hosek P, Treska V, Hes O, Kralickova M, Liska V. Immunohistochemical detection of cancer stem cell related markers CD44 and CD133 in metastatic colorectal cancer patients. *Biomed Res Int* 2014; **2014**: 432139 [PMID: 24864242 DOI: 10.1155/2014/432139]

27 **Langley RR**, Fidler IJ. The seed and soil hypothesis revisited--the role of tumor-stroma interactions in metastasis to different organs. *Int J Cancer* 2011; **128**: 2527-2535 [PMID: 21365651 DOI: 10.1002/ijc.26031]

28 **Bravo-Cordero JJ**, Hodgson L, Condeelis J. Directed cell invasion and migration during metastasis. *Curr Opin Cell Biol* 2012; **24**: 277-283 [PMID: 22209238 DOI: 10.1016/j.ceb.2011.12.004]

29 **Chao HM**, Huang HX, Chang PH, Tseng KC, Miyajima A, Chern E. Y-box binding protein-1 promotes hepatocellular carcinoma-initiating cell progression and tumorigenesis *via* Wnt/β-catenin pathway. *Oncotarget* 2017; **8**: 2604-2616 [PMID: 27911878 DOI: 10.18632/oncotarget.13733]

30 **Pandurangan AK**, Divya T, Kumar K, Dineshbabu V, Velavan B, Sudhandiran G. Colorectal carcinogenesis: Insights into the cell death and signal transduction pathways: A review. *World J Gastrointest Oncol* 2018; **10**: 244-259 [PMID: 30254720 DOI: 10.4251/wjgo.v10.i9.244]

31 **Jubb AM**, Chalasani S, Frantz GD, Smits R, Grabsch HI, Kavi V, Maughan NJ, Hillan KJ, Quirke P, Koeppen H. Achaete-scute like 2 (ascl2) is a target of Wnt signalling and is upregulated in intestinal neoplasia. *Oncogene* 2006; **25**: 3445-3457 [PMID: 16568095 DOI: 10.1038/sj.onc.1209382]

32 **Tanabe S**, Aoyagi K, Yokozaki H, Sasaki H. Regulation of CTNNB1 signaling in gastric cancer and stem cells. *World J Gastrointest Oncol* 2016; **8**: 592-598 [PMID: 27574551 DOI: 10.4251/wjgo.v8.i8.592]

33 **Chang PH**, Sekine K, Chao HM, Hsu SH, Chern E. Chitosan promotes cancer progression and stem cell properties in association with Wnt signaling in colon and hepatocellular carcinoma cells. *Sci Rep* 2017; **8**: 45751 [PMID: 28367998 DOI: 10.1038/srep45751]

34 **Rauff B**, Malik A, Bhatti YA, Chudhary SA, Qadri I, Rafiq S. Notch signalling pathway in development of cholangiocarcinoma. *World J Gastrointest Oncol* 2020; **12**: 957-974 [PMID: 33005291 DOI: 10.4251/wjgo.v12.i9.957]

35 **Yang Q**, Bermingham NA, Finegold MJ, Zoghbi HY. Requirement of Math1 for secretory cell lineage commitment in the mouse intestine. *Science* 2001; **294**: 2155-2158 [PMID: 11739954 DOI: 10.1126/science.1065718]

36 **van Dop WA**, Uhmann A, Wijgerde M, Sleddens-Linkels E, Heijmans J, Offerhaus GJ, van den Bergh Weerman MA, Boeckxstaens GE, Hommes DW, Hardwick JC, Hahn H, van den Brink GR. Depletion of the colonic epithelial precursor cell compartment upon conditional activation of the hedgehog pathway. *Gastroenterology* 2009; **136**: 2195-2203.e1-7 [PMID: 19272384 DOI: 10.1053/j.gastro.2009.02.068]

37 **He XC**, Zhang J, Tong WG, Tawfik O, Ross J, Scoville DH, Tian Q, Zeng X, He X, Wiedemann LM, Mishina Y, Li L. BMP signaling inhibits intestinal stem cell self-renewal through suppression of Wnt-beta-catenin signaling. *Nat Genet* 2004; **36**: 1117-1121 [PMID: 15378062 DOI: 10.1038/ng1430]

38 **Qi Z**, Li Y, Zhao B, Xu C, Liu Y, Li H, Zhang B, Wang X, Yang X, Xie W, Li B, Han JJ, Chen YG. BMP restricts stemness of intestinal Lgr5+ stem cells by directly suppressing their signature genes. *Nat Commun* 2017; **8**: 13824 [PMID: 28059064 DOI: 10.1038/ncomms13824]

