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TOPIC HIGHLIGHT

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Dysregulation of non-coding RNAs in gastric cancer

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Abstract

Gastric cancer (GC) is one of the most common cancers in the world and a significant threat to the health of patients, especially those from China and Japan. The prognosis for patients with late stage GC receiving the standard of care treatment, including surgery, chemotherapy and radiotherapy, remains poor. Developing novel treatment strategies, identifying new molecules for targeted therapy, and devising screening techniques to detect this cancer in its early stages are needed for GC patients. The discovery of non-coding RNAs (ncRNAs), primarily microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), helped to elucidate the mechanisms of tumorigenesis, diagnosis and treatment of GC. Recently, significant research has been conducted on non-coding RNAs and how the regulatory dysfunction of these RNAs impacts the tumorigenesis of GC. In this study, we review papers published in the last five years concerning the dysregulation of non-coding RNAs, especially miRNAs and lncRNAs, in GC. We summarize instances of aberrant expression of the ncRNAs in GC and their effect on survival-related events, including cell cycle regulation, AKT signaling, apoptosis and drug resistance. Additionally, we evaluate how ncRNA dysregulation affects the metastatic process, including the epithelial-mesenchymal transition, stem cells, transcription factor activity, and oncogene and tumor suppressor expression. Lastly, we determine how ncRNAs affect angiogenesis in the microenvironment of GC. We further discuss the use of ncRNAs as potential biomarkers for use in clinical screening, early diagnosis and prognosis of GC. At present, no ideal ncRNAs have been identified as targets for the treatment of GC.

Key words: Gastric cancer; Dysregulation; Non-coding RNA; Tumorigenesis; Biomarker

Core tip: Gastric cancer (GC) is a significant threat to the health of patients. Non-coding RNAs, primarily microRNAs and long non-coding RNAs, play important roles in gastric tumorigenesis. In this study, we review papers published in the last five years on the dysregulation of non-coding RNAs, especially microRNAs and long non-coding RNAs, in GC. We summarize how aberrant expression of the non-coding RNAs in GC affects cancer cell survival and metastasis, as well as angiogenesis within the tumor microenvironment. We additionally discuss the potential use of non-coding RNAs in the clinic as biomarkers for the diagnosis and prognosis of GC.

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INTRODUCTION

Gastric cancer (GC) is the fourth most common cancer in the world[1] and has high incidence and mortality in Asia, especially in China and Japan. The addition of widespread gastroscopy to normal practice in Japan has resulted in improved early detection rates[2]. In addition to traditional pathogenic pathways that lead to the genesis of GC, *Helicobacter pylori* (*H. pylori*) infection has also been shown to induce gastric tumor growth[3]. Previous studies of the mechanisms leading to GC hypothesized that tumorigenesis was occurring primarily through abnormal protein-protein interactions[4-6]. There has been interest in uncovering these underlying mechanisms[7,8]. Recently, significant research has been conducted on non-coding RNAs, including small non-coding RNAs and long non-coding RNAs (lncRNAs)[9-11]. Non-coding RNA regulatory dysfunction plays a significant role in the development of GC.

MicroRNAs (miRNAs) are noncoding single-stranded RNA molecules of approximately 22 nucleotides that are coded by endogenous genes and target specific mRNA molecules by forming miRNA-induced silencing complexes, resulting in mRNA degradation or hindrance of mRNA translation to functional protein. At present, miRNAs have been found to have many biological functions[12-14], including regulation of cell growth and differentiation. Thus, miRNAs play a key role in the life cycle of the cell, and their dysfunction can lead to a diseased state[15-18]. Most miRNAs are highly conserved in the genome and have a high degree of tissue specificity and temporal regulation[19-21]. These properties make miRNAs ideal biomarkers that can be detected for cancer identification. Early detection and accurate monitoring of biomarkers are crucial for treatment and positive prognosis in cancer patients, making biomarker identification particularly significant[22,23]. Recently, cell-free nucleic acids, including a population of miRNAs, have been identified in the blood of cancer patients, and their clinical relevance is attracting considerable attention[24].

LncRNAs are RNA molecules longer than 200 nucleotides that are not translated into protein. They constitute a major, although still poorly characterized, component of the human transcriptome. However, growing evidence suggests that they play an important regulatory role in many cell processes[25-27]. Nonetheless, lncRNAs remain among the least well understood of the RNA transcripts. Although previously dismissed as transcriptional "noise", several lines of evidence have suggested that lncRNAs are biologically functional[28]. LncRNAs, particularly highly conserved ones, are generally actively regulated and may function predominantly during embryonic development. Most lncRNAs evolved rapidly in terms of sequence and expression levels, but tissue specificity is often conserved[29]. It is becoming increasingly clear that many lncRNAs are deregulated in cancer, and some are functionally tied to mechanisms that may allow them to be important drivers of malignant transformation.

Protein-protein interaction networks are increasingly being employed to characterize cellular processes. These networks will have to be expanded considerably to characterize all of the possible modes of action that can occur. For example, miRNAs can silence target genes, and lncRNAs in turn can interfere with gene silencing. In contrast, lncRNA interference with target proteins can be influenced by miRNAs. For example, lncRNA-RoR is a key competing endogenous RNA that links the network of miRNAs to core transcription factors[30]. Besides protein-miRNA interactions, protein-lncRNA interactions, and micRNA-lncRNA interactions, there are many possible and uncharacterized interactions that could become dysfunctional and drive tumor development. Consequently, the development of appropriate biomarkers derived from these non-coding RNAs that reflect an individual's cancer risk is essential to reduce GC-related mortality.

