ISSN 1948-5204 (online)

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2024 February 15; 16(2): 251-570

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Oncology

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ABOUT COVER

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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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The *WJGO* is now abstracted and indexed in PubMed, PubMed Central, Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJGO* as 3.0; IF without journal self cites: 2.9; 5-year IF: 3.0; Journal Citation Indicator: 0.49; Ranking: 157 among 241 journals in oncology; Quartile category: Q3; Ranking: 58 among 93 journals in gastroenterology and hepatology; and Quartile category: Q3. The *WJGO*'s CiteScore for 2022 is 4.1 and Scopus CiteScore rank 2022: Gastroenterology is 71/149; Oncology is 197/366.

RESPONSIBLE EDITORS FOR THIS ISSUE

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

NAME OF JOURNAL
World Journal of Gastrointestinal Oncology

ISSN
ISSN 1948-5204 (online)

LAUNCH DATE
February 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5204/editorialboard.htm

PUBLICATION DATE
February 15, 2024

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World J Gastrointest Oncol 2024 February 15; 16(2): 300-313

DOI: 10.4251/wjgo.v16.i2.300

ISSN 1948-5204 (online)

MINIREVIEWS

Multifaceted role of microRNAs in gastric cancer stem cells: Mechanisms and potential biomarkers

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Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: She XK, United States

Received: October 14, 2023
Peer-review started: October 14, 2023
First decision: December 22, 2023
Revised: December 31, 2023
Accepted: January 19, 2024
Article in press: January 19, 2024
Published online: February 15, 2024

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Abstract

MicroRNAs (miRNAs) have received much attention in the past decade as potential key epigenomic regulators of tumors and cancer stem cells (CSCs). The abnormal expression of miRNAs is responsible for different phenotypes of gastric cancer stem cells (GCSCs). Some specific miRNAs could be used as promising biomarkers and therapeutic targets for the identification of GCSCs. This review summarizes the coding process and biological functions of miRNAs and demonstrates their role and efficacy in gastric cancer (GC) metastasis, drug resistance, and apoptosis, especially in the regulatory mechanism of GCSCs. It shows that the overexpression of onco-miRNAs and silencing of tumor-suppressor miRNAs can play a role in promoting or inhibiting tumor metastasis, apart from the initial formation of GC. It also discusses the epigenetic regulation and potential clinical applications of miRNAs as well as the role of CSCs in the pathogenesis of GC. We believe that this review may help in designing novel therapeutic approaches for GC.

Key Words: Gastric cancer, Cancer stem cells; MicroRNAs; Epigenetics; Therapeutic target

Core Tip: Gastric cancer stem cells (GCSCs), as progenitor cells of gastric cancer (GC), are closely related to invasion, metastasis, drug resistance, and other biological processes. MicroRNAs (miRNAs) are involved in controlling the growth and differentiation mechanism of GCSC by regulating cell cycle, angiogenesis, cell invasion and migration, GCSC phenotype, and other signaling pathways. In addition, miRNAs directly or indirectly regulate the expression of tumor-promoting genes or tumor suppressor genes through different signaling pathways and it is suggested that miRNAs could be related to the initial formation of GC. *In vivo*, studies have shown that the biological function of GCSCs could be modulated by delivering therapeutic miRNA mimics *into vivo* or transgene and knockout with miRNA antagonists. It's vital to focus on whether interfering with certain miRNA levels by the methods described above leads to reversal or prevention of GC metastasis.

Citation: Sun QH, Kuang ZY, Zhu GH, Ni BY, Li J. Multifaceted role of microRNAs in gastric cancer stem cells: Mechanisms and potential biomarkers. *World J Gastrointest Oncol* 2024; 16(2): 300-313
URL: https://www.wjgnet.com/1948-5204/full/v16/i2/300.htm
DOI: https://dx.doi.org/10.4251/wjgo.v16.i2.300

INTRODUCTION

Gastric cancer (GC) is one of the top five most prevalent cancers worldwide[1]. It is characterized by a high recurrence rate, high drug resistance, and extensive metastasis. As it does not exhibit many evident symptoms in its early stages, most patients of GC are diagnosed at advanced stages, making it difficult to perform surgery and resulting in a poor prognosis. Fortunately, the development of precision medicine in recent years has extended the range of targeted therapy beyond trastuzumab for treating GC. Immune checkpoint inhibitors can also improve the prognosis of patients with advanced GC to some extent[2]. However, despite various advancements in treatment methods, patients with GC still have a median 5-year survival rate of 32%, while those with distant metastases have a median 5-year survival rate of only 6%. Patients with metastases or recurrence have a particularly terrible prognosis, with a median survival period of only 8 months[3].

As a self-renewing tumor-initiating cell subgroup in tumors, cancer stem cells (CSCs) can not only divide and differentiate into different tumor cell types[4] but can also increase the expression of drug-efflux pumps, activate anti-apoptotic pathways, and enhance the DNA-repair capacity[5,6]. According to Takaishi *et al*[1], CSCs can be found in various solid tumors, including those of GC. In 2008, surface markers were first used to distinguish GC stem cells (GCSCs) from normal human GC cell lines[7]. However, the origin of GCSCs has not yet been determined. There are currently two dominant opinions regarding their origin. According to one, gastric normal stem cells undergo a malignant transition to produce GCSCs, which then undergo carcinogenic mutations and become tumor progenitor cells that promote tumor invasion, metastasis, and heterogeneity[8]. According to the second opinion, GCSCs are derived from bone marrow-derived stem cells (BMSCs), which are recruited to the site of infection or tissue injury to repair inflammatory damage[9]. BMSCs are thought to be the progenitor cells of *Helicobacter pylori* (Hp)-associated GC. BMSCs also participate in the development of Hp-associated GC by differentiating into gastric epithelial cells and tumor-associated fibroblasts.

GCSCs are a subset of GC cells that exhibit unlimited self-renewal proliferation (also called "pluripotency"), multi-differentiation potential, high tumorigenicity, and significant angiogenesis abilities. Numerous variables control the stemness of GCSCs. Polar epithelial cells acquire fibroblast characteristics through a multistep process known as the epithelial–mesenchymal transition (EMT), which involves intercellular contact loss and cytoskeletal recombination during embryonic development. The EMT process improves the ability of GC cells to invade and metastasize. The feedback encourages the production of GCSCs, which then take part in the start-up and maintenance of EMTs. EMT-related gene expression endows GC cells with invasion and metastasis characteristics, treatment resistance, and GCSC phenotypes such as CD133, CD44, and EpCAM. They are not only the main means to identify and isolate GCSCs but also the biological basis for regulating their stemness.

MicroRNAs (miRNAs) control various cellular functions, including self-renewal and cell differentiation. They also participate in GC development, apoptosis, angiogenesis, EMT, and other such processes. They mechanically impede translation and control the expression of their target genes by inserting themselves into the 3′-untranslated region (UTR) of the target mRNA or by degrading the target mRNA. The relationship between the gene-expression profiles of miRNAs and the clinical outcomes of GC has been extensively studied[10]. This review discusses the epigenetic regulation and potential clinical applications of miRNAs as well as the increasing involvement of CSCs in the pathogenesis of GC.

BIOGENESIS AND FUNCTIONS OF MIRNAS

Typically, miRNAs, which are evolutionarily conserved non-coding single-stranded RNAs, comprise 19–25 nucleotides [11]. Most miRNA genes are transcribed by RNA polymerase II (Pol II), and sometimes by RNA polymerase III (Pol III), with the long primary transcript (pri-miRNAs), harboring a hairpin structure, which comprises the miRNA sequence[12]. The following are the two crucial components of the microprocessor complex involved in miRNA synthesis: A double-stranded RNase III enzyme (DROSHA) and cofactor DiGeorge syndrome Critical Region 8 (Figure 1). Both are partic-

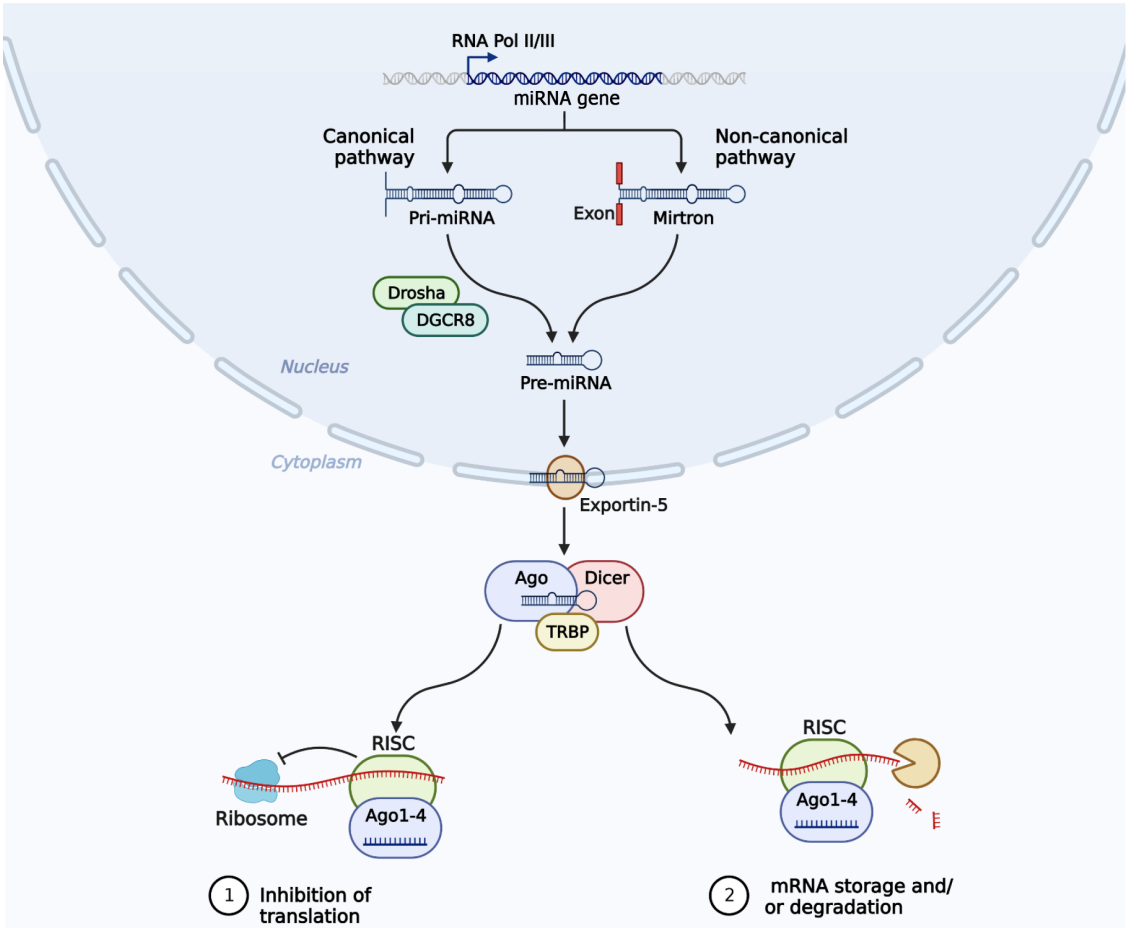

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Figure 1 Transcription and synthesis of microRNAs. These figures were created with BioRender.com, https://www.biorender.com/. miRNAs: MicroRNAs; Pol: Polymerase; pri-miRNA: primary transcript.