39 **Whissell G**, Montagni E, Martinelli P, Hernando-Momblona X, Sevillano M, Jung P, Cortina C, Calon A, Abuli A, Castells A, Castellvi-Bel S, Nacht AS, Sancho E, Stephan-Otto Attolini C, Vicent GP, Real FX, Batlle E. The transcription factor GATA6 enables self-renewal of colon adenoma stem cells by repressing BMP gene expression. *Nat Cell Biol* 2014; **16**: 695-707 [PMID: 24952462 DOI: 10.1038/ncb2992]

40 **Zhang Q**, Xu HF, Song WY, Zhang PJ, Song YB. Potential microRNA panel for the diagnosis and prediction of overall survival of hepatocellular carcinoma with hepatitis B virus infection. *World J Gastrointest Oncol* 2020; **12**: 383-393 [PMID: 32368317 DOI: 10.4251/wjgo.v12.i4.383]

41 **Yan LX**, Huang XF, Shao Q, Huang MY, Deng L, Wu QL, Zeng YX, Shao JY. MicroRNA miR-21 overexpression in human breast cancer is associated with advanced clinical stage, lymph node metastasis and patient poor prognosis. *RNA* 2008; **14**: 2348-2360 [PMID: 18812439 DOI: 10.1261/rna.1034808]

42 **Hernandez YG**, Lucas AL. MicroRNA in pancreatic ductal adenocarcinoma and its precursor lesions. *World J Gastrointest Oncol* 2016; **8**: 18-29 [PMID: 26798434 DOI: 10.4251/wjgo.v8.i1.18]

43 **Yu F**, Yao H, Zhu P, Zhang X, Pan Q, Gong C, Huang Y, Hu X, Su F, Lieberman J, Song E. let-7 regulates self renewal and tumorigenicity of breast cancer cells. *Cell* 2007; **131**: 1109-1123 [PMID: 18083101 DOI: 10.1016/j.cell.2007.10.054]

44 **Ji Q**, Hao X, Zhang M, Tang W, Yang M, Li L, Xiang D, Desano JT, Bommer GT, Fan D, Fearon ER, Lawrence TS, Xu L. MicroRNA miR-34 inhibits human pancreatic cancer tumor-initiating cells. *PLoS One* 2009; **4**: e6816 [PMID: 19714243 DOI: 10.1371/journal.pone.0006816]

45 **Bader AG**, Brown D, Stoudemire J, Lammers P. Developing therapeutic microRNAs for cancer. *Gene Ther* 2011; **18**: 1121-1126 [PMID: 21633392 DOI: 10.1038/gt.2011.79]

46 **Dai E**, Yu X, Zhang Y, Meng F, Wang S, Liu X, Liu D, Wang J, Li X, Jiang W. EpimiR: a database of curated mutual regulation between miRNAs and epigenetic modifications. *Database (Oxford)* 2014; **2014**: bau023 [PMID: 24682734 DOI: 10.1093/database/bau023]

47 **Iliou MS**, da Silva-Diz V, Carmona FJ, Ramalho-Carvalho J, Heyn H, Villanueva A, Muñoz P, Esteller M. Impaired DICER1 function promotes stemness and metastasis in colon cancer. *Oncogene* 2014; **33**: 4003-4015 [PMID: 24096488 DOI: 10.1038/onc.2013.398]

48 **Viswanathan V**, Damle S, Zhang T, Opdenaker L, Modarai S, Accerbi M, Schmidt S, Green P, Galileo D, Palazzo J, Fields J, Haghighat S, Rigoutsos I, Gonye G, Boman BM. An miRNA Expression Signature for the Human Colonic Stem Cell Niche Distinguishes Malignant from Normal Epithelia. *Cancer Res* 2017; **77**: 3778-3790 [PMID: 28487386 DOI: 10.1158/0008-5472.CAN-16-2388]

49 **Wang TW**, Chern E, Hsu CW, Tseng KC, Chao HM. SIRT1-Mediated Expression of CD24 and Epigenetic Suppression of Novel Tumor Suppressor miR-1185-1 Increases Colorectal Cancer Stemness. *Cancer Res* 2020; **80**: 5257-5269 [PMID: 33046442 DOI: 10.1158/0008-5472.CAN-19-3188]

50 **Fu F**, Yang X, Zheng M, Zhao Q, Zhang K, Li Z, Zhang H, Zhang S. Role of Transmembrane 4 L Six Family 1 in the Development and Progression of Cancer. *Front Mol Biosci* 2020; **7**: 202 [PMID: 33015133 DOI: 10.3389/fmolb.2020.00202]