DYSREGULATION OF NON-CODING RNAS IN GC

MiRNAs

MiRNAs play critical roles in physiological and pathological processes[31-33]. Using miRNA microarray technology, it has been discovered that thousands of miRNAs are dysregulated in GC compared with adjacent tissues; however, only a fraction of these were confirmed through quantitative real-time PCR. Table 1, Table 2 and Table 3 show the major miRNAs that have been confirmed by quantitative

Table 1 MicroRNAs down-regulated in gastric cancer

ncRNA	Summary of findings/ clinical relevance	q-PCR	Targets	Roles	Cases	Location	Ref.
miR-141	Reduced in metastasis positive tissues; Might be a prognostic marker and therapeutic target	√	TAZ	Proliferation, invasion and migration	36 GC *vs* paired adjacent tissues	China	[223]
miR-874	Reduced miR-874 promotes angiogenesis *via* STAT3; Might be a therapeutic target	√	STAT3	Tumor growth and angiogenesis	80 GC *vs* paired adjacent tissues	China	[187]
miR-101	Lower level parallels with EZH2 overexpression	√	EZH2	E-cadherin dysfunction	37 GC *vs* 5 normal gastric mucosa	Portugal	[224]
miR-103a	Tumor suppressor by targeting c-Myb	√	c-Myb	Proliferation, invasion and migration	80 GC *vs* paired adjacent tissues	China	[225]
miR-335	Can be silenced by promoter hypermethylation which might be a predictive epigenetic marker and a therapeutic strategy	√	RASA1	Invasion and metastasis	15 GC *vs* paired adjacent tissues	China	[52]
miR-335	Could be a therapeutic target for GC therapies and a prognostic factor	√	Bcl-w, SP1	Proliferation, invasion and metastasis	70 GC *vs* paired adjacent tissues	China	[226]
let-7a	A potential target for diagnosis and therapy	√	RAB40C	Proliferation and colony formation	27 GC *vs* paired adjacent tissues	China	[227]
miR-490-3p	Reduced miR-490-3p reactivates SMARCD1 to confer malignant phenotypes	√	SMARCD1	Growth and metastasis	14 GC *vs* 15 normal gastric tissues	Hong Kong	[228]
miR-200c/141	Reduced miRNA decreases ZEB1/2 expression and increases E-cadherin expression	√	ZEB1/2	Invasion and migration	64 GC *vs* paired adjacent tissues	China	[229]
miR-200b /c	Might be a marker of prognosis and therapeutic target	√	DNMT3A, DNMT3B, SP1	Proliferation, invasion and migration	36 GC *vs* paired adjacent tissues	China	[230]
miR-200	Down-regulated miR-200 reduced E-cadherin expression, playing a role in the carcinogenesis of EBV-associated GC	√	ZEB1, ZEB2	Cell-to-cell adhesion and migration	36 GC *vs* paired adjacent tissues (EBV-associated and EBV-negative)	Japan	[231]
miR-204-5p	Restoration of miR-204-5p might provide a therapeutic strategy for GC	√	USP47, RAB22A	Proliferation	102 GC *vs* paired adjacent tissues	China	[232]
miR-367	A key negative regulator of invasion and metastasis of GC; Might be a therapeutic target	√	Rab23	Invasion and migration	37 GC *vs* paired adjacent tissues	China	[233]
miR-328	MiR-328-mediated CD44 overexpression may associate with the carcinogenesis of GC	√	CD44v9	Survival and proliferation of metaplastic cells	54 patients underwent gastric resection without preoperative treatment	Japan	[181]
miR-328	Macrophages mediated miR-328-CD44 signaling may be a therapeutic target for gastrointestinal cancer	√	CD44	Cell growth and drug resistance	63 GC *vs* paired adjacent tissues	Japan	[234]
miR-495	A tumor suppressor and potential therapeutic target for GC peritoneal metastasis	√	PRL-3	Invasion and metastasis	20 GC *vs* 10 normal gastric tissues	China	[53]
miR-551a	A tumor suppressor targeting PRL-3 oncogene to inhibit GC cell migration and invasion	√	PRL-3	Invasion and migration	30 malignant *vs* 4 normal gastric tissues	China	[235]
miR-133b	A potential diagnostic marker and therapeutic target	√	FSCN1	Proliferation, invasion and migration	100 GC *vs* paired adjacent tissues	China	[236]
miR-542-3p	A tumor suppressor and a potential therapeutic target	√	AEG-1	Cell growth	22 GC *vs* paired adjacent tissues	China	[112]
miR-126	Suppresses tumor growth and angiogenesis through targeting VEGF-A; A potential therapeutic target	√	VEGF-A	Tumori-genicity and angiogenesis	68 GC *vs* paired adjacent tissues	China	[119]
miR-126	May function as a tumor suppressor in GC	√	Crk	Proliferation, cell cycle, apoptosis, invasion and migration	60 GC *vs* paired adjacent tissues	China	[237]
miR-29s	Increasing the expression of miR-29s may be a therapeutic strategy for GC	√	AKT2	Invasion	20 GC *vs* paired adjacent tissues	China	[120]