ularly important in the cleavage reaction in the nucleus, which produces approximately 70 nucleotides stem–loop precursor miRNAs, termed pre-miRNAs[13,14]. The mirtron pathway, also called the non-canonical pathway of miRNA, is the primary alternative mechanism for miRNA processing. A mirtron is a short hairpin intron with a splicing receptor and a donor site. Hence, the mirtron pathway is thought to be dependent on DICER but independent of DROSHA. Pre-miRNAs have been remapped to the nucleus of exportin-5 for processing[12]. In the cytoplasm, DICER enzymes (a subclass of RNase III enzymes) cleave the hairpin structure to form a double-stranded miRNA with approximately 22 nucleotides. Helicases convert these double-stranded miRNAs into single-stranded miRNAs, which interact with Argonaute (AGO) proteins to form a multiprotein RNA-induced silencing complex (Figure 1). In this complex, the translation of a particular mRNA is prevented or degraded by miRNAs[15]. After interacting with a particular mRNA, miRNAs divide the mRNA chain into two pieces, decreasing the stability of mRNA and blocking its translation into protein[16]. miRNAs play a regulatory role in the gene expression involved in numerous biological processes, including cell differentiation and proliferation, cell death, and cell-cycle progression[17]. A single miRNA can simultaneously anchor numerous targets. In addition, multiple miRNAs can impact a single mRNA. This phenomenon demonstrates the bidirectional nature of the effect of miRNAs and highlights their critical role in both healthy and unhealthy cellular processes[10].

DYSREGULATION OF MIRNAS IN CANCER

Most miRNAs are located at fragile sites or around cancer-related genomes[18]. They can simultaneously target Wnt/β-catenin, transforming growth factor β (TGF-β), Notch, and other signal pathways. Disorders of miRNA are present in almost all cancers. These disorders play an important role in the development of cancer by contributing to the generation, proliferation, metastasis, and apoptosis of cancer cells. The link between miRNAs and various cancers has been extensively studied over the past two decades. The plasma levels of miR-135b in patients with GC are noticeably greater than those in healthy individuals[19]. miR-23 and miR-21a could be responsible for poor prognosis in non-small cell lung cancer[20]. Abnormal methylation and expression of the promoters of miR-124, miR-218, and miR-193b are frequent in cervical cancer[21]. Methylation of the ataxia-telangiectasia group D complementing gene reduces the Wnt signal activation, while miR-449a overexpression inhibits the catenin expression[22]. miR-29b retards the growth of prostate

cancers and triggers cell apoptosis by boosting the expression of BIM and Bcl-2[23].

The functional diversity of miRNA reflected in cancers is related to many factors. Single nucleotide polymorphisms (SNPs) can be found in both coding and non-coding genes. Some SNPs associated with miRNA are located in the miRNA promoter region, the miRNA gene sequence, and at the miRNA-binding site of the target gene[24]. SNPs control the biological activity, transcription, and expression of target genes, which eventually affect the propensity of a person for disease and the efficacy of pharmacological treatments. Many of these SNPs related to miRNAs can be used as potential biomarkers for cancer prognosis[25]. Additionally, epigenetic changes in the CpG island or histone modifications that activate or repress transcription can affect the promoter regions of miRNA genes. These regulatory mechanisms can increase the gene expression of oncogenic miRNAs and reduce that of tumor-suppressor miRNAs[10]. Furthermore, host genes may occasionally control the production of miRNAs in genes. Additionally, modifications in the host-gene expression, such as hypermethylation, can reduce the miRNA-expression level[26]. Moreover, miRNAs can be affected when DROSHA genes contain SNPs or mutations[27], which indicates that mutations not only stop DROSHA processing but also cause pri-miRNA to express at a lower level. A direct connection has been reported between the regulation of miRNA in tumors, its regulation by lncRNA and circRNA, and the self-regulation of miRNA. lncRNA and circRNA are spongy miRNA architectures with several miRNA-binding sites. lncRNA and circRNA can directly bind miRNAs as competing endogenous RNAs[28], thereby controlling the expression levels of miRNA target genes. The expression of pre-miRNA or mature miRNA can also be controlled directly or indirectly by other miRNAs. For instance, miR-424 or miR-503 interacts with pri-miR-9 and maintains a certain dynamic equilibrium. The expression of miR-9 increases when homeostasis is disturbed, which affects the state of stemness-regulated tumor cells[29].

MICRORNA IN GCSCS: AN OVERVIEW

Abnormal expression of miRNAs is attracting increasing interest because such an expression could be closely related to GCSCs and play an integral role in the development of certain features of GC. However, as this is a relatively new field, there are some uncertainties. For example, miRNAs are involved in controlling the growth and differentiation mechanisms of GCSCs by targeting and regulating various signaling pathways such as the regulation of the cell cycle (Figure 2A), angiogenesis (Figure 2B), invasion and migration of cells (Figure 2C), and regulation of the GCSC phenotype. The mechanism of the action of miRNAs in regulating the stemness of GCSCs and GC cells is shown in Table 1.

Onco-miRNAs in GCSCs

miR-17-92 cluster: The miR-17-92 cluster, comprising miR-17-3p, miR-17-5p, miR-18, miR-19a, miR-20a, miR-19b, and miR-92a, is one of the most extensively investigated miRNA clusters[30]. The CSC spheroid formation assay (involving the size and number of tumors) is the standard method to measure the stemness of tumor cells[31]. miR-17-5p is highly expressed in CD44 (+)/EpCAM (+) GCSCs. Its expression is positively correlated with the GC cell-colony-formation ability. The number and density of tumor spheroids in GC cell lines with a high expression of miR-17-5p are greater than those in the control group. Tolerance to cisplatin and paclitaxel also improved in GC cell lines with a high expression of miR-17-5p[32]. Furthermore, the activity of the p21 3′-UTR reduced in the miR-17-5p-transfected GC cell line, indicating that miR-17-5p controls the cell cycle by targeting p21[33]. miR-18, another member of this cluster, improves the stemness of GC cells by: (1) Increasing the proportion of CD44 (+) in GC cell lines; (2) controlling the phenotype of GCSCs (such as ALDH1, SOX2, and OCT4); and (3) targeting Meis Homeobox 2 down-regulation of HMGB3 expression[34]. Similarly, the frequency of CD44 (+)/EpCAM (+) cells rose in the GC cell line transfected with pre-miR-19b, pre-miR-20a, pre-miR-92a, and miR-92a. In addition, miR-19 and miR-92a could bind to the 3'-UTR of HIPK1, while miR-20a could bind to the 3'-UTR of E2F1 and activate the β-catenin signal transduction pathway. Consequently, enhanced GCSC-colony formation and improved resistance to 5-FU are observed[35]. Cyclin-dependent kinase (CDK) 4 and CDK6, proliferating cell nuclear antigens, and p53 gene-expression levels downregulate when miR-92a is knocked down, which also greatly decreases the ability of GC cell lines to form colonies[36].

miR-21: In GC cells, miR-21 is abundantly expressed. A clinical study showed that the high expression of miR-21-5p is linked to poor prognosis[37]. The expression of miR-21 in the colonies formed by two cell lines (MKN-45 and AGS) was up-regulated by 1.8-fold and 4.7-fold[38], respectively. Another *in vitro* study confirmed its high expression in GCSCs [39]. miR-21 participates in the regulation of GCSCs by acting on multiple genes and pathways. For example, it acts on exosome miR-21-5p to induce the MMT of PMCs and on Smad7 to promote GC transfer[40]. In addition, miR-21 participates in the maintenance of GCSCs mediated by Chromobox protein homolog 7 (CBX7). CBX7 positively regulates the expression of miR-21 through the AKT-NF-κB pathway, up-regulates the expression of stem cell markers such as CD44, CD24, and Oct-4 in GC cells, and increases the size and number of colonies formed[41]. PTEN and p53 are downstream target genes of miR-21. They are also two important tumor-suppressor genes. The expression of Bmi-1 and miR-21 in GC tissues is positively correlated. miR-21 mediates the function of Bmi-1 in regulating stem-cell-like properties, while miR-34a negatively regulates stem-cell-like properties by down-regulating Bmi-1. Bmi-1 binds to the PTEN promoter and directly inhibits PTEN, resulting in the activation of AKT. p53 and PTEN can also be regulated *via* miR-21. NF-κB can be activated with AKT. Binding of NF-κB to miR-21 promoters can be promoted and its expression level can be positively regulated. PTEN and p53 expressions are down-regulated by overexpressed miR-21. The level of phosphorylated AKT downstream of PTEN increases, which in turn increases the EMT and invasion capacity of GC cells [42].