51 **Park YR**, Kim SL, Lee MR, Seo SY, Lee JH, Kim SH, Kim IH, Lee SO, Lee ST, Kim SW. MicroRNA-30a-5p (miR-30a) regulates cell motility and EMT by directly targeting oncogenic TM4SF1 in colorectal cancer. *J Cancer Res Clin Oncol* 2017; **143**: 1915-1927 [PMID: 28528497 DOI: 10.1007/s00432-017-2440-4]

52 **Powell AE**, Wang Y, Li Y, Poulin EJ, Means AL, Washington MK, Higginbotham JN, Juchheim A, Prasad N, Levy SE, Guo Y, Shyr Y, Aronow BJ, Haigis KM, Franklin JL, Coffey RJ. The pan-ErbB negative regulator Lrig1 is an intestinal stem cell marker that functions as a tumor suppressor. *Cell* 2012; **149**: 146-158 [PMID: 22464327 DOI: 10.1016/j.cell.2012.02.042]

53 **Viswanathan V**, Opdenaker L, Modarai S, Fields JZ, Gonye G, Boman BM. MicroRNA Expression Profiling of Normal and Malignant Human Colonic Stem Cells Identifies *miRNA92a* as a Regulator of the *LRIG1* Stem Cell Gene. *Int J Mol Sci* 2020; **21** [PMID: 32316543 DOI: 10.3390/ijms21082804]

54 **Chang PH**, Chao HM, Chern E, Hsu SH. Chitosan 3D cell culture system promotes naïve-like features of human induced pluripotent stem cells: A novel tool to sustain pluripotency and facilitate differentiation. *Biomaterials* 2021; **268**: 120575 [PMID: 33341735 DOI: 10.1016/j.biomaterials.2020.120575]

55 **Bialkowska AB**, Yang VW, Mallipattu SK. Krüppel-like factors in mammalian stem cells and development. *Development* 2017; **144**: 737-754 [PMID: 28246209 DOI: 10.1242/dev.145441]

56 **Ou C**, Sun Z, Li X, Li X, Ren W, Qin Z, Zhang X, Yuan W, Wang J, Yu W, Zhang S, Peng Q, Yan Q, Xiong W, Li G, Ma J. Corrigendum to "MiR-590-5p, a density-sensitive microRNA, inhibits tumorigenesis by targeting YAP1 in colorectal cancer", [Canc. Lett. 399 (2017) 53-63]. *Cancer Lett* 2018; **420**: 260 [PMID: 29429755 DOI: 10.1016/j.canlet.2018.01.073]

57 **Tremblay M**, Sanchez-Ferras O, Bouchard M. GATA transcription factors in development and disease. *Development* 2018; **145** [PMID: 30348673 DOI: 10.1242/dev.164384]

58 **Lai HT**, Tseng WK, Huang SW, Chao TC, Su Y. MicroRNA-203 diminishes the stemness of human colon cancer cells by suppressing GATA6 expression. *J Cell Physiol* 2020; **235**: 2866-2880 [PMID: 31544978 DOI: 10.1002/jcp.29192]

59 **Chang S**, Sun G, Zhang D, Li Q, Qian H. MiR-3622a-3p acts as a tumor suppressor in colorectal cancer by reducing stemness features and EMT through targeting spalt-like transcription factor 4. *Cell Death Dis* 2020; **11**: 592 [PMID: 32719361 DOI: 10.1038/s41419-020-02789-z]

60 **Shayimu P**, Yusufu A, Rehemutula A, Redati D, Jiapaer R, Tuerdi R. MicroRNA-377 Counteracts With Cancer Stem Cell Phenotypes and Epithelial Mesenchymal Transformation by Targeting ZEB2 in Colon Cancer. *Technol Cancer Res Treat* 2020; **19**: 1533033820967475 [PMID: 33084522 DOI: 10.1177/1533033820967475]

61 **Liao TT**, Cheng WC, Yang CY, Chen YQ, Su SH, Yeh TY, Lan HY, Lee CC, Lin HH, Lin CC, Lu RH, Chiou AE, Jiang JK, Hwang WL. The microRNA-210-Stathmin1 Axis Decreases Cell Stiffness to Facilitate the Invasiveness of Colorectal Cancer Stem Cells. *Cancers (Basel)* 2021; **13** [PMID: 33921319 DOI: 10.3390/cancers13081833]