miR-29c	Reduced miR-29c expression is an early event in GC development; Potential diagnostic and therapeutic biomarkers	√	ITGB1	Proliferation, adhesion, invasion and migration	274 GC *vs* paired adjacent tissues	South Korea, Japan, United States	[215]
miR-29 family	Might be potential prognostic markers and therapeutic targets	√	CCND2, MMP-2	Proliferation apoptosis and invasion	115 GC *vs* paired adjacent tissues	China	[238]
miR-29c	Might be a tumor suppressor	√	RCC2	Proliferation and colony formation	12 GC *vs* paired adjacent tissues	Japan	[239]
miR-193b	Might be a potential prognostic marker	√	Unknown	Differentiation and survival	48 GC *vs* paired adjacent tissues	China	[240]
miR-203	Might be a therapeutic target for *H. pylori* infection induced GC	√	CASK	Proliferation and invasion	50 pairs of *H. pylori* positive and negative gastric tissues	China	[241]
miR-210	Epigenetic silencing of miR-210 involves in chronic *H. pylori* infection associated GC	√	STMN1, DIMT1	Proliferation	20 GC *vs* paired adjacent tissues	Japan	[242]
miR-34 family	Plays a role in the control of GC development	√	Yin Yang 1	Growth, colony formation, migration, invasion, and tumorsphere formation	32 GC *vs* paired adjacent tissues	Taiwan	[243]
miR-34b and miR-129-3p	Down-regulated by hypermethylation of upstream CpG islands indicating a poor clinical outcome	√	Unknown	Unknown	72 GC *vs* paired adjacent tissues	Taiwan	[244]
miR-24	A novel tumor suppressor and a potential therapeutic target	√	RegⅣ	Proliferation, invasion and migration	63 GC *vs* paired adjacent tissues	China	[245]
miR-185	Regulating the sensitivity of GC to chemotherapy	√	ARC	Chemotherapeutic sensitivity	25 GC *vs* paired adjacent tissues	China	[246]
miR-1207-5p and miR-1266	hTERT suppressors in GC and potential therapeutic targets	√	hTERT	Cell growth, cell cycle and invasion	58 GC *vs* adjacent tissues	China	[108]
miR-365	Playing a role in tumorigenesis; A potential therapeutic target	√	Cyclin D1, cdc25A	Proliferation and colony formation	127 GC *vs* paired adjacent tissues	China	[105]
miR-760	A potential prognostic predictor and therapeutic target	√	Histone mRNA	Unknown	53 bone marrow samples from stage Ⅳ patients *vs* 52 stage Ⅰ patients; 22 stage Ⅳ GC *vs* 29 stage Ⅰ GS tissues	Japan	[247]
miR-143/145	DDX6 contributes to the control of NCR143/145 RNA stability in P-bodies and post-transcriptionally regulated miR-143/145 expression	√	Unknown	Cell survival, proliferation and malignant transformation	14 GC tissues *vs* paired adjacent tissues	Japan	[84]
miR-206	A potential tumor suppressor and therapeutic target	√	CyclinD2	Proliferation, cell cycle and tumor growth	30 primary GC *vs* paired distant tissues	China	[248]
miR-204	A potential target for preventive and therapeutic strategies	√	Bcl-2	Migration, colony forming and chemotherapy resistance	92 gastric tumor specimens *vs* paired adjacent tissues	Italy	[249]
miR-124	A tumor suppressor; Play a role in miRNA-mediated SPHK1 expression	√	SPHK1	Proliferation and tumourigenicity	20 GC *vs* paired adjacent tissues	China	[117]
miR-409-3p	A tumor suppressor involving the direct targeting and inhibition of PHF10	√	PHF10	Proliferation and apoptosis	67 GC *vs* paired adjacent tissues	China	[250]
miR-409-3p	Suppresses GC invasion and metastasis by directly targeting RDX; Reduced miR-409-3p is prone to lymph node metastasis	√	RDX	Invasion and migration	90 GC *vs* paired adjacent tissues	China	[251]
miR-148a	Reduced miR-148a contributes to GC lymph node-metastasis and progression; A potential therapeutic target for GC metastasis	√	ROCK1	Invasion, migration and metastasis	90 GC *vs* paired normal tissues	China	[252]
miR-148b	A potential biomarker and therapeutic target	√	CCKBR	Proliferation and tumorigenicity	106 GC *vs* paired adjacent tissues	China	[253]
miR-449	A member of the miR-34 family playing an important role in GC	√	GMNN, MET, CCNE2, SIRT1	Cell cycle, proliferation and induce senescence	10 GC *vs* paired adjacent tissues	Denmark	[254]
miR-486	A tumor-suppressor; Associated with the direct targeting and inhibition of OLFM4	√	OLFM4	Proliferation, invasion and migration	29 GC *vs* paired adjacent tissues	Singapore	[255]

miR-142-5p	A potential predictor of progression and predict recurrence risk for GC	√	MAPK, Wnt, VEGF	Recurrence risk related	65 GC samples	China	[256]
miR-125a-5p	Reduced miR-125a-5p is associated with enhanced malignant potential; A potential prognostic marker	√	ERBB2	Proliferation	87 GC samples	Japan	[257]
miR-516a-3p	An anti-metastamir with therapeutic potential in blocking metastatic dissemination of GC	√	SULF1	Proliferation, invasion and migration	8 normal stomach tissues, 12 GC tissues from the patients with peritoneal dissemination and 12 GC tissues without peritoneal dissemination	Japan	[258]
miR-181c	Silenced through methylation playing important roles in gastric carcinogenesis	√	NOTCH4, and KRAS	Proliferation	16 GC surgical specimens *vs* paired non-cancerous counterparts	Japan	[259]
miR-212	Reduced miR-212 may be related to gastric carcinogenesis	√	MECP2	Proliferation	11 GC *vs* paired adjacent tissues	Japan	[260]
miR-338-3p	MiR-338-3p inhibits the EMT progression in GC cells by targeting ZEB2 and MACC1/Met/Akt pathway	√	ZEB2, MACC1	Invasion and migration	20 GC *vs* paired adjacent tissues	China	[261]
miR-217	A potential prognostic marker; miR-217-EZH2 axis may be a potential therapeutic target	√	EZH2	Proliferation, invasion and migration	83 GC tissues *vs* adjacent tissues	China, United States	[262]
miR-15a and miR-16-1	MiR-15a and miR-16-1 have inhibitory effect providing a therapeutic potential in GC	√	YAP1	Proliferation, colony formation, invasion and migration	60 GC *vs* paired adjacent tissues	Hong Kong	[263]

GC: Gastric cancer.

reverse transcription-PCR (qRT-PCR) and found to be dysregulated in GC tissues since 2010. Many of these miRNAs were demonstrated to act as tumor promoters or suppressors by regulating the expression levels of their target mRNAs in GC cells. However, the mechanisms that control miRNA regulation are as of yet unknown. Below, we have listed some mechanisms linked to altered miRNA expression in GC cells.