Table 1 MicroRNA dysregulation on gastric cancer stem cells

Function	miRNAs	Validated targets	Pathological process involved	Ref.
Oncogenic (promotion)	miR-17-5p	p21	Enhances the colony-forming ability of GCSCs, regulates the cell cycle of GCSCs, and promotes the drug resistance of GCSCs	[38]
	miR-18	Meis2, HMGB3	Enhances the colony-forming ability of GCSCs and promotes the drug resistance of GCSCs	[39]
	miR-19b	HIPK1, β-catenin	Enhances the colony-forming ability of GCSCs and promotes the drug resistance of GCSCs	[40]
	miR-20a	E2F1, β-catenin	Enhances the colony-forming ability of GCSCs and promotes the drug resistance of GCSCs	[40]
	miR-92a	HIPK1, β-catenin, CDK 4, CDK6, p53	Enhances the colony-forming ability of GCSCs, regulates the cell cycle of GCSCs, and promotes the drug resistance of GCSCs	[41]
	miR-21	Bmi-1, PTEN, p53, AKT	Targets Smad 7, promotes GC metastasis while down-regulating the expression of PTEN and p53 to increase the EMT and invasiveness of GC cells	[47]
	miR-95	DUSP5, ERK, JNK	Promotes GC cell stemness through activation of the DUSP5-mediated MAPK axis	[49]
	miR-106b	Smad 7, TGF-β	Up-regulates EMT markers and TGF-β/Smad signaling pathway to preserve GCSC characteristics	[51]
	miR-132	SIRT1, CREB	Up-regulates the SIRT1/CREB/ABCG2 signaling pathway to promote cisplatin resistance	[53]
	miR-151a-3p	YTHDF3, SUMO1, Smad2/3	Targets YTHDF3, activates Smad 2/3 pathway, and increases GC cell dryness	[56]
	miR-196a-5p	Smad4	Negative regulates Smad4 expression and inhibits GCSC stemness	[58]
	miR-451b	KREMEN1, CASK, LRP5/6, Fzd, AKT, PI3K, PCNA, Bcl-2	Promotes the migration and drug resistance of GCSCs	[59]
	miR-483-5p	Cyclin D1, Bcl-2, matrix metalloproteinase 2	Regulates the Wnt/β-catenin pathway and promotes the proliferation, invasion, and self-renewal of GCSCs	[60]
	miR-492	DNMT3B	Targets DNMT3B to maintain GCSC dryness, reduces the sensitivity of GCSCs to DDP	[61]
	miR-501-5p	BLID, Caspase-9, Caspase-3, AKT, DKK1, NKD1, GSK3β	Targets DKK1, NKD1, and GSK3β, activates the Wnt/β-catenin signaling pathway, maintains self-renewal, and promotes GCSC phenotype	[63, 64]
	miR-6778-5p	SHMT1	Up-regulates the stemness of GCSCs and reduces their sensitivity to 5-FU	[65, 66]
Tumor-suppressive (inhibition)	miR-7-5p	Smo, Hes1	Inhibits the expression of Smo and Hes1 as well as the stemness and invasion of GCSCs	[67]
	miR-15a-5p	ONECUT2, β-catenin, Cyclin D1	Inhibits the expression of ONECUT2, down-regulates the expression of β-catenin and Cyclin D1, and inhibits the proliferation of GCSCs	[69]
	miR-26a	HOXC9, MMP2	Inhibits EMT and angiogenesis of GCSCs by inhibiting the expression of HOXC9	[70]
	miR-29c	VEGFA, VEGFR2, ERK	Inhibits the migration, invasion, and angiogenesis of GC cells by inhibiting the VEGFA/VEGFR2/ERK pathway	[71]
	miR-34a	Bcl-2, Notch, HMGA2, Caspase-3	Up-regulates the expression of Bcl-2, increases the sensitivity of GCSCs to chemotherapeutic drugs, and inhibits EMT	[74]
	miR-98	BCAT1	Inhibits the stemness of GC cells and the expression of EMT markers, and down-regulates ABCG2 to increase the sensitivity of GCSCs to DDP	[75]
	miR-101	SOCS2, C-myc, CDK2, CDK4, CDK6, CCND2, CCND3, CCNE2, p14, p16, p21, p27	Negatively regulates SOCS2, inhibits the expression of C-myc, CDK2, CDK4, CDK6 and CCNE2, and promotes the expression of cancer inhibitors p14, p16, p21, and p27 to inhibit cell proliferation	[77]
	miR-144-3p	GLI2	Negatively regulates GLI2 expression and inhibits proliferation, invasion, and EMT of GC cells	[79]
	miR-155-5p	-	Down-regulates NF-kB p65 to reprogram BM-MSCs to GC-MSCs	[82, 83]
	miR-216a-3p	Wnt3a	BRD4 enhances GC cell stemness by targeting miR-216a-3p and subsequently activating the Wnt/β-catenin pathway	[84]

	miR-345	EPS8	Spheroid-formation ability of GCSCs, inhibits the expression of EPS8, and reduces the migration ability of GCSCs	[85]
	miR-375	SLC7A11	Inhibits the stemness of GC cells while acting on SLC7A11 to induce ferroptosis in GC cells	[86]
	miR-449a	CDK6	Regulates CDK-rb-E2F1 and down-regulates CDK6 protein to inhibit the proliferation of GC cells	[90]
	miR-449c-5p	MYC/Notch1	Regulates MYC/Notch1 and increases GC cell migration or invasion capacity	[88]
	miR-867-3p	TMED3	Negatively regulates TMED3 expression to enhance the sensitivity of GC cells to DDP	[91]

miRNAs: MicroRNAs; GCSCs: Gastric cancer stem cells; GC: Gastric cancer; DUSP5: Dual-specificity phosphatase 5; TGF-β: Transforming growth factor β; EMT: Epithelial–mesenchymal transition; Smo: Smoothened; CDK: Cyclin-dependent kinase; BM-MSCs: Bone marrow-derived mesenchymal stem/stromal cells.

miR-95: CRISPR-Cas9 Library screening showed that the miR-95-3p level is elevated in GC tissues[43]. Du *et al*[44] verified this result through *in vitro* experiments and revealed the relationship between the miR-95 expression and stemness and EMT in GC cells. Dual-specificity phosphatase 5 (DUSP5) is a miR-95 target and it inhibits the expression of MAPK signals. Notably, miR-95 may promote the stemness of GC cells by activating the DUSP5-mediated MAPK axis. Hence, after the transfection of the miR-95 mimic, the GCSC phenotype and colony-formation ability of cell lines significantly improve, DUSP5 down-regulates, the phosphorylation degree of ERK and JNK increases, the MAPK pathway gets activated, the expression of the EMT-related marker vimentin up-regulates, and the expression of E-cadherin is reduced. One explanation is that miR-95 may promote GC cell stemness by activating the DUSP5-mediated MAPK axis.

miR-106b: Elevated miR-106b expression is often associated with lymph node metastases in GC[45]. Knockdown of miR-106b significantly reduces the spheroiding ability of CD44 (+) GC cells as well as the expression of TGF-β receptor I, phosphorylated Smad 2/3, and Slug. In contrast, EMT markers E-cadherin and Occludin are up-regulated, while vimentin and a-SMA are down-regulated. Smad 7 is an inhibitor of TGF-β1 signaling[46] and a downstream target of miR-106b. The latter activates the TGF-β/Smad signaling pathway by down-regulating Smad 7. Therefore, miR-106b may retain GCSC features by upregulating EMT markers and the TGF-β/Smad signaling pathway[47].

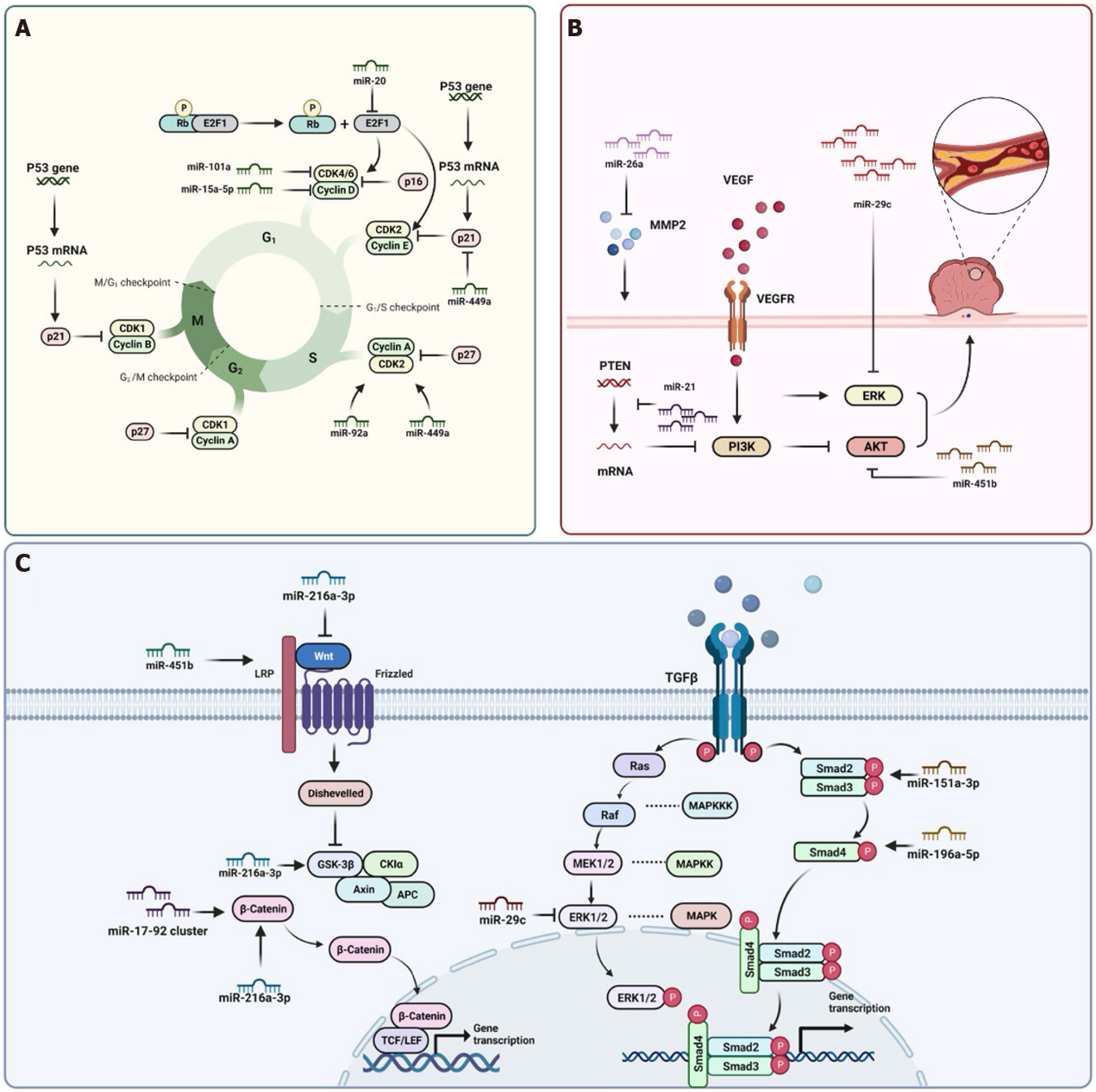
miR-132: Compared with LGR5(+) stem cells, LGR5(-) stem cells can form compact spheroids and have a higher survival rate under cisplatin. In addition, compared with LGR5(-) cells, the expression of miR-132 in LGR5(+) GCSCs is significantly increased and its resistance to cisplatin is positively correlated with the overexpression of miR-132. The expression of miR-132 tends to be negatively correlated with the SIRT1 expression[48]. Therefore, miR-132 can activate the ABCG2 signaling pathway by reducing the SIRT1 Levels ($P < 0.05$), resulting in increased CREB acetylation levels. Hence, miR-132 may promote cisplatin resistance by regulating SIRT1/CREB/ABCG2 signaling pathways[49].