62 **Chen T**, Richard S. Structure-function analysis of Qk1: a lethal point mutation in mouse quaking prevents homodimerization. *Mol Cell Biol* 1998; **18**: 4863-4871 [PMID: 9671495 DOI: 10.1128/MCB.18.8.4863]

63 **Mukohyama J**, Isobe T, Hu Q, Hayashi T, Watanabe T, Maeda M, Yanagi H, Qian X, Yamashita K, Minami H, Mimori K, Sahoo D, Kakeji Y, Suzuki A, Dalerba P, Shimono Y. miR-221 Targets QKI to Enhance the Tumorigenic Capacity of Human Colorectal Cancer Stem Cells. *Cancer Res* 2019; **79**: 5151-5158 [PMID: 31416845 DOI: 10.1158/0008-5472.CAN-18-3544]

64 **Keith B**, Simon MC. Hypoxia-inducible factors, stem cells, and cancer. *Cell* 2007; **129**: 465-472 [PMID: 17482542 DOI: 10.1016/j.cell.2007.04.019]

65 **Li H**, Rokavec M, Jiang L, Horst D, Hermeking H. Antagonistic Effects of p53 and HIF1A on microRNA-34a Regulation of PPP1R11 and STAT3 and Hypoxia-induced Epithelial to Mesenchymal Transition in Colorectal Cancer Cells. *Gastroenterology* 2017; **153**: 505-520 [PMID: 28435028 DOI: 10.1053/j.gastro.2017.04.017]

66 **Ullmann P**, Nurmik M, Schmitz M, Rodriguez F, Weiler J, Qureshi-Baig K, Felten P, Nazarov PV, Nicot N, Zuegel N, Haan S, Letellier E. Tumor suppressor miR-215 counteracts hypoxia-induced colon cancer stem cell activity. *Cancer Lett* 2019; **450**: 32-41 [PMID: 30790680 DOI: 10.1016/j.canlet.2019.02.030]

67 **Kumar P**, Anaya J, Mudunuri SB, Dutta A. Meta-analysis of tRNA derived RNA fragments reveals that they are evolutionarily conserved and associate with AGO proteins to recognize specific RNA targets. *BMC Biol* 2014; **12**: 78 [PMID: 25270025 DOI: 10.1186/s12915-014-0078-0]

68 **Huang B**, Yang H, Cheng X, Wang D, Fu S, Shen W, Zhang Q, Zhang L, Xue Z, Li Y, Da Y, Yang Q, Li Z, Liu L, Qiao L, Kong Y, Yao Z, Zhao P, Li M, Zhang R. tRF/miR-1280 Suppresses Stem Cell-like Cells and Metastasis in Colorectal Cancer. *Cancer Res* 2017; **77**: 3194-3206 [PMID: 28446464 DOI: 10.1158/0008-5472.CAN-16-3146]

69 **Li Y**, Hu H, Wang Y, Fan Y, Yang Y, Guo B, Xie X, Lian J, Jiang B, Han B, Wang Y, Shao C, Gong Y. CUL4B contributes to cancer stemness by repressing tumor suppressor miR34a in colorectal cancer. *Oncogenesis* 2020; **9**: 20 [PMID: 32054830 DOI: 10.1038/s41389-020-0206-3]

70 **Hsu SH**, Huang GS. Substrate-dependent Wnt signaling in MSC differentiation within biomaterial-derived 3D spheroids. *Biomaterials* 2013; **34**: 4725-4738 [PMID: 23562051 DOI: 10.1016/j.biomaterials.2013.03.031]

71 **Wu F**, Xing T, Gao X, Liu F. miR‑501‑3p promotes colorectal cancer progression *via* activation of Wnt/β‑catenin signaling. *Int J Oncol* 2019; **55**: 671-683 [PMID: 31364752 DOI: 10.3892/ijo.2019.4852]

72 **Zhang GJ**, Li LF, Yang GD, Xia SS, Wang R, Leng ZW, Liu ZL, Tian HP, He Y, Meng CY, Liu DZ, Hou SL, Tang XG, Zhou T. MiR-92a promotes stem cell-like properties by activating Wnt/β-catenin signaling in colorectal cancer. *Oncotarget* 2017; **8**: 101760-101770 [PMID: 29254202 DOI: 10.18632/oncotarget.21667]

73 **Jiang S**, Miao D, Wang M, Lv J, Wang Y, Tong J. MiR-30-5p suppresses cell chemoresistance and stemness in colorectal cancer through USP22/Wnt/β-catenin signaling axis. *J Cell Mol Med* 2019; **23**: 630-640 [PMID: 30338942 DOI: 10.1111/jcmm.13968]