Multiple miRNAs were found to be dysregulated in *H. pylori*-positive GC tissues compared with *H. pylori*-negative GC tissues. It was reported that a total of 219 of the 3523 measured miRNAs showed a 2-fold up- or down-regulation in *H. pylori*-positive GC tissues compared with *H. pylori*-negative GC tissues[34]. Further studies revealed three miRNAs (miR-99b-3p, miR-564, and miR-638) that were significantly up-regulated in three *H. pylori*-positive GC samples, while four miRNAs (miR-204-5p, miR-338-5p, miR-375, and miR-548c-3p) were significantly down-regulated in all eight *H. pylori*-positive GC samples. In addition, the levels of miR-223 and miR-222 were up-regulated while miR-375 and miR-320 were down-regulated in *H. pylori*-infected gastric mucosa[35-38]. MiR-146a was up-regulated in *H. pylori*-infected human gastric epithelial cells and has been shown to decrease the inflammatory response induced by *H. pylori* partially through reducing the level of PTGS2[39]. Further work revealed that miR-146a could enhance apoptosis in GC cells, and there was a positive correlation between miR-146a level and the apoptosis rate in *H. pylori*-positive GC tissues. The mechanism by which these miRNAs become dysregulated is still unclear and requires further investigation, but NF-κB, a key transcription factor in the development of *H. pylori*-induced chronic inflammation, may play a critical role in this process. Accordingly, the level of miR-200 was increased in *H. pylori*-infected GC cells, which was driven by a functional NF-κB binding site in the promoter of the miR-200b-200a-429 cluster. This strongly suggests that NF-κB plays an important role in the direct regulation of miR-200 transcription[40]. Increased expression of miR-200 may be a response to the unalterable loss of the epithelial phenotype of GC cells induced by *H. pylori*. MiR-155 was up-regulated by *H. pylori* both *in vitro* and *in vivo*, and this induction was NF-κB dependent[41]. In addition, *H. pylori* could also induce the expression of miR-155 in T cells in a cAMP-Foxp3-dependent manner[42] and in macrophages in a T4SS-dependent manner[43]. MiR-155 was proven to be necessary for Th17/Th1 differentiation and the induction of chronic gastritis in a mouse model infected with *H. pylori*[44]. Furthermore, increased levels of miR-155 suppressed the production of IL-8 induced by *H. pylori* in gastric epithelial cells[41] by regulating the expression of MyD88[45]. IL-6 is a pro-inflammatory cytokine negatively regulated by miR-155 and miR-146b in *H. pylori*(cagA+)-induced gastroduodenal ulcers[46]. Let-7b was found to be involved in the activation of NF-κB in response to *H. pylori* induced inflammation and immune responses[47]. Let-7b was down-regulated in *H. pylori*-infected gastric epithelial cell lines and the forced overexpression of let-7b inhibited the activation of NF-κB by suppressing the level of TLR4 in these cells. These results demonstrate that let-7b is a negative regulator of NF-κB and that this may be the reason for let-7b down-regulation in *H. pylori*-infected gastric epithelial cells. The levels of several pro-inflammatory cytokines in *H. pylori* induced chronic inflammation, including IL-1β, IL-6, IL-8, and TNF-α, were found to be correlated