miR-151a-3p: Small extracellular vesicles (sEVs) play an important role in intercellular communication[50]. Li *et al*[51] found that miR-151a-3p sEV is highly expressed in the plasma of patients with liver metastasis (LM) of GC, and that the use of miR-151a-3p-rich sEVs in mice with GC promotes GC-LM without any effect on GC cell proliferation in situ. Subsequent studies showed that miR-151a-3p sEV targets YTHDF3, reduces SP6 transcriptional inhibition by decreasing the translation of SUMO1 in an N6-methyladenosine-dependent fashion, activates the Smad 2/3 pathway, and increases the GC cell stemness. miR-151a-3p could be an LM-specific miRNA that enhances the GC cell stemness and promotes LM.

miR-196a-5p: A translational study showed that miR-196-a2 is a genetic factor significantly related to overall survival [52], and that miR-196a-5p knockdown significantly decreases the cell number and colony formation of aggressive CD44 (+). Luciferase reporter assays have shown that Smad 4 is a direct specific target of miR-196a-5p, whose expression is negatively correlated with Smad 4. The positive regulatory effect of miR-196a-5p on GCSCs may be achieved by targeting Smad4 and by negatively regulating its expression[53].

miR-451b: In GC cell lines, the proportion of CD45 (+) cells is up-regulated under the action of docetaxel, and the stemness-related expression of SIRT1, CXCR4, and miR-451 and resistance to chemical radiation are up-regulated[39]. The miR-451b inhibitor reduces the migration ability of GCSCs by 38% within 48 h. The transcription level of the CASK gene involved in cell adhesion decreases by 40%. The expression of KREMEN1, which antagonizes the Wnt signaling pathway, is up-regulated, while that of AKT is down-regulated. P53, Bax, and CASP3 are positively regulated by the expression of PI3K, PCNA, and Bcl-2, respectively[54].

miR-483-5p: In GCSCs isolated from MKN-45 GC cell lines, the expression levels of miR-483-5p are up-regulated ($P < 0.01$). MTT experiments have shown that the overexpression of miR-483-5p following the transfection of its mimic significantly promotes the proliferation, invasion, and self-renewal of GCSCs. Annexin V propidium iodide staining showed that miR-483-5p inhibits apoptosis. In addition, β-catenin and its downstream targets Cyclin D1, Bcl-2, and matrix metalloproteinase 2 are up-regulated. Thus, miR-483-5p might function as an oncogene that regulates GCSCs through the



DOI: 10.4251/wjgo.v16.i2.300

Figure 2 Regulatory role of microRNAs in gastric cancer stem cells. A: Process by which MicroRNAs (miRNAs) regulate the cell cycle of gastric cancer stem cells (GCSCs), where miR-20 inhibits the cell cycle by inhibiting E2F1. miR-92a and miR-449a promote the cell cycle by upregulating the expression of Cyclin-dependent kinase 2. miR-449a can also inhibit the expression of p21, thereby promoting the cell cycle. B: Process by which miRNAs participate in the angiogenesis process associated with GCSCs. miR-21 promotes angiogenesis by inhibiting the expression of PTEN, while miR-26 promotes it by down-regulating MMP. miR-451b inhibits the formation of blood vessels by inhibiting the expression of AKT. C: Process through which miRNAs are involved in cell invasion and transfer, which mainly involves the Wnt/β-catenin and transforming growth factor β (TGF-β) pathways. miR-17-92a, miR-216-3p, and miR-451b up-regulation of the Wnt/β-catenin pathway. miR-151a-3p and miR-196a-3p positively regulate the TGF-β pathway, while miR-29c negatively regulates it. These figures were created with BioRender.com, https://www.biorender.com/.

Wnt/β-catenin signaling pathway[55].

miR-492: Wu *et al*[56] studied the association between miR-492 and the stemness maintenance of GCSCs and drug resistance through *in vitro* and *in vivo* experiments. The miR-492 overexpression significantly up-regulates the expression of GCSC markers in GC cells. The maintenance of GCSC stemness by miR-492 is achieved by targeting DNMT3B. In addition, knocking down miR-492 can increase and promote the sensitivity of cisplatin to GCSCs. However, the mechanism needs to be further explored.

miR-501-5p: In human hepatocellular carcinoma, miR-501-5p is overexpressed. It promotes the proliferation, migration, invasion, and drug resistance of cancer cells[57]. The overexpression of miR-501 has been reported in doxorubicin-resistant GC SGC7901/ADR cell secretory exosomes (ADR Exo). The mechanism of resistance may involve the down-

regulation of BLID, caspase-9/-3 inactivation, and AKT phosphorylation[58]. Fan *et al*[59] explored the association of miR-501 with GC pathogenesis by examining clinical specimens and by conducting *in vitro* experiments. They indicated that miR-501-5p is significantly up-regulated in GC cell lines as well as in clinical tissues, and that miR-501-5p overexpression could significantly enhance the GC cell-colony-forming ability. Luciferase reporter assays and western blotting confirmed that miR-501-5p activates the Wnt/β-catenin signaling pathway by targeting DKK1, NKD1, and GSK3β, thereby maintaining the self-renewal and promoting the GCSC phenotype.

miR-6778-5p: MiR-6778-5p is an atypical miRNA that is a key regulator for maintaining stemness in DROSHA-silent GC cells. It promotes the occurrence of GC malignancies by targeting the expression of SHMT1 in YWHAE in DROSHA-knockdown GC cells[60]. Zhao *et al*[61] showed that the knockdown of miR-6778-5p significantly decreases the formation of GCSC spheroids by down-regulating the expression of SHMT1 and increases the sensitivity of DROSHA-knockdown GCSCs to 5-FU, thereby improving the efficacy of chemotherapy.

Tumor-suppressor miRNAs in GCSCs

miR-7-5p: Smoothened (Smo) and Hairy/Enhancer of split-1 (Hes1) enhance the sphere-formation and cell-invasion ability of CD44 (+) cells by participating in the regulation of Notch and Hedgehog pathways. Various *in vivo* experiments have shown that the miR-7-5p mimic inhibits the activity of Smo 3′-UTR-WT and Hes1 3′-UTR-WT. In addition, *in vivo* experiments using lenti-miR-7-5p CD44 (+) cells were used for verification. The results were consistent with those of *in vitro* experiments, indicating that miR-7-5p inhibits GCSC sphere-formation ability, cell-invasion ability, and the occurrence and development of GC through the consistent expression of Smo and Hes1[62].

miR-15a-5p: *ONECUT2* is an oncogene of GC[63]. Its elevated expression positively correlates with lymphatic metastases. miR-15a-5p is weakly expressed, whereas *ONECUT2* is strongly expressed in CD133 (+)/CD44 (+) GC cells. Experiments using the diluciferase reporter gene have shown that miR-15a-5p inhibits *ONECUT2* transcription levels by conservatively binding to the 3′-UTR of *ONECUT2*. The *ONECUT2* overexpression can upregulate the β-catenin and Cyclin D1 expression, thereby significantly increasing the proportion of G0/G1 phase cells and reducing that of G2/M phase cells. The overexpression of miR-15a-5p can significantly inhibit the expression of β-catenin. Cyclin D1, C-myc, and survivin have also been shown to inhibit GCSC proliferation[64].

miR-26a: HOXC9 is a member of the homeobox gene family. Its overexpression is linked to the progression of GC. It has been suggested that it could be used as a marker of poor prognosis in patients with GC[65]. After silencing HOXC9, the percentage of CD44 (+)/EpCAM (+) cells in BGC823 cells significantly decreases, the expression of MMP2 down-regulates, and the expression of the markers of EMT (N-cadherin and vimentin) reduces, thus mediating angiogenesis. After transfection using lenti-miR-26a, the expression of the mRNA level of HOXC9 decreases by 78.3%, while that of the protein level decreases by 65.3%. These results show that HOXC9 promotes the transfer of GC cells through EMT. In addition, the expression of GCSC markers is up-regulated. And the deletion of miR-26a could be a key factor for the abnormal overexpression of HOXC9 in GC.

miR-29c: Overexpression of miR-29c reduces the number of migratory and invasive cells in *in vitro* experiments[66]. miR-29c overexpression in endosomes from nude mice significantly reduces the number of peritoneal nodules and lung metastasis. In miR-29c-overexpressed cells, N-cadherin, vimentin, and stem cell markers CD24, CD44, CD90, and CD133 significantly downregulate. Mechanistically, the overexpression of miR-29c is shown to reduce both VEGFA mRNA expression and luciferase activity in GCSCs. The ability to generate blood vessels is lower in miR-29c-overexpressed cells than it is in the miR-29c NC group, and the level of ERK 1/2 phosphorylation becomes lower than that in control cells. Thus, VEGFA is a direct target of miR-29c. Notably, miR-29c could inhibit the migration, invasion, and angiogenesis of GC cells through the inhibition of the VEGFA/VEGFR2/ERK pathway[66].

miR-34a: The miR-34 family (miR-34a/b/c) can be used as an indicator of tumor suppressor in GC. Induced by p53, it arrests the cell cycle and inhibits GC cell proliferation, migration, and metastasis[67]. The regulation of GCSCs by miR-34 was first investigated in 2008 when Ji *et al*[68] reported a decrease in the expression of pri-miR-34a and mature miR-34a in Kato III cells and a significant decrease in the size of tumor spheres formed by Kato III cell lines transfected with the miR-34a mimic. In terms of the mechanism, miR-34a may enhance the GCSC sensitivity to doxorubicin, cisplatin, gemcitabine, and docetaxel through positive regulation of the Bcl-2 expression. Another study showed that miR-34a overexpression significantly reduces the expression of GCSC surface markers and the EMT-promoting protein Snail, promotes apoptosis, and inhibits the proliferation and migration of GC cells[69].

miR-98: Zhan *et al*[70] used RT-qPCR to detect the miR-98 expression in the GCSCs of CD44 (+) cells. The expression level of miR-98 was found to decrease in CD44 (+) GCSCs. Further transfection of CD44 (+) GCSCs with lenti-miR-98 showed that the up-regulation of miR-98 significantly reduces the expression of SOX2 protein, NANOG, and OCT4 in CD44 (+) GCSCs. Branched-chain aminotransferases 1 (BCAT1), a target gene of miR-98, can reverse the xenograft tumor-formation ability after overexpression. Furthermore, it was suggested that the overexpression of miR-98 significantly reduces BCAT1 protein expression in the GCSCs of CD44 (+) mice, while it up-regulates the vimentin expression, down-regulates the E-cadherin expression, and inhibits the EMT process. CD44 (+) GCSCs were incubated with cisplatin to test the effect of miR-98 on resistance exhibited by GCSCs. Down-regulation of ABCG2 by the overexpression of miR-98 significantly reduces the half-maximal (50%) inhibitory concentration (IC50) values of cisplatin compared to that of the negative control strain.