74 **Hongdan L**, Feng L. miR-3120-5p promotes colon cancer stem cell stemness and invasiveness through targeting Axin2. *Biochem Biophys Res Commun* 2018; **496**: 302-308 [PMID: 29307822 DOI: 10.1016/j.bbrc.2018.01.021]

75 **Wang G**, Zhou J, Lu F, Qiu L, Xu L, Yang X, Miao Y. Downregulation of microRNA‑183‑5p inhibits the proliferation and invasion of colorectal cancer cells by inactivating the reticulocalbin‑2/Wnt/β‑catenin signaling pathway. *Mol Med Rep* 2019; **19**: 4475-4483 [PMID: 30896885 DOI: 10.3892/mmr.2019.10059]

76 **Dong W**, Cao Z, Pang Y, Feng T, Tian H. CARF, As An Oncogene, Promotes Colorectal Cancer Stemness By Activating ERBB Signaling Pathway. *Onco Targets Ther* 2019; **12**: 9041-9051 [PMID: 31802911 DOI: 10.2147/OTT.S225733]

77 **Zhang Y**, Meng H, Guo K. Inhibition of MicroRNA-302c on Stemness of Colon Cancer Stem Cells via the CARF/Wnt/β-Catenin Axis. *Dig Dis Sci* 2021; **66**: 1906-1915 [PMID: 32617772 DOI: 10.1007/s10620-020-06435-8]

78 **Ye J**, Lei J, Fang Q, Shen Y, Xia W, Hu X, Xu Q, Yuan H, Huang J, Ni C. miR-4666-3p and miR-329 Synergistically Suppress the Stemness of Colorectal Cancer Cells *via* Targeting TGF-β/Smad Pathway. *Front Oncol* 2019; **9**: 1251 [PMID: 31824844 DOI: 10.3389/fonc.2019.01251]

79 **Ning X**, Wang C, Zhang M, Wang K. Ectopic Expression of miR-147 Inhibits Stem Cell Marker and Epithelial-Mesenchymal Transition (EMT)-Related Protein Expression in Colon Cancer Cells. *Oncol Res* 2019; **27**: 399-406 [PMID: 29426374 DOI: 10.3727/096504018X15179675206495]

80 **Núñez-Olvera SI**, Chávez-Munguía B, Del Rocío Terrones-Gurrola MC, Marchat LA, Puente-Rivera J, Ruíz-García E, Campos-Parra AD, Vázquez-Calzada C, Lizárraga-Verdugo ER, Ramos-Payán R, Salinas-Vera YM, López-Camarillo C. A novel protective role for microRNA-3135b in Golgi apparatus fragmentation induced by chemotherapy *via* GOLPH3/AKT1/mTOR axis in colorectal cancer cells. *Sci Rep* 2020; **10**: 10555 [PMID: 32601379 DOI: 10.1038/s41598-020-67550-0]

81 **Sun B**, Fang YT, Jin DJ, Chen ZY, Li ZY, Gu XD, Xiang JB. miR-194 Inhibits the Proliferation of SW620 Colon Cancer Stem Cells Through Downregulation of SSH2 Expression. *Cancer Manag Res* 2019; **11**: 10229-10238 [PMID: 31824193 DOI: 10.2147/CMAR.S221150]

82 **Pisano A**, Griñan-Lison C, Farace C, Fiorito G, Fenu G, Jiménez G, Scognamillo F, Peña-Martin J, Naccarati A, Pröll J, Atzmüller S, Pardini B, Attene F, Ibba G, Solinas MG, Bernhard D, Marchal JA, Madeddu R. The Inhibitory Role of miR-486-5p on CSC Phenotype Has Diagnostic and Prognostic Potential in Colorectal Cancer. *Cancers (Basel)* 2020; **12** [PMID: 33227890 DOI: 10.3390/cancers12113432]

83 **Lv L**, Li Q, Chen S, Zhang X, Tao X, Tang X, Wang S, Che G, Yu Y, He L. miR-133b suppresses colorectal cancer cell stemness and chemoresistance by targeting methyltransferase DOT1L. *Exp Cell Res* 2019; **385**: 111597 [PMID: 31525340 DOI: 10.1016/j.yexcr.2019.111597]

84 **Yao RW**, Wang Y, Chen LL. Cellular functions of long noncoding RNAs. *Nat Cell Biol* 2019; **21**: 542-551 [PMID: 31048766 DOI: 10.1038/s41556-019-0311-8]