Table 2 MicroRNAs up-regulated in gastric cancer

ncRNA	Summary of findings/clinical relevance	q-PCR	Targets	Roles	Cases	Location	Ref.
miR-23a/b	Implicated in the progression of GC. A potential prognosis marker	√	Unknown	Unknown	160 GC *vs* adjacent tissues	China	[264]
miR-500	Highly correlated with malignant progression and poor survival of GC	√	CYLD, TAX1BP1, OTUD7B	Proliferation, survival and tumorigenicity	10 GC *vs* adjacent tissues	China	[137]
miR-374a	A promising therapeutic target	√	SRCIN1	Proliferation, tumor growth migration and invasion	18 GC tissues *vs* adjacent tissues	China	[265]
miR-199a-3p	A tumor promoter in GC targeting and inhibition of ZHX1; A potential target for GC prevention and therapy	√	ZHX1	Proliferation and apoptosis	52 GC *vs* adjacent tissues	China	[266]
miR-18a	A potential marker for risk stratification in the management of GC patients	√	PIAS3, STAT3	Unknown	82 patients with GC and 65 healthy controls (plasma)	China	[204]
miR-196a	A potential prognostic marker in GC	√	Unknown	Differentiation and survival	48 GC *vs* adjacent tissues	China	[240]
miR-223, miR-16, miR-100	Up-regulated in serum implicates their potential diagnostic value; Significantly elevated expression of the three miRNAs in advanced GC patients suggests their availability in cancer staging	√	PIAS3	Unknown	50 GC patients and 47 healthy controls (serum)	China	[202]
miR-135a-5p	Play a role in miRNA-135a-5p-AP-2α-BCL-2 pathway providing therapeutic potential for GC and solution for insensitivity of GC to chemotherapy	√	AP-2α	Cell resistance to apoptosis, sensitivity to adriamycin	20 GC *vs* adjacent tissues	China	[267]
miR-199a-5p	SRF/miR-199a-5p/E-cadherin pathway promotes GC EMT and metastasis; A potential therapeutic target or biomarker for GC progression	√	E-cadherin	Adhesion, invasion, and metastasis	7 GC *vs* pairs adjacent tissues	China	[268]
miR-25	A potential biomarker for the prognosis of GC	√	ERBB2, 1(TOB1)	Migration, invasion and proliferation	33 GC *vs* paired adjacent tissues	China	[269]
miR-942	A potential drug response biomarker and therapeutic target for TRAIL resistant tumors	√	ISG12a	Apoptosis	28 GC tissues	China	[134]
miR-196a/b	A potential therapeutic target in suppressing GC metastasis	√	Radixin	Metastasis	109 GC *vs* paired adjacent tissues	Taiwan	[172]
miR-19a/b	A member of miR-19a/b facilitating GC cell migration, invasion and metastasis, implicating a novel mechanism for the malignant phenotypes of GC	√	MXD1	Migration and invasion	141 GC *vs* paired adjacent tissues	China	[173]
miR-423-5p	A potential therapeutic target	√	TFF1	Proliferation and invasion	15 GC *vs* paired adjacent tissues	China	[270]
miR-183-96-182 cluster	A novel role for GSK3β in the regulation of miR-183-96-182 biogenesis through β-catenin/TCF/ LEF-1 pathway in GC	√	FoxO1	Proliferation and migration	8 GC *vs* paired adjacent tissues	United States	[83]
miR-215	Influencing cell proliferation by targeting RB1	√	RB1	Proliferation	51 GC *vs* paired adjacent tissues	China	[271]
miR-17-92 cluster	Cluster including miR-19b, miR-20a and miR-92a associates with the development of GC stem cells; and miR-92a as a potential predictive prognostic marker for miR-92a in GC	√	E2F1, HIPK1	Self-renewal and proliferation	97 GC specimens	China	[272]
miR-296-5p	MiR-296-5p-CDX1-ERK1/2 axis play a role in gastric tumorigenesis; A potential therapeutic target	√	CDX1	Proliferation	16 GC *vs* paired adjacent tissues	China	[273]
miR-181a	Associated with increased risk and poor survival of GC	√	MTMR3	Unknown	50 GC *vs* paired adjacent tissues	China	[274]
miR-196a	Contributing to gastric carcinogenesis; A potential therapeutic target and prognostic factor	√	p27	Proliferation, apoptosis and tumorigenesis	36 GC *vs* paired adjacent tissues	China	[275]
miR-196b	Transcriptionally regulated by ETS2; A potential diagnostic marker and therapeutic target	√	AnnexinA1, HOXB8	Migration and invasion	63 GC *vs* paired adjacent tissues	Taiwan	[276]
miR-378	Up-regulated in serum while down-regulated in GC tissues. A potential serum biomarker in GC detection	√	Unknown	Unknown	4 GC *vs* paired adjacent tissues, 40 GC serum samples *vs* 41 healthy controls	China	[277]

miR-370	Associated with GC progression by targeting TGFβ-RII	√	TGFβ-RII	Migration	33 GC *vs* adjacent tissues	Taiwan	[278]
miR-192 miR-215	Exerting cell growth and migration-promoting effects	√	ALCAM	Migration, invasion, proliferation, cell cycle and apoptosis	31 non-neoplastic stomach tissues and 25 GC tissues	United States	[279]
miR-200b	A potential diagnostic and prognostic biomarker; A potential therapeutic target for peritoneal dissemination	√	Unknown	Migration and invasion	173 GC *vs* paired normal gastric epithelium tissues	Japan	[280]

GC: Gastric cancer.

Table 3 MicroRNAs up-regulated or down-regulated in gastric cancer

ncRNA	Summary of findings/clinical relevance	q-PCR	Targets	Roles	Cases	Location	Ref.
miR-183 ↑	A potential biomarker for GC progression and therapeutic target	√	PDCD4	Proliferation, migration, invasion, and apoptosis	80 GC *vs* 20 non-tumorous gastric mucosa tissues	China	[131]
miR-183 ↓	A tumor suppressor partially through regulation of Ezrin; A potential therapeutic target	√	Ezrin	Invasion	52 pairs of paraffin-embedded GC and adjacent tissues; 5 fresh tissues samples from three patients	China	[281]
miR-146a ↑	A key factor in the regulation of NF-κB activity	√	CARD10, COPS8	Inhibits NF-κB activation	37 GC *vs* paired adjacent tissues	Denmark	[282]
miR-146a/b ↓	MiR-146a/b/UHRF1 axis associates with the GC metastasis; A potential therapeutic target in blocking GC metastasis	√	UHRF1	Invasion and metastasis	15 primary GC tissues compared with matched adjacent normal tissues	China	[180]
miR-146a ↓	MiR-146a/WASF2 axis may associate with the migration and invasion of GC cells; A potential therapeutic target	√	WASF2	Invasion and metastasis	20 GC *vs* paired adjacent tissues	China	[283]
miR-146a ↓	Targeting EGFR and IRAK1; A potential prognostic factor	√	EGFR, IRAK1	Invasion and metastasis	90 GC *vs* paired adjacent tissues	Japan	[179]
miR-9 ↑	Targeting and suppressing CDX2 expression promote GC cell proliferation	√	CDX2	Proliferation	27 GC tissues	Japan	[284]
miR-9 ↓	Ectopic expression of miR-9 inhibits the proliferation, migration and invasion of GC cells	√	MMP2, MMP9, Twist, N-cadherin	Invasion and metastasis	72 GC *vs* adjacent tissues	Taiwan	[285]
miR-9 ↓	A tumor suppressor targeting NF-κB1	√	NF-κB1	Proliferation	9 GC *vs* paired adjacent tissues	China	[286]
miR-375 ↑	A predictor of GC; progression and recurrence risk for GC patients	√	P53, MAPK, Wnt, VEGF	High frequency recurrence and poor survival	34 frozen fresh tissues and 38 paraffin-embedded tissues	China	[256]
miR-375 ↓	A tumor suppressor; Playing a role in gastric tumorigenesis	√	JAK2	Proliferation	48 GC *vs* paired adjacent tissues	China	[287]
miR-375 ↓	A tumor suppressor	√	PDK1, 14-3-3zeta	Apoptosis, proliferation	22 samples from GC and 5 normal control tissues	Japan	[288]
miR-218-5p ↑	MiR-218-5p targets and suppresses TFF1 and influences the progression of GC in an Erk1/2-dependent manner; A potential therapeutic target	√	TFF1	Proliferation	42 GC *vs* paired adjacent tissues	China	[289]
miR-218 ↓	Disruption of Slit-miR-218-Robo1 regulatory circuit may contribute to GC metastasis. A potential therapeutic target in blocking GC metastasis	√	Robo1	Invasion and metastasis	40 GC *vs* paired adjacent tissues	China	[290]

GC: Gastric cancer.

with miRNA expression[48]. This evidence suggests the possibility that chronic inflammation mediated by pro-inflammatory cytokines plays a role in regulating the expression of miRNAs in *H. pylori*-infected GC, though the mechanism by which this might occur remains unknown.