miR-101: SOCS2 is a member of the inhibitors of cytokine signaling proteins. Its down-regulation can result in the inhibition of cell growth[71]. Zhou *et al*[72] showed that miR-101 inhibits SOCS2 expression in a dose-dependent manner and supports it as a direct target of miR-101 in GC cells. Various mechanistic studies have shown that miR-101 can inhibit the expression of c-myc, CDK2, CDK4, CDK6, and CCNE2 by negatively regulating SOCS2, and promote the expression of cancer suppressors p14, p16, p21, and p27 to inhibit cell proliferation.

miR-144-3p: GLI2, an end effector of the Hedgehog signaling pathway[73], which is highly expressed in GC tissues, indicates a poor prognosis. Lu *et al*[74] found that the expression of GLI2 was up-regulated, whereas that of miR-144-3p was down-regulated in 14/21 patients and most of the GC cell lines. Diluciferase assays confirmed that miR-144-3p can bind directly to the 3′-UTR of GLI2 mRNA. Thus, the miR-144-3p expression is negatively correlated with the GLI2 expression. Transfection of the miR-144-3p mimic reduces the GCSC-colony-forming ability and phenotype. The expression of E-cadherin is up-regulated, while that of N-cadherin is down-regulated. The results showed that miR-144-3p inhibits the proliferation, invasion, and EMT of GC cells, and weakens their stemness, while negatively regulating the GLI2 expression, which may be associated with better GC prognosis.

miR-155-5p: miR-155 participates in the reprogramming of normal cells to tumor cells. In ovarian cancer, miR-155-5p is involved in the reprogramming of normal fibroblasts to cancer-associated fibroblasts (CAFs)[75]. In the marrow with miR-155 deletion, macrophages first accumulate in the cancer microenvironment and then polarize to become tumor-promoting M2-type macrophages[76]. Bone marrow-derived mesenchymal stem/stromal cells (BM-MSCs) are important tumor stromal cell precursors and one of the major sources of GCSCs. Studies have demonstrated that miR-155-5p in GC-MSCs is significantly down-regulated relative to that in BM-MSCs. Knockdown of miR-155-5p in BM-MSCs results in the acquisition of its GC-MSC-like phenotype and function, whereas the miR-155-5p overexpression reverses the phenotype and function of the protumor in GC-MSCs[77,78]. Mechanistically, the miR-155-5p mimic binds to the luc-NF-κB p65 3'-UTR, inhibiting its luciferase activity. miR-155-5p has also been implicated in the reprogramming of BM-MSCs to GC-MSCs through the down-regulation of NF-κB p65, which could be a therapeutic target for GC.

miR-216a-3p: Song *et al*[79] suggested that the expression of BRD4 in GC tissues is significantly up-regulated compared to that in normal paracancerous tissues. The expressions of ALDH1, NANOG, Oct 1/2/4, SOX2, SOX9, and CD44 are significantly reduced in the BRD4-knocked GC cell lines. The expression of the Wnt/β-catenin pathway is also significantly decreased. RNA sequencing showed that miR-216a-3p is the most significantly up-regulated miRNA in the BRD4 knockdown reaction. BRD4 bound directly to the promoter increases the methylation level of the miR-216a promoter, thus reducing the level of the miR-216a-3p gene expression. After the overexpression of miR-216a-3p, the luciferase activity of Luc-Wnt3a-3'-UTR-wt significantly reduces, which indicates that Wnt3a is a direct target of miR-216a-3p. Hence, it can be suggested that BRD4 enhances the GC cell stemness by targeting miR-216a-3p and subsequently activating the Wnt/β-catenin pathway. Thus, miR-216a-3p could be a potential therapeutic target for GC.

miR-345: The miR-345 expression in tumor tissues is significantly lower than that in normal tissues. In addition, the degree of expression has been reported to correlate with the TNM grade ($P < 0.05$)[80]. In transwell and sphere-formation experiments, overexpressed miR-345 could inhibit the migration and spheroid-forming ability of GC cell lines. The expression of Oct 4, CD24, and E-cadherin decreases, while that of Snail and Slug increases. As an oncogene, *EPS8* promotes the migration and formation of GC cell spheres, because miR-345 could target *EPS8* by binding directly to its 3'-UTR.

miR-375: The overexpression of miR-375 *in vitro* inhibits the colony-formation ability, making it almost impossible for GC cells to form spheres. The expression of Oct 3/4, ALDH1, and CD44 decreases. Overexpression of miR-375 in nude mice also inhibits the number of tumor formations. The protein and mRNA levels of SLC7A11 decrease in GC cells overexpressing miR-375. Further studies have revealed that the luciferase activity of miR-3'-UTR-wt is significantly inhibited by the overexpression of miR-375. Therefore, SLC7A11 has been identified as a direct target of miR-375, whereas the miR-375/SLC7A11 axis has been shown to inhibit GC cell stemness by inducing ferroptosis[81].

miR-449: miR-449 is a cancer-suppressor miRNA that induces aging and apoptosis *via* activation of the p53 pathway[82]. Zhao *et al*[83] showed that the miR-449c-5p/MYC/Notch1 axis plays an important regulatory role in GC migration or invasion capacity and stem maintenance. CDK6, a member of the CDK family, is an important cell-cycle control factor. Up-regulation of the CDK6 protein expression prolongs the G1 phase of cells and the proliferation rate changes positively [84]. Li *et al*[85] found that the miR-449a expression and CDK6 protein expression were down-regulated in GC tissues. Studies on its mechanism showed that miR-449a could not only regulate CDK-rb-E2F1 through self-regulating feedback loops but also downregulate CDK6 protein to inhibit GC cell proliferation.

miR-867-3p: miR-876-3p is down-regulated in GCs. Its miRNA levels have been found to be negatively correlated with cisplatin resistance in GC patients. It inhibits the resistance of SGC-7901/DDP and MKN-45/DDP, which are cisplatin-resistant cell lines. It also reduces the stemness, manifested as reduced cell viability, IC_{50}, and colony-forming ability. In addition, it down-regulates the Sox 2, Oct 4, CD133, and CD44 expression. Luciferase assays confirmed that TMED3 is a direct target of miR-876-3p, and that miR-876-3p enhances the sensitivity of GC cells to DDP by negatively regulating the TMED3 expression[86].

MIRNAS AS THERAPEUTIC TARGETS IN GC: FROM BENCH TO BEDSIDE

Current chemotherapy and radiotherapy treatments usually involve killing differentiated GC cells. However, they cannot eliminate all GCSCs with a high renewal capacity, which is often a major cause of GC treatment failure or drug resistance [87]. miRNAs have already been identified as potential therapeutic targets for anti-cancer drugs. Hence, understanding their role in the maintenance of the stemness of GCSCs is of clinical value. Some characteristics of miRNAs make them a particularly good target for early clinical studies to inhibit EMT. The identification and diagnosis of miRNAs in GCSCs have been extensively investigated. For example, studies have been conducted on the up-regulation of miR-15b-5p in CD44 (+) GCSCs, miR-3631-3p in CD90 (+) GCSCs, and miR-1910-5p in CD2 (+) GCSCs[88].

miRNAs are considered to exhibit possible tumor-promoting roles in various GCSC subtypes. Many preclinical and clinical studies on miRNAs as targets are underway. However, their effective delivery to target tissues faces substantial obstacles. Viral vectors can be used for the *in vivo* delivery of genes. Viral vectors afford low vector-related toxicity risk and high gene-transfer efficiency, making them highly useful for miRNA therapy. Several studies have reported on the lentivirus-based therapeutic miRNA delivery[40,73]. Therapeutic miRNAs can be delivered to specific sites with the help of nanovesicles, thereby affording specifically targeted effects[89]. For example, intelligent gelatinase-stimuli-infused nanoparticles (NPs) have been employed to deliver miR-200c. These NPs promote the integration of miR-200c into GCSCs and realize its sustained expression in cancer cells[90].

Aging involves DNA hypermethylation, whereas cancer cells are generally characterized by hypomethylation. Because the DNA methylation clock is an important marker of aging, hypermethylation at specific sites in some tumor cells is considered to be owing to age-related epigenetic changes[91]. Aberrant methylation and expression of some miRNA promoters are common in GC. Accelerated aging owing to epigenetic methylation in GC patients has a certain prognostic value in GC. Hence, epigenetic methylation can be used as an indicator of molecular subtypes[92]. Despite its importance, the mechanism of how this epigenetic clock affects cancer and even CSCs has not yet been elucidated. Hence, further *in vivo* and *in vitro* model experiments on the epigenetic clock are needed.

CONCLUSION

This review discussed some promising early results that highlight the clinical value of miRNAs as therapeutic targets affecting stemness in GC. In addition, the results support further investigation of miRNAs in other diseases as well. The review also showed that miRNAs related to the stemness regulation of cancer stem cells, such as miR-17-92 cluster and miR-95, play an important role in the tumor phenotype and cell activity. Hence, they can be used as prognostic indicators for GC treatment and chemotherapy resistance. The discovery of miR-449 and miR-15a-5p suggests that some miRNAs with tumor-suppressor genes can intervene in the early apoptosis of GC cells and inhibit the initial formation of tumors. This review shows that the early stage of GC tumors can also be metastatic. Moreover, it suggested that miRNAs have a therapeutic potential and can be used as an effective novel cancer therapy. Optimized therapeutic miRNA mimics can be delivered *in vivo* or gene knockout can be conducted using miRNA antagonists to regulate GCSCs, which may help in reversing or preventing GC metastasis. We believe emerging therapeutic approaches for GC would benefit from a strong understanding of the regulatory role of miRNAs in GCSCs, including the characterization of certain overexpressed miRNAs that help in the diagnosis and differentiation of GCSC subtypes and in elucidating their tumor-promoting mechanisms. Robust *in vitro* and *in vivo* models should be developed to test candidate therapies that will accelerate further research in this exciting field.

FOOTNOTES

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Author contributions: Sun QH and Kuang ZY contributed equally to this work, as the co-first authors, reviewed the literature and drafted the manuscript; Zhu GH and Ni BY reviewed the literature and drew charts; Li J conceived this article.