85 **Wilusz JE**, Sunwoo H, Spector DL. Long noncoding RNAs: functional surprises from the RNA world. *Genes Dev* 2009; **23**: 1494-1504 [PMID: 19571179 DOI: 10.1101/gad.1800909]

86 **Gao F**, Cai Y, Kapranov P, Xu D. Reverse-genetics studies of lncRNAs-what we have learnt and paths forward. *Genome Biol* 2020; **21**: 93 [PMID: 32290841 DOI: 10.1186/s13059-020-01994-5]

87 **Tjalsma SJD**, Hori M, Sato Y, Bousard A, Ohi A, Raposo AC, Roensch J, Le Saux A, Nogami J, Maehara K, Kujirai T, Handa T, Bagés-Arnal S, Ohkawa Y, Kurumizaka H, da Rocha ST, Żylicz JJ, Kimura H, Heard E. H4K20me1 and H3K27me3 are concurrently loaded onto the inactive X chromosome but dispensable for inducing gene silencing. *EMBO Rep* 2021; **22**: e51989 [PMID: 33605056 DOI: 10.15252/embr.202051989]

88 **Vydzhak O**, Luke B, Schindler N. Non-coding RNAs at the Eukaryotic rDNA Locus: RNA-DNA Hybrids and Beyond. *J Mol Biol* 2020; **432**: 4287-4304 [PMID: 32446803 DOI: 10.1016/j.jmb.2020.05.011]

89 **Thakur J**, Henikoff S. Architectural RNA in chromatin organization. *Biochem Soc Trans* 2020; **48**: 1967-1978 [PMID: 32897323 DOI: 10.1042/BST20191226]

90 **Malakar P**, Stein I, Saragovi A, Winkler R, Stern-Ginossar N, Berger M, Pikarsky E, Karni R. Long Noncoding RNA MALAT1 Regulates Cancer Glucose Metabolism by Enhancing mTOR-Mediated Translation of TCF7L2. *Cancer Res* 2019; **79**: 2480-2493 [PMID: 30914432 DOI: 10.1158/0008-5472.CAN-18-1432]

91 **Ding H**, Liu J, Zou R, Cheng P, Su Y. Long non-coding RNA TPTEP1 inhibits hepatocellular carcinoma progression by suppressing STAT3 phosphorylation. *J Exp Clin Cancer Res* 2019; **38**: 189 [PMID: 31072375 DOI: 10.1186/s13046-019-1193-0]

92 **Ge JN**, Yan D, Ge CL, Wei MJ. LncRNA C9orf139 can regulate the growth of pancreatic cancer by mediating the miR-663a/Sox12 axis. *World J Gastrointest Oncol* 2020; **12**: 1272-1287 [PMID: 33250960 DOI: 10.4251/wjgo.v12.i11.1272]

93 **Sun CB**, Wang HY, Han XQ, Liu YN, Wang MC, Zhang HX, Gu YF, Leng XG. LINC00511 promotes gastric cancer cell growth by acting as a ceRNA. *World J Gastrointest Oncol* 2020; **12**: 394-404 [PMID: 32368318 DOI: 10.4251/wjgo.v12.i4.394]

94 **Yao L**, Ye PC, Tan W, Luo YJ, Xiang WP, Liu ZL, Fu ZM, Lu F, Tang LH, Xiao JW. Decreased expression of the long non-coding RNA *HOXD-AS2* promotes gastric cancer progression by targeting HOXD8 and activating PI3K/Akt signaling pathway. *World J Gastrointest Oncol* 2020; **12**: 1237-1254 [PMID: 33250958 DOI: 10.4251/wjgo.v12.i11.1237]

95 **Zhang C**, Ma MH, Liang Y, Wu KZ, Dai DQ. Novel long non-coding RNA LINC02532 promotes gastric cancer cell proliferation, migration, and invasion *in vitro*. *World J Gastrointest Oncol* 2019; **11**: 91-101 [PMID: 30788037 DOI: 10.4251/wjgo.v11.i2.91]

96 **Guo K**, Gong W, Wang Q, Gu G, Zheng T, Li Y, Li W, Fang M, Xie H, Yue C, Yang J, Zhu Z. LINC01106 drives colorectal cancer growth and stemness through a positive feedback loop to regulate the Gli family factors. *Cell Death Dis* 2020; **11**: 869 [PMID: 33067422 DOI: 10.1038/s41419-020-03026-3]

97 **Li X**, Chen W, Jia J, You Z, Hu C, Zhuang Y, Lin Z, Liu Y, Yang C, Xu R. The Long Non-Coding RNA-RoR Promotes the Tumorigenesis of Human Colorectal Cancer by Targeting miR-6833-3p Through SMC4. *Onco Targets Ther* 2020; **13**: 2573-2581 [PMID: 32273727 DOI: 10.2147/OTT.S238947]