Accumulated evidence shows that DNA methylation of miRNA promoter sites is a critical mechanism for miRNA dysregulation in tumors, including GC. Investigation of the methylation frequency of 9 miRNA CpG islands in human gastric samples, including gastritis, GC and normal tissues, revealed that methylation frequency was increased in 5 CpG islands (miR-9-1, miR-9-3, miR-137, miR-34b, and

miR-210) and decreased in 1 CpG island (miR-200b) during gastric carcinogenesis[49]. Furthermore, the methylation of those 6 miRNA CpG islands in cells significantly suppressed the expression of the corresponding miRNAs. MiR-137, which acts as a tumor suppressor, was found to be down-regulated in GC[50] through methylation of a CpG island in its promoter, and an analysis of clinical samples showed that methylation of miR-137 occurred frequently in GC and played a role in gastric carcinogenesis[51]. Methylation-induced miRNA silencing in GC was also observed with miR-335[52], miR-495[53], miR-9[54], miR-10b[55], miR-219-2-3p[56], miR-212[57], miR-941 and miR-1247[58]. Aberrant expression of these miRNAs and consequent regulation of their corresponding targets resulted in changes in GC cell growth, invasion and migration[52-56,58]. Furthermore, the suppression of miRNA expression was restored after treatment with 5-aza-2′-deoxycytidine, an agent designed to reduce the degree of methylation in GC cells at specific miRNA sites. MiR-129-5p is a multi-drug resistance-related miRNA that becomes down-regulated in the drug-resistant cell line SGC7901/VCR *via* methylation, as evidenced by a restoration of miR-129-5p levels upon 5-aza-2′-deoxycytidine treatment in these cells[59]. MiR-34c-5p also negatively regulates paclitaxel resistance of GC cells and is down-regulated by a methylation of CpG islands that are near the miR-34 promoter[60]. These experiments show that methylation can regulate the levels of miRNAs. Conversely, miRNAs can regulate DNA methylation by targeting DNA methyltransferases (DNMTs). Previous experiments have shown that miR-148a modulated the expression of DNMT1 and caused the overexpression of miR-148a, and miR-148a reduced the methylation of the RUNX3 promoter, culminating in increased RUNX3 mRNA and protein in GC cells[61].

There are other regulatory elements that can induce aberrant expression of miRNAs. For example, TGF-β, a critical cytokine in cancer, can regulate miRNA expression. Specifically, this cytokine can up-regulate miR-155[62] and miR-181a[63] in hepatocyte cell lines and down-regulate miR-203 through direct binding to the promoter[64]. TGF-β1 treatment has been shown to alter miRNA expression in GC cells, causing the up-regulation of 3 miRNAs and down-regulation of 3 miRNAs[65]. TGF-β1 regulate gene expression in a Smad-dependent or -independent manner. However, the role that TGF-β1 plays in regulating the expression of miRNAs in GC is not often reported and the mechanism still requires elucidation. In addition, certain oncogenes play a critical role in the dysregulation of miRNAs in cancer. For example, miR-29b was inhibited by c-myc in non-small cell lung cancer[66] possibly through the regulation of Drosha[67]. P53 has also been reported to modulate the expression of miR-34a[68]; however, this protein has not been found in GC, and the role it plays in miRNA regulation is still uncertain. Hypoxia is another modulator of miRNA expression and functions through HIF-1α. MiR-382 was demonstrated to be induced by HIF-1α in GC cells under a hypoxic stress[69], and this phenomenon was also observed in ovarian carcinoma[70], lung cancer[71] and other cancer cell lines[72-74]. The expression profile of miRNAs also changes in GC when the cells undergo treatment with anti-tumor drugs. Treatment of GC patients with cisplatin and docetaxel significantly increased the expression of members of the miR-29 family, causing an inhibition of GC metastasis[75]. Moreover, some miRNAs that are modulated by anti-tumor drugs, such as miR-508-5p[76], miR-1271[77], and miR-503[78], might participate in the development of drug resistance in GC cells[79-82]. MiRNA regulation also occurs at the protein level in GC cell lines. For example, GSK3β, a critical protein kinase, suppresses the expression of the miRNA-183-96-182 cluster, resulting in a reduction of miR-96, miR-182 and miR-183 levels in GC cells[83]. Another protein, DDX6, suppresses the expression of the miR-143/145 cluster post-transcriptionally in GC cells[84].

LncRNAs

Dysregulation of lncRNAs is involved in tumorigenesis[85], but the underlying mechanisms remain elusive. Here, we describe some recent published data linked to the mechanisms of dysregulation of lncRNAs in GC.