Supported by the National Natural Science Foundation of China, No. 82074402; and the Science and Technology Innovation Project of China Academy of Chinese Medical Sciences; No. CI2021A01802.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Li L

L-Editor: A
P-Editor: Zhang XD

REFERENCES

1 **Zhao Q**, Cao L, Guan L, Bie L, Wang S, Xie B, Chen X, Shen X, Cao F. Immunotherapy for gastric cancer: dilemmas and prospect. *Brief Funct Genomics* 2019; **18**: 107-112 [PMID: 30388190 DOI: 10.1093/bfgp/ely019]
2 **Takahari D**, Chin K, Ishizuka N, Takashima A, Minashi K, Kadowaki S, Nishina T, Nakajima TE, Amagai K, Machida N, Goto M, Taku K, Wakatsuki T, Shoji H, Hironaka S, Boku N, Yamaguchi K. Multicenter phase II study of trastuzumab with S-1 plus oxaliplatin for chemotherapy-naïve, HER2-positive advanced gastric cancer. *Gastric Cancer* 2019; **22**: 1238-1246 [PMID: 31102009 DOI: 10.1007/s10120-019-00973-5]
3 **Ferlay J**, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, Znaor A, Bray F. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 2019; **144**: 1941-1953 [PMID: 30350310 DOI: 10.1002/ijc.31937]
4 **Lee TK**, Guan XY, Ma S. Cancer stem cells in hepatocellular carcinoma - from origin to clinical implications. *Nat Rev Gastroenterol Hepatol* 2022; **19**: 26-44 [PMID: 34504325 DOI: 10.1038/s41575-021-00508-3]
5 **Abad E**, Graifer D, Lyakhovich A. DNA damage response and resistance of cancer stem cells. *Cancer Lett* 2020; **474**: 106-117 [PMID: 31968219 DOI: 10.1016/j.canlet.2020.01.008]
6 **Fukui R**, Saga R, Matsuya Y, Tomita K, Kuwahara Y, Ohuchi K, Sato T, Okumura K, Date H, Fukumoto M, Hosokawa Y. Tumor radioresistance caused by radiation-induced changes of stem-like cell content and sub-lethal damage repair capability. *Sci Rep* 2022; **12**: 1056 [PMID: 35058559 DOI: 10.1038/s41598-022-05172-4]
7 **Takaishi S**, Okumura T, Wang TC. Gastric cancer stem cells. *J Clin Oncol* 2008; **26**: 2876-2882 [PMID: 18539967 DOI: 10.1200/JCO.2007.15.2603]
8 **Seeneevassen L**, Bessède E, Mégraud F, Lehours P, Dubus P, Varon C. Gastric Cancer: Advances in Carcinogenesis Research and New Therapeutic Strategies. *Int J Mol Sci* 2021; **22** [PMID: 33810350 DOI: 10.3390/ijms22073418]
9 **Ma Y**, Qi M, An Y, Zhang L, Yang R, Doro DH, Liu W, Jin Y. Autophagy controls mesenchymal stem cell properties and senescence during bone aging. *Aging Cell* 2018; **17** [PMID: 29210174 DOI: 10.1111/acel.12709]
10 **de Rooij LA**, Mastebroek DJ, Ten Voorde N, van der Wall E, van Diest PJ, Moelans CB. The microRNA Lifecycle in Health and Cancer. *Cancers (Basel)* 2022; **14** [PMID: 36497229 DOI: 10.3390/cancers14235748]
11 **Volovat SR**, Volovat C, Hordila I, Hordila DA, Mirestean CC, Miron OT, Lungulescu C, Scripcariu DV, Stolniceanu CR, Konsoulova-Kirova AA, Grigorescu C, Stefanescu C, Volovat CC, Augustin I. MiRNA and LncRNA as Potential Biomarkers in Triple-Negative Breast Cancer: A Review. *Front Oncol* 2020; **10**: 526850 [PMID: 33330019 DOI: 10.3389/fonc.2020.526850]
12 **Michlewski G**, Cáceres JF. Post-transcriptional control of miRNA biogenesis. *RNA* 2019; **25**: 1-16 [PMID: 30333195 DOI: 10.1261/rna.068692.118]
13 **Han J**, Lee Y, Yeom KH, Kim YK, Jin H, Kim VN. The Drosha-DGCR8 complex in primary microRNA processing. *Genes Dev* 2004; **18**: 3016-3027 [PMID: 15574589 DOI: 10.1101/gad.1262504]
14 **Zeng Y**, Yi R, Cullen BR. Recognition and cleavage of primary microRNA precursors by the nuclear processing enzyme Drosha. *EMBO J* 2005; **24**: 138-148 [PMID: 15565168 DOI: 10.1038/sj.emboj.7600491]
15 **Zhang X**, Liu F, Yang F, Meng Z, Zeng Y. Selectivity of Exportin 5 binding to human precursor microRNAs. *RNA Biol* 2021; **18**: 730-737 [PMID: 34592896 DOI: 10.1080/15476286.2021.1984096]
16 **Lin S**, Gregory RI. MicroRNA biogenesis pathways in cancer. *Nat Rev Cancer* 2015; **15**: 321-333 [PMID: 25998712 DOI: 10.1038/nrc3932]
17 **Ross SA**, Davis CD. The emerging role of microRNAs and nutrition in modulating health and disease. *Annu Rev Nutr* 2014; **34**: 305-336 [PMID: 25033062 DOI: 10.1146/annurev-nutr-071813-105729]
18 **Kabekkodu SP**, Shukla V, Varghese VK, Adiga D, Vethil Jishnu P, Chakrabarty S, Satyamoorthy K. Cluster miRNAs and cancer: Diagnostic, prognostic and therapeutic opportunities. *Wiley Interdiscip Rev RNA* 2020; **11**: e1563 [PMID: 31436881 DOI: 10.1002/wrna.1563]
19 **Wu Y**, Hu G, Wu R, Gong N. High expression of miR-135b predicts malignant transformation and poor prognosis of gastric cancer. *Life Sci* 2020; **257**: 118133 [PMID: 32710946 DOI: 10.1016/j.lfs.2020.118133]
20 **Hetta HF**, Zahran AM, Shafik EA, El-Mahdy RI, Mohamed NA, Nabil EE, Esmaeel HM, Alkady OA, Elkady A, Mohareb DA, Hosni A, Mostafa MM. Circulating miRNA-21 and miRNA-23a Expression Signature as Potential Biomarkers for Early Detection of Non-Small-Cell Lung Cancer. *Microrna* 2019; **8**: 206-215 [PMID: 30652656 DOI: 10.2174/1573399815666190115151500]
21 **Jiménez-Wences H**, Martínez-Carrillo DN, Peralta-Zaragoza O, Campos-Viguri GE, Hernández-Sotelo D, Jiménez-López MA, Muñoz-Camacho JG, Garzón-Barrientos VH, Illades-Aguiar B, Fernández-Tilapa G. Methylation and expression of miRNAs in precancerous lesions and cervical cancer with HPV16 infection. *Oncol Rep* 2016; **35**: 2297-2305 [PMID: 26797462 DOI: 10.3892/or.2016.4583]
22 **Li F**, Liang J, Bai L. MicroRNA-449a functions as a tumor suppressor in pancreatic cancer by the epigenetic regulation of ATDC expression. *Biomed Pharmacother* 2018; **103**: 782-789 [PMID: 29684857 DOI: 10.1016/j.biopha.2018.04.101]
23 **Sur S**, Steele R, Shi X, Ray RB. miR-29b Inhibits Prostate Tumor Growth and Induces Apoptosis by Increasing Bim Expression. *Cells* 2019; **8** [PMID: 31752117 DOI: 10.3390/cells8111455]
24 **Pan L**, Shi Y, Zhang J, Luo G. Association Between Single Nucleotide Polymorphisms of miRNAs and Gastric Cancer: A Scoping Review. *Genet Test Mol Biomarkers* 2022; **26**: 459-467 [PMID: 36251855 DOI: 10.1089/gtmb.2021.0258]
25 **Yuan Y**, Weidhaas JB. Functional microRNA binding site variants. *Mol Oncol* 2019; **13**: 4-8 [PMID: 30536617 DOI: 10.1002/1878-0261.12421]
26 **Newie I**, Søkilde R, Persson H, Jacomasso T, Gorbatenko A, Borg Å, de Hoon M, Pedersen SF, Rovira C. HER2-encoded mir-4728 forms a receptor-independent circuit with miR-21-5p through the non-canonical poly(A) polymerase PAPD5. *Sci Rep* 2016; **6**: 35664 [PMID: 27752128 DOI: 10.1038/srep35664]
27 **Le CT**, Nguyen TL, Nguyen TD, Nguyen TA. Human disease-associated single nucleotide polymorphism changes the orientation of DROSHA on pri-mir-146a. *RNA* 2020; **26**: 1777-1786 [PMID: 32994184 DOI: 10.1261/rna.077487.120]

28 **Landeros N**, Santoro PM, Carrasco-Avino G, Corvalan AH. Competing Endogenous RNA Networks in the Epithelial to Mesenchymal Transition in Diffuse-Type of Gastric Cancer. *Cancers (Basel)* 2020; **12** [PMID: 32987716 DOI: 10.3390/cancers12102741]

29 **Forrest AR**, Kanamori-Katayama M, Tomaru Y, Lassmann T, Ninomiya N, Takahashi Y, de Hoon MJ, Kubosaki A, Kaiho A, Suzuki M, Yasuda J, Kawai J, Hayashizaki Y, Hume DA, Suzuki H. Induction of microRNAs, mir-155, mir-222, mir-424 and mir-503, promotes monocytic differentiation through combinatorial regulation. *Leukemia* 2010; **24**: 460-466 [PMID: 19956200 DOI: 10.1038/leu.2009.246]

30 **Zhang X**, Li Y, Qi P, Ma Z. Biology of MiR-17-92 Cluster and Its Progress in Lung Cancer. *Int J Med Sci* 2018; **15**: 1443-1448 [PMID: 30443163 DOI: 10.7150/ijms.27341]

31 **Jinesh GG**, Choi W, Shah JB, Lee EK, Willis DL, Kamat AM. Blebbishields, the emergency program for cancer stem cells: sphere formation and tumorigenesis after apoptosis. *Cell Death Differ* 2013; **20**: 382-395 [PMID: 23175184 DOI: 10.1038/cdd.2012.140]

32 **Dai ZT**, Xiang Y, Duan YY, Wang J, Li JP, Zhang HM, Cheng C, Wang Q, Zhang TC, Liao XH. MiR-17-5p and MKL-1 modulate stem cell characteristics of gastric cancer cells. *Int J Biol Sci* 2021; **17**: 2278-2293 [PMID: 34239355 DOI: 10.7150/ijbs.57338]

33 **Wang Z**, Ji F. Downregulation of microRNA-17-5p inhibits drug resistance of gastric cancer cells partially through targeting p21. *Oncol Lett* 2018; **15**: 4585-4591 [PMID: 29541229 DOI: 10.3892/ol.2018.7822]