98 **Fuortes L**, Phillips K, Muldoon J. Traumatic head and spinal cord injury in Iowa. *Iowa Med* 1990; **80**: 560-562 [PMID: 2269616]

99 **Zhao H**, Su W, Sun Y, Wu Z. WBSCR22 Competes with Long Non-coding RNA Linc00346 for miR-509-5p Binding Site to Regulate Cancer Stem Cell Phenotypes of Colorectal Cancer. *Biochem Genet* 2020; **58**: 384-398 [PMID: 32008219 DOI: 10.1007/s10528-020-09949-y]

100 **Zhou H**, Xiong Y, Peng L, Wang R, Zhang H, Fu Z. LncRNA-cCSC1 modulates cancer stem cell properties in colorectal cancer *via* activation of the Hedgehog signaling pathway. *J Cell Biochem* 2020; **121**: 2510-2524 [PMID: 31680315 DOI: 10.1002/jcb.29473]

101 **Zhao Y**, Li Y, Sheng J, Wu F, Li K, Huang R, Wang X, Jiao T, Guan X, Lu Y, Chen X, Luo Z, Zhou Y, Hu H, Liu W, Du B, Miao S, Cai J, Wang L, Zhao H, Ying J, Bi X, Song W. P53-R273H mutation enhances colorectal cancer stemness through regulating specific lncRNAs. *J Exp Clin Cancer Res* 2019; **38**: 379 [PMID: 31455383 DOI: 10.1186/s13046-019-1375-9]

102 **Wang S**, Li J, Yang X. Long Non-Coding RNA LINC00525 Promotes the Stemness and Chemoresistance of Colorectal Cancer by Targeting miR-507/ELK3 Axis. *Int J Stem Cells* 2019; **12**: 347-359 [PMID: 31242722 DOI: 10.15283/ijsc19041]

103 **He F**, Song Z, Chen H, Chen Z, Yang P, Li W, Yang Z, Zhang T, Wang F, Wei J, Wei F, Wang Q, Cao J. Long noncoding RNA PVT1-214 promotes proliferation and invasion of colorectal cancer by stabilizing Lin28 and interacting with miR-128. *Oncogene* 2019; **38**: 164-179 [PMID: 30076414 DOI: 10.1038/s41388-018-0432-8]

104 **Li T**, Zhu J, Wang X, Chen G, Sun L, Zuo S, Zhang J, Chen S, Ma J, Yao Z, Zheng Y, Chen Z, Liu Y, Wang P. Long non-coding RNA lncTCF7 activates the Wnt/β-catenin pathway to promote metastasis and invasion in colorectal cancer. *Oncol Lett* 2017; **14**: 7384-7390 [PMID: 29344178 DOI: 10.3892/ol.2017.7154]

105 **Chen DL**, Lu YX, Zhang JX, Wei XL, Wang F, Zeng ZL, Pan ZZ, Yuan YF, Wang FH, Pelicano H, Chiao PJ, Huang P, Xie D, Li YH, Ju HQ, Xu RH. Long non-coding RNA UICLM promotes colorectal cancer liver metastasis by acting as a ceRNA for microRNA-215 to regulate ZEB2 expression. *Theranostics* 2017; **7**: 4836-4849 [PMID: 29187907 DOI: 10.7150/thno.20942]

106 **Yu X**, Mi L, Dong J, Zou J. Long intergenic non-protein-coding RNA 1567 (LINC01567) acts as a "sponge" against microRNA-93 in regulating the proliferation and tumorigenesis of human colon cancer stem cells. *BMC Cancer* 2017; **17**: 716 [PMID: 29110645 DOI: 10.1186/s12885-017-3731-5]

107 **Wang K**, Song W, Shen Y, Wang H, Fan Z. LncRNA KLK8 modulates stem cell characteristics in colon cancer. *Pathol Res Pract* 2021; **224**: 153437 [PMID: 34271345 DOI: 10.1016/j.prp.2021.153437]

108 **Wu K**, Xu T, Song X, Shen J, Zheng S, Zhang L, Tao G, Jiang B. LncRNA SLCO4A1-AS1 modulates colon cancer stem cell properties by binding to miR-150-3p and positively regulating SLCO4A1. *Lab Invest* 2021; **101**: 908-920 [PMID: 33958701 DOI: 10.1038/s41374-021-00577-7]