PVT1 expression is increased in GC tissues and cells, and the knockdown of PVT1 inhibits GC cell proliferation and lymph node invasion[7,86]. PVT1 shows potential as a novel therapeutic target for patients who would otherwise have a poor prognosis. In addition, HOTAIR was found to be critically involved in the function of GC cells and has an inverse relationship with PCBP-1 in both expression level and function. Accordingly, PCBP1 was confirmed to be an inhibitor of GC pathogenesis. SiRNA-mediated knockdown of HOTAIR in GC cells significantly inhibited cell proliferation, migration and invasion. Additionally, the impact of HOTAIR on apoptosis, cell proliferation and cell cycle regulation was investigated to dissect the carcinogenesis of GC[87,88]. In addition to these findings, HOTAIR is a target of miR-331-3p and miR-124, and therefore, it may act as a competitive endogenous RNA for the targets of those miRNAs[89].

C-Myc induces lncRNA H19 expression, with the expression of lncRNA H19 positively correlating with the c-Myc levels in 80 GC samples[90]. Overexpression of lncRNA H19 directly promotes ISM1 expression and indirectly promotes miR-675 expression in GC. An inverse relationship was also revealed between the expression of RUNX1 and lncRNA H19/miR-675 in GC tissues and cell lines. Overexpression of lncRNA H19 was shown to promote tumorigenic features of GC including proliferation, migration, invasion and metastasis[25,91]. In addition, MALAT1 and MALAT2 were

aberrantly highly expressed in gastric cell lines and tissues, and MALAT1 can mediate the overexpression of SF2/ASF in the nucleolus. Therefore, MALAT1 may function as a promoter of GC cell proliferation through the regulation of SF2/ASF[92]. Overexpression of MALAT2 in GC cells increased the migration of GC cells and induced the epithelial-mesenchymal transition (EMT) through an MAP kinase pathway[93].

TUSC7 is a p53-regulated tumor suppressor that acts in part by repressing miR-23b. It has been shown that TUSC7 expression suppressed tumor cell growth *in vitro* and *in vivo*[94]. In addition, the expression of lncRNAs LET, FENDRR, FER1L4 and HMlincRNA717 was markedly down-regulated in tumor tissues compared with adjacent non-tumor tissues. These decreases in specific lncRNA expression were correlated with deeper tumor invasion, lymph node metastasis, distant metastasis, and higher TNM stages[95-98]. However, FENDRR overexpression suppressed invasion and migration by down-regulating FN1 and MMP2/MMP9 expression in GC cells[96]. The lncRNA GAS5 was demonstrated to decrease GC cell proliferation partly *via* regulating E2F1 and P21 expression and to induce apoptosis[99]. Ectopic expression of lncRNA MEG3 was able to inhibit cell proliferation, promote cell apoptosis, and modulate p53 expression in GC cell lines, however, its expression level was significantly correlated with TNM stage, depth of invasion, and tumor size[100]. Overexpression of the lncRNA LEIGC was able to suppress tumor growth and cell proliferation and to enhance the sensitivity of GC cells to 5-fluorouracil (5-FU), whereas knockdown of LEIGC had the opposite effect. It was further demonstrated that LEIGC functions by inhibiting the EMT in GC[101].

FUNCTION

Survival

MiRNAs in cell cycle regulation: MiRNAs can regulate cell growth by influencing cell cycle-related gene expression. MiR-101 functions as a suppressor in *H. pylori*-infected GC. The ectopic expression of miR-101 results in the down-regulation of c-myc, CDK2, CDK4, CDK6, CCND2, CCND3 and CCNE2 and the up-regulation of p14, p16, p21 and p27. These changes culminate in the induction of G1-phase cell cycle arrest in GC cells, leading to an inhibition of cell growth and colony formation[102]. MiR-137 suppresses GC cell proliferation both *in vitro* and *in vivo*, through the induction of a G1/S arrest by targeting CDK6[103]. MiR-520d-3p down-regulates c-myc and CyclinD1 expression in GC cells and suppresses cell growth by binding to the 3′ untranslated region (UTR) of EphA2 mRNA[104]. MiR-365 expression is reduced at the transcriptional level in GC tissue *via* AKT signaling in a p53-dependent manner. Overexpression of miR-365 suppresses GC cell proliferation both *in vitro* and *in vivo* through direct binding to the 3′UTR of Cyclin D1 and cdc25A mRNAs[105]. Some miRNAs, including miR-300, are involved in regulating cell cycle arrest caused by ionizing radiation such as X-rays, indicating that this miRNA may play a role in regulating the GC cell cycle[106]. The MiR-191/425 cluster was found to be overexpressed in GC tissue. A loss-of-function assay indicated that the cluster has roles in cell cycle regulation, although the mechanism is unknown[107]. MiR-1207-5p and miR-1266 are both reported to reduce the expression of hTERT, resulting in G1/S cell cycle arrest and reduction of GC cell growth both *in vitro* and *in vivo*[108]. MiR-212 inhibited GC cell growth by directly reducing RBP2 expression and up-regulating critical cell cycle related proteins such as p21 and p27[109]. MiR-17-5p/20a acted as an oncogene in GC cells by directly targeting p21 and TP53INP1, which have negative roles in the cell cycle and promote GC cell growth when inhibited[110]. Some miRNAs, such as miR-101, miR-137, miR-520d-3p and miR-17-5p/20a, directly bind to the 3′UTR of cell cycle related mRNAs and reduce their expression, resulting in progression or arrest of the cell cycle[35,102,103,110]. Other miRNAs, such as miR-300, miR-191/425 cluster, miR-1207-5p, miR-1266 and miR-212[106-109], indirectly modulate cell cycle related protein levels by regulating the expression of upstream target genes, but it is unclear how these miRNAs affect the cell cycle. Changing a single factor may cause a series of diversifications of the signaling network in cell cycle activity, and the mechanisms by which this occurs still require further research and exploration.