34 **Zhang Y**, Lin W, Jiang W, Wang Z. MicroRNA-18 facilitates the stemness of gastric cancer by downregulating HMGB3 though targeting Meis2. *Bioengineered* 2022; **13**: 9959-9972 [PMID: 35416122 DOI: 10.1080/21655979.2022.2062529]

35 **Shao Q**, Xu J, Guan X, Zhou B, Wei W, Deng R, Li D, Xu X, Zhu H. *In vitro* and *in vivo* effects of miRNA-19b/20a/92a on gastric cancer stem cells and the related mechanism. *Int J Med Sci* 2018; **15**: 86-94 [PMID: 29333091 DOI: 10.7150/ijms.21164]

36 **Tao XC**, Zhang XY, Sun SB, Wu DQ. miR92a contributes to cell proliferation, apoptosis and doxorubicin chemosensitivity in gastric carcinoma cells. *Oncol Rep* 2019; **42**: 313-320 [PMID: 31180538 DOI: 10.3892/or.2019.7168]

37 **Zhang C**, Zhang CD, Liang Y, Wu KZ, Pei JP, Dai DQ. The comprehensive upstream transcription and downstream targeting regulation network of miRNAs reveal potential diagnostic roles in gastric cancer. *Life Sci* 2020; **253**: 117741 [PMID: 32360623 DOI: 10.1016/j.lfs.2020.117741]

38 **Bakhshi M**, Asadi J, Ebrahimi M, Moradi AV, Hajimoradi M. Increased expression of miR-146a, miR-10b, and miR-21 in cancer stem-like gastro-spheres. *J Cell Biochem* 2019; **120**: 16589-16599 [PMID: 31095782 DOI: 10.1002/jcb.28918]

39 **Motamedi M**, Razmkhah F, Rezakhani L, Ghasemi S. Altered Expression of CD44, SIRT1, CXCR4, miR-21, miR-34a, and miR-451 Genes in MKN-45 Cell Line After Docetaxel Treatment. *J Gastrointest Cancer* 2020; **51**: 520-526 [PMID: 31273630 DOI: 10.1007/s12029-019-00274-1]

40 **Li Q**, Li B, Li Q, Wei S, He Z, Huang X, Wang L, Xia Y, Xu Z, Li Z, Wang W, Yang L, Zhang D. Exosomal miR-21-5p derived from gastric cancer promotes peritoneal metastasis *via* mesothelial-to-mesenchymal transition. *Cell Death Dis* 2018; **9**: 854 [PMID: 30154401 DOI: 10.1038/s41419-018-0928-8]

41 **Ni SJ**, Zhao LQ, Wang XF, Wu ZH, Hua RX, Wan CH, Zhang JY, Zhang XW, Huang MZ, Gan L, Sun HL, Dimri GP, Guo WJ. CBX7 regulates stem cell-like properties of gastric cancer cells *via* p16 and AKT-NF-κB-miR-21 pathways. *J Hematol Oncol* 2018; **11**: 17 [PMID: 29422082 DOI: 10.1186/s13045-018-0562-z]

42 **Wang X**, Wang C, Zhang X, Hua R, Gan L, Huang M, Zhao L, Ni S, Guo W. Bmi-1 regulates stem cell-like properties of gastric cancer cells *via* modulating miRNAs. *J Hematol Oncol* 2016; **9**: 90 [PMID: 27644439 DOI: 10.1186/s13045-016-0323-9]

43 **Kurata JS**, Lin RJ. MicroRNA-focused CRISPR-Cas9 Library screen reveals fitness-associated miRNAs. *RNA* 2018; **24**: 966-981 [PMID: 29720387 DOI: 10.1261/rna.066282.118]

44 **Du M**, Zhuang Y, Tan P, Yu Z, Zhang X, Wang A. microRNA-95 knockdown inhibits epithelial-mesenchymal transition and cancer stem cell phenotype in gastric cancer cells through MAPK pathway by upregulating DUSP5. *J Cell Physiol* 2020; **235**: 944-956 [PMID: 31309567 DOI: 10.1002/jcp.29010]

45 **LArki P**, Ahadi A, Zare A, Tarighi S, Zaheri M, Souri M, Zali MR, Ghaedi H, Omrani MD. Up-Regulation of miR-21, miR-25, miR-93, and miR-106b in Gastric Cancer. *Iran Biomed J* 2018; **22**: 367-373 [PMID: 29859516 DOI: 10.29252/.22.6.367]

46 **Troncone E**, Monteleone G. Smad7 and Colorectal Carcinogenesis: A Double-Edged Sword. *Cancers (Basel)* 2019; **11** [PMID: 31052449 DOI: 10.3390/cancers11050612]

47 **Yu D**, Shin HS, Lee YS, Lee YC. miR-106b modulates cancer stem cell characteristics through TGF-β/Smad signaling in CD44-positive gastric cancer cells. *Lab Invest* 2014; **94**: 1370-1381 [PMID: 25286029 DOI: 10.1038/labinvest.2014.125]

48 **Han S**, Lin F, Ruan Y, Zhao S, Yuan R, Ning J, Jiang K, Xie J, Li H, Li C, Rao T, Yu W, Xia Y, Zhou X, Cheng F. miR-132-3p promotes the cisplatin-induced apoptosis and inflammatory response of renal tubular epithelial cells by targeting SIRT1 *via* the NF-κB pathway. *Int Immunopharmacol* 2021; **99**: 108022 [PMID: 34339961 DOI: 10.1016/j.intimp.2021.108022]

49 **Zhang L**, Guo X, Zhang D, Fan Y, Qin L, Dong S, Zhang L. Upregulated miR-132 in Lgr5(+) gastric cancer stem cell-like cells contributes to cisplatin-resistance *via* SIRT1/CREB/ABCG2 signaling pathway. *Mol Carcinog* 2017; **56**: 2022-2034 [PMID: 28383763 DOI: 10.1002/mc.22656]

50 **Urabe F**, Kosaka N, Ito K, Kimura T, Egawa S, Ochiya T. Extracellular vesicles as biomarkers and therapeutic targets for cancer. *Am J Physiol Cell Physiol* 2020; **318**: C29-C39 [PMID: 31693397 DOI: 10.1152/ajpcell.00280.2019]

51 **Li B**, Xia Y, Lv J, Wang W, Xuan Z, Chen C, Jiang T, Fang L, Wang L, Li Z, He Z, Li Q, Xie L, Qiu S, Zhang L, Zhang D, Xu H, Xu Z. miR-151a-3p-rich small extracellular vesicles derived from gastric cancer accelerate liver metastasis *via* initiating a hepatic stemness-enhancing niche. *Oncogene* 2021; **40**: 6180-6194 [PMID: 34535770 DOI: 10.1038/s41388-021-02011-0]

52 **Stenholm L**, Stoehlmacher-Williams J, Al-Batran SE, Heussen N, Akin S, Pauligk C, Lehmann S, Senff T, Hofheinz RD, Ehninger G, Kramer M, Goekkurt E. Prognostic role of microRNA polymorphisms in advanced gastric cancer: a translational study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Ann Oncol* 2013; **24**: 2581-2588 [PMID: 23975664 DOI: 10.1093/annonc/mdt330]

53 **Pan Y**, Shu X, Sun L, Yu L, Yang Z, Ran Y. miR-196a-5p modulates gastric cancer stem cell characteristics by targeting Smad4. *Int J Oncol* 2017; **50**: 1965-1976 [PMID: 28440445 DOI: 10.3892/ijo.2017.3965]

54 **Farahani DB**, Akrami H, Moradi B, Mehdizadeh K, Fattahi MR. The Effect of hsa-miR-451b Knockdown on Biological Functions of Gastric Cancer Stem-Like Cells. *Biochem Genet* 2021; **59**: 1203-1224 [PMID: 33725258 DOI: 10.1007/s10528-021-10057-8]

55 **Wu K**, Ma L, Zhu J. miR4835p promotes growth, invasion and selfrenewal of gastric cancer stem cells by Wnt/βcatenin signaling. *Mol Med Rep* 2016; **14**: 3421-3428 [PMID: 27511210 DOI: 10.3892/mmr.2016.5603]

56 **Wu S**, Xie J, Shi H, Wang ZW. miR-492 promotes chemoresistance to CDDP and metastasis by targeting inhibiting DNMT3B and induces stemness in gastric cancer. *Biosci Rep* 2020; **40** [PMID: 32065219 DOI: 10.1042/BSR20194342]

57 **Huang DH**, Wang GY, Zhang JW, Li Y, Zeng XC, Jiang N. MiR-501-5p regulates CYLD expression and promotes cell proliferation in human hepatocellular carcinoma. *Jpn J Clin Oncol* 2015; **45**: 738-744 [PMID: 25917358 DOI: 10.1093/jjco/hyv063]

58 **Liu X**, Lu Y, Xu Y, Hou S, Huang J, Wang B, Zhao J, Xia S, Fan S, Yu X, Du Y, Hou L, Li Z, Ding Z, An S, Huang B, Li L, Tang J, Ju J, Guan H, Song B. Exosomal transfer of miR-501 confers doxorubicin resistance and tumorigenesis *via* targeting of BLID in gastric cancer. *Cancer Lett* 2019; **459**: 122-134 [PMID: 31173853 DOI: 10.1016/j.canlet.2019.05.035]

59 **Fan D**, Ren B, Yang X, Liu J, Zhang Z. Upregulation of miR-501-5p activates the wnt/β-catenin signaling pathway and enhances stem cell-like phenotype in gastric cancer. *J Exp Clin Cancer Res* 2016; **35**: 177 [PMID: 27846906 DOI: 10.1186/s13046-016-0432-x]

60 **Li H**, Jin X, Liu B, Zhang P, Chen W, Li Q. CircRNA CBL.11 suppresses cell proliferation by sponging miR-6778-5p in colorectal cancer. *BMC Cancer* 2019; **19**: 826 [PMID: 31438886 DOI: 10.1186/s12885-019-6017-2]

61 **Zhao M**, Hou Y, Du YE, Yang L, Qin Y, Peng M, Liu S, Wan X, Qiao Y, Zeng H, Cui X, Teng Y, Liu M. Drosha-independent miR-6778-5p strengthens gastric cancer stem cell stemness *via* regulation of cytosolic one-carbon folate metabolism. *Cancer Lett* 2020; **478**: 8-21 [PMID: 32142918 DOI: 10.1016/j.canlet.2020.02.040]

62 **Xin L**, Liu L, Liu C, Zhou LQ, Zhou Q, Yuan YW, Li SH, Zhang HT. DNA-methylation-mediated silencing of miR-7-5p promotes gastric cancer stem cell invasion *via* increasing Smo and Hes1. *J Cell Physiol* 2020; **235**: 2643-2654 [PMID: 31517391 DOI: 10.1002/jcp.29168]