109 **Li QG**, Xu XQ, Zhou DY, Jia ZB, Yu BF, Xu FG, Zhang L. Long non-coding RNA DILC as a potentially useful biomarker for the diagnosis and prognosis of colorectal cancer. *Eur Rev Med Pharmacol Sci* 2019; **23**: 3320-3325 [PMID: 31081085 DOI: 10.26355/eurrev\_201904\_17694]

110 **Liu W**, Yu Q, Ma J, Cheng Y, Zhang H, Luo W, Yao J, Zhang H. Knockdown of a DIS3L2 promoter upstream long noncoding RNA (AC105461.1) enhances colorectal cancer stem cell properties *in vitro* by down-regulating DIS3L2. *Onco Targets Ther* 2017; **10**: 2367-2376 [PMID: 28496335 DOI: 10.2147/OTT.S132708]

111 **Schmidt CA**, Giusto JD, Bao A, Hopper AK, Matera AG. Molecular determinants of metazoan tricRNA biogenesis. *Nucleic Acids Res* 2019; **47**: 6452-6465 [PMID: 31032518 DOI: 10.1093/nar/gkz311]

112 **Pamudurti NR**, Bartok O, Jens M, Ashwal-Fluss R, Stottmeister C, Ruhe L, Hanan M, Wyler E, Perez-Hernandez D, Ramberger E, Shenzis S, Samson M, Dittmar G, Landthaler M, Chekulaeva M, Rajewsky N, Kadener S. Translation of CircRNAs. *Mol Cell* 2017; **66**: 9-21.e7 [PMID: 28344080 DOI: 10.1016/j.molcel.2017.02.021]

113 **Guarnerio J**, Bezzi M, Jeong JC, Paffenholz SV, Berry K, Naldini MM, Lo-Coco F, Tay Y, Beck AH, Pandolfi PP. Oncogenic Role of Fusion-circRNAs Derived from Cancer-Associated Chromosomal Translocations. *Cell* 2016; **165**: 289-302 [PMID: 27040497 DOI: 10.1016/j.cell.2016.03.020]

114 **Rengganaten V**, Huang CJ, Tsai PH, Wang ML, Yang YP, Lan YT, Fang WL, Soo S, Ong HT, Cheong SK, Choo KB, Chiou SH. Mapping a Circular RNA-microRNA-mRNA-Signaling Regulatory Axis That Modulates Stemness Properties of Cancer Stem Cell Populations in Colorectal Cancer Spheroid Cells. *Int J Mol Sci* 2020; **21** [PMID: 33114016 DOI: 10.3390/ijms21217864]

115 **Jian X**, He H, Zhu J, Zhang Q, Zheng Z, Liang X, Chen L, Yang M, Peng K, Zhang Z, Liu T, Ye Y, Jiao H, Wang S, Zhou W, Ding Y, Li T. Hsa\_circ\_001680 affects the proliferation and migration of CRC and mediates its chemoresistance by regulating BMI1 through miR-340. *Mol Cancer* 2020; **19**: 20 [PMID: 32005118 DOI: 10.1186/s12943-020-1134-8]

116 **Zhan W**, Liao X, Wang Y, Li L, Li J, Chen Z, Tian T, He J. circCTIC1 promotes the self-renewal of colon TICs through BPTF-dependent c-Myc expression. *Carcinogenesis* 2019; **40**: 560-568 [PMID: 30403769 DOI: 10.1093/carcin/bgy144]

**Footnotes**

**Conflict-of-interest statement:** Authors declare no conflict of interests for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** February 22, 2021

**First decision:** July 29, 2021

**Article in press:** March 25, 2022

**Specialty type:** Oncology

**Country/Territory of origin:** Taiwan

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

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Hou L, China; Luo ZW, China **S-Editor:** Wang JJ **L-Editor:** A **P-Editor:** Wang JJ

**Figure Legends**



**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; APC: Adenomatous polyposis coli.



**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; EIciRNA: Exon-intron circular RNA; ecircRNA: Exonic circular RNA.



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

**Table 1 Non-coding RNAs in colorectal cancer**

|  |  |  |  |
| --- | --- | --- | --- |
| **Gene** | **Molucular 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, GSK3β, 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-βR1 | [78] |
| MiR-329 | Tumor suppressor genes in quiescent CSCs | TGF-βR1 | [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 chemoresistanc | NA | [101] |
| Lnc273-34 | Promotes migration, invasion, cancer stem cell self-renewal and chemoresistanc | 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: Krüppel-like factor; DKK: Dickkopf.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2022 Baishideng Publishing Group Inc. All rights reserved.**