63 **Wang GH**, Zhou YM, Yu Z, Deng JP, Liu SF, Wei CZ, Feng Y, Mao M, Wang Z. Up-regulated ONECUT2 and down-regulated SST promote gastric cell migration, invasion, epithelial-mesenchymal transition and tumor growth in gastric cancer. *Eur Rev Med Pharmacol Sci* 2020; **24**: 9378-9390 [PMID: 33015779 DOI: 10.26355/eurrev_202009_23021]

64 **Shen C**, Wang J, Xu Z, Zhang L, Gu W, Zhou X. ONECUT2 which is targeted by hsa-miR-15a-5p enhances stemness maintenance of gastric cancer stem cells. *Exp Biol Med (Maywood)* 2021; **246**: 2645-2659 [PMID: 34365839 DOI: 10.1177/15353702211038496]

65 **Zhao XF**, Yang YS, Park YK. HOXC9 overexpression is associated with gastric cancer progression and a prognostic marker for poor survival in gastric cancer patients. *Int J Clin Oncol* 2020; **25**: 2044-2054 [PMID: 32816159 DOI: 10.1007/s10147-020-01772-0]

66 **Yu B**, Zhu N, Fan Z, Li J, Kang Y, Liu B. miR-29c inhibits metastasis of gastric cancer cells by targeting VEGFA. *J Cancer* 2022; **13**: 3566-3574 [PMID: 36484007 DOI: 10.7150/jca.77727]

67 **Xiong S**, Hu M, Li C, Zhou X, Chen H. Role of miR34 in gastric cancer: From bench to bedside (Review). *Oncol Rep* 2019; **42**: 1635-1646 [PMID: 31432176 DOI: 10.3892/or.2019.7280]

68 **Ji Q**, Hao X, Meng Y, Zhang M, Desano J, Fan D, Xu L. Restoration of tumor suppressor miR-34 inhibits human p53-mutant gastric cancer tumorspheres. *BMC Cancer* 2008; **8**: 266 [PMID: 18803879 DOI: 10.1186/1471-2407-8-266]

69 **Jang E**, Kim E, Son HY, Lim EK, Lee H, Choi Y, Park K, Han S, Suh JS, Huh YM, Haam S. Nanovesicle-mediated systemic delivery of microRNA-34a for CD44 overexpressing gastric cancer stem cell therapy. *Biomaterials* 2016; **105**: 12-24 [PMID: 27497057 DOI: 10.1016/j.biomaterials.2016.07.036]

70 **Zhan P**, Shu X, Chen M, Sun L, Yu L, Liu J, Yang Z, Ran Y. miR-98-5p inhibits gastric cancer cell stemness and chemoresistance by targeting branched-chain aminotransferases 1. *Life Sci* 2021; **276**: 119405 [PMID: 33798550 DOI: 10.1016/j.lfs.2021.119405]

71 **Jian F**, Che X, Zhang J, Liu C, Liu G, Tang Y, Feng W. The long-noncoding RNA SOCS2-AS1 suppresses endometrial cancer progression by regulating AURKA degradation. *Cell Death Dis* 2021; **12**: 351 [PMID: 33824269 DOI: 10.1038/s41419-021-03595-x]

72 **Zhou X**, Xia Y, Li L, Zhang G. MiR-101 inhibits cell growth and tumorigenesis of Helicobacter pylori related gastric cancer by repression of SOCS2. *Cancer Biol Ther* 2015; **16**: 160-169 [PMID: 25561270 DOI: 10.4161/15384047.2014.987523]

73 **Wang Y**, Li Y, Hu G, Huang X, Rao H, Xiong X, Luo Z, Lu Q, Luo S. Nek2A phosphorylates and stabilizes SuFu: A new strategy of Gli2/Hedgehog signaling regulatory mechanism. *Cell Signal* 2016; **28**: 1304-1313 [PMID: 27297360 DOI: 10.1016/j.cellsig.2016.06.010]

74 **Lu Y**, Zhang B, Wang B, Wu D, Wang C, Gao Y, Liang W, Xi H, Wang X, Chen L. MiR-144-3p inhibits gastric cancer progression and stemness *via* directly targeting GLI2 involved in hedgehog pathway. *J Transl Med* 2021; **19**: 432 [PMID: 34657624 DOI: 10.1186/s12967-021-03093-w]

75 **Mitra AK**, Zillhardt M, Hua Y, Tiwari P, Murmann AE, Peter ME, Lengyel E. MicroRNAs reprogram normal fibroblasts into cancer-associated fibroblasts in ovarian cancer. *Cancer Discov* 2012; **2**: 1100-1108 [PMID: 23171795 DOI: 10.1158/2159-8290.CD-12-0206]

76 **Yu F**, Jia X, Du F, Wang J, Wang Y, Ai W, Fan D. miR-155-deficient bone marrow promotes tumor metastasis. *Mol Cancer Res* 2013; **11**: 923-936 [PMID: 23666369 DOI: 10.1158/1541-7786.MCR-12-0686]

77 **Zhu M**, Wang M, Yang F, Tian Y, Cai J, Yang H, Fu H, Mao F, Zhu W, Qian H, Xu W. miR-155-5p inhibition promotes the transition of bone marrow mesenchymal stem cells to gastric cancer tissue derived MSC-like cells *via* NF-κB p65 activation. *Oncotarget* 2016; **7**: 16567-16580 [PMID: 26934326 DOI: 10.18632/oncotarget.7767]

78 **Wang M**, Yang F, Qiu R, Zhu M, Zhang H, Xu W, Shen B, Zhu W. The role of mmu-miR-155-5p-NF-κB signaling in the education of bone marrow-derived mesenchymal stem cells by gastric cancer cells. *Cancer Med* 2018; **7**: 856-868 [PMID: 29441735 DOI: 10.1002/cam4.1355]

79 **Song H**, Shi L, Xu Y, Xu T, Fan R, Cao M, Xu W, Song J. BRD4 promotes the stemness of gastric cancer cells *via* attenuating miR-216a-3p-mediated inhibition of Wnt/β-catenin signaling. *Eur J Pharmacol* 2019; **852**: 189-197 [PMID: 30876979 DOI: 10.1016/j.ejphar.2019.03.018]

80 **Zhang J**, Wang C, Yan S, Yang Y, Zhang X, Guo W. miR-345 inhibits migration and stem-like cell phenotype in gastric cancer *via* inactivation of Rac1 by targeting EPS8. *Acta Biochim Biophys Sin (Shanghai)* 2020; **52**: 259-267 [PMID: 32147678 DOI: 10.1093/abbs/gmz166]

81 **Ni H**, Qin H, Sun C, Liu Y, Ruan G, Guo Q, Xi T, Xing Y, Zheng L. MiR-375 reduces the stemness of gastric cancer cells through triggering ferroptosis. *Stem Cell Res Ther* 2021; **12**: 325 [PMID: 34090492 DOI: 10.1186/s13287-021-02394-7]

82 **Bou Kheir T**, Futoma-Kazmierczak E, Jacobsen A, Krogh A, Bardram L, Hother C, Grønbæk K, Federspiel B, Lund AH, Friis-Hansen L. miR-449 inhibits cell proliferation and is down-regulated in gastric cancer. *Mol Cancer* 2011; **10**: 29 [PMID: 21418558 DOI: 10.1186/1476-4598-10-29]

83 **Zhao X**, Zhong Q, Cheng X, Wang S, Wu R, Leng X, Shao L. miR-449c-5p availability is antagonized by circ-NOTCH1 for MYC-induced NOTCH1 upregulation as well as tumor metastasis and stemness in gastric cancer. *J Cell Biochem* 2020; **121**: 4052-4063 [PMID: 31943342 DOI: 10.1002/jcb.29575]

84 **Gao X**, Leone GW, Wang H. Cyclin D-CDK4/6 functions in cancer. *Adv Cancer Res* 2020; **148**: 147-169 [PMID: 32723562 DOI: 10.1016/bs.acr.2020.02.002]

85 **Li LP**, Wu WJ, Sun DY, Xie ZY, Ma YC, Zhao YG. miR-449a and CDK6 in gastric carcinoma. *Oncol Lett* 2014; **8**: 1533-1538 [PMID: 25202363 DOI: 10.3892/ol.2014.2370]

86 **Peng C**, Huang K, Liu G, Li Y, Yu C. MiR-876-3p regulates cisplatin resistance and stem cell-like properties of gastric cancer cells by

targeting TMED3. *J Gastroenterol Hepatol* 2019; **34**: 1711-1719 [PMID: 30843262 DOI: 10.1111/jgh.14649]

87 **Otaegi-Ugartemendia M**, Matheu A, Carrasco-Garcia E. Impact of Cancer Stem Cells on Therapy Resistance in Gastric Cancer. *Cancers (Basel)* 2022; **14** [PMID: 35326607 DOI: 10.3390/cancers14061457]

88 **Liu HQ**, Shu X, Ma Q, Wang R, Huang MY, Gao X, Liu YN. Identifying specific miRNAs and associated mRNAs in CD44 and CD90 cancer stem cell subtypes in gastric cancer cell line SNU-5. *Int J Clin Exp Pathol* 2020; **13**: 1313-1323 [PMID: 32661467]

89 **Yan Y**, Du C, Duan X, Yao X, Wan J, Jiang Z, Qin Z, Li W, Pan L, Gu Z, Wang F, Wang M. Inhibiting collagen I production and tumor cell colonization in the lung *via* miR-29a-3p loading of exosome-/Liposome-based nanovesicles. *Acta Pharm Sin B* 2022; **12**: 939-951 [PMID: 35256956 DOI: 10.1016/j.apsb.2021.08.011]

90 **Liu Q**, Li RT, Qian HQ, Wei J, Xie L, Shen J, Yang M, Qian XP, Yu LX, Jiang XQ, Liu BR. Targeted delivery of miR-200c/DOC to inhibit cancer stem cells and cancer cells by the gelatinases-stimuli nanoparticles. *Biomaterials* 2013; **34**: 7191-7203 [PMID: 23806972 DOI: 10.1016/j.biomaterials.2013.06.004]

91 **Horvath S**, Raj K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. *Nat Rev Genet* 2018; **19**: 371-384 [PMID: 29643443 DOI: 10.1038/s41576-018-0004-3]

92 **Zhou YJ**, Lu XF, Meng JL, Wang QW, Chen JN, Zhang QW, Zheng KI, Rocha CS, Martins CB, Yan FR, Li XB. Specific epigenetic age acceleration patterns among four molecular subtypes of gastric cancer and their prognostic value. *Epigenomics* 2021; **13**: 767-778 [PMID: 33876652 DOI: 10.2217/epi-2020-0290]

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