Regulation of AKT pathway by miRNAs: The AKT pathway is dysfunctional and hyperactive in many human cancers, including GC, and plays an important role in cell survival. MiRNAs can regulate cell survival through activation or inactivation of the AKT pathway through their targets in GC. For example, miR-1274a was found to be up-regulated in GC tissue as well as in GC cell lines such as HGC27, MGC803, SGC-7901 and AGS. Interestingly, miR-1274a inhibits FOXO4 protein expression in HGC27 and MGC803 with no effect on mRNA level. A dual-luciferase reporter assay confirmed that FOXO4, which functions as an inhibitor of the PI3K/AKT pathway, was directly modulated by miR-1274a in GC cells. MiR-1274a therefore activates the PI3K/AKT pathway through inhibition of FOXO4 expression in GC cells, resulting in enhanced cell proliferation and migration. GC xenograft mouse models also indicate that miR-1274a overexpression in GC cells can promote tumorigenesis[111]. While miR-542-3p is normally expressed at a low level in GC tissues and cells, overexpression of miR-542-3p can potentially markedly inhibit the activation of the AKT pathway and reduce cell growth by directly binding to the 3′UTR of AEG-1[112]. MiR-137 could inhibit the activation of the AKT pathway through its target gene Cox-2 and suppress GC cell growth both *in vitro* and *in vivo*[50]. MiR-34a[113], miR-338[114,115], miR-21[116], miR-124[117], miR-10b[118] and other miRNAs can

also regulate AKT pathway activity through similar gene targeting. Overexpression of miR-126, which normally acts as a suppressor of angiogenesis in GC, also inhibited cell growth by reducing the activation of the AKT pathway[119]. Similarly, hypoxia-induced miR-382 expression reduced the level of PTEN in GC cells, causing an inhibition of AKT pathway. *In vivo*, down-regulation of miR-382 caused a reduction of tumor growth and reduced microvessel density[69]. The miR-29 family contains three miRNAs with identical seed sequences: miR-29a, miR-29b, miR-29c. This family was reported to reduce the expression of AKT2, a key member of AKT pathway, by directly targeting its 3'UTR in GC cell lines HGC27 and MGC803. Clinical GC tissue analysis also illustrated that the expression of miR-29 and AKT2 has a negative correlation. Finally, ectopic expression of miR-29 induced a suppression of the AKT pathway in GC cells[120]. In addition to the miR-29 family, let-7b/g also directly binds to the 3'UTR of AKT2 and subsequently results in an inhibition of AKT pathway activity in GC[121].

MiRNAs in apoptosis: Inducing or inhibiting cell apoptosis is also an important function of miRNAs in GC cells, making them important regulators of tumor suppressors and oncogenes. Generally, miRNAs that are down-regulated in GC tissues and cells have tumor suppressive functions, and some, including miR-449a[122], miR-133a[123,124], miR-224[125], miR-338[114,115,126], miR-143[127], miR-874[128] and others, are capable of inducing cell apoptosis in GC cells. Overexpression of these miRNAs induces a suppression of cell proliferation in GC cells concurrent with other effects such as cell cycle arrest, and suppression of invasion and metastasis. Tumor suppressive miRNAs have complex functions in GC cells through their known targets or potentially other pathways and may be useful targets for GC therapy. Because miR-449a acts as a tumor suppressor by directly targeting bcl-2, which is known for its anti-apoptotic function, the overexpression of miR-449a in GC cells enhances cell apoptosis and results in G1/G0 arrest[129,130].

MiRNAs can also act as oncogenes to promote tumor growth and are referred to as oncomirs. MiR-183 is an oncomir that is up-regulated in GC tissues, and its increased expression level is associated with high clinical stage, enhanced invasion, and lymph node metastasis. Moreover, overexpression of miR-183 in GC cells reduces the rate of apoptosis by affecting the expression of PDCD4[131]. Other miRNAs, such as miR-645[132], miR-181a[133], and miR-942[134], can act as oncomirs by inhibiting cell apoptosis and promoting tumor growth.

NF-κB signaling has been shown to interact with miRNAs in GC cells. IL-1β activates NF-κB in GC cells, and the activated NF-κB directly binds to the promoter of miR-425 to enhance its transcription. Up-regulated miR-425 promotes GC cell proliferation and helps the cells resist apoptosis induced by cisplatin through direct targeting of the 3'UTR of PTEN mRNA[135]. Alternatively, some miRNAs, such as miR-362, are capable of activating the NF-κB signaling pathway in GC cells[136]. MiR-362 activates the NF-κB signaling pathway by reducing the expression of the tumor suppressor CYLD, which is its direct target in GC cells. Similar to previously mentioned miRNAs, the activation of NF-κB through overexpression of miR-362 inhibited the apoptosis induced by cisplatin and promoted GC cell proliferation. MiR-500 also activates NF-κB by suppressing the expression of CYLD, OTUD7B and TAX1BP1, which are all negative regulators of NF-κB signaling. Overexpression of miR-500 leads to activation of NF-κB signaling in GC cells, and promotes resistance to apoptosis, resulting in cell proliferation and high tumorigenicity *in vivo*[137].

MiRNAs in drug resistance: Tumor resistance to chemotherapeutic drugs has become increasingly problematic in GC. Recent findings show that miRNAs affect the sensitivity of cancer cells to chemical drugs in GC by regulating the expression of target genes. Using an miRNA expression profiling chip, it was reported that there was a significant dysregulation of miRNAs in the drug resistant sublines SGC-7901/VCR and SGC-7901/ADR compared with the parental SGC-7901 line. Quantitative RT-PCR analysis demonstrated that miR-99b-5p, let-7e-5p, miR-125a-5p, miR-181a-5p and miR-100-5p were significantly down-regulated, and miR-1273g-3p, miR-378a-5p and miR-425-5p were up-regulated in drug resistant sublines[138]. Up-regulated miRNAs in drug resistant sublines prevent cancer cell death induced by chemotherapeutics, while down-regulated miRNAs promote cancer cell death during chemotherapeutic treatment.

MiR-106a was found to be up-regulated in the drug resistant sublines SGC-7901/VCR and SGC-7901/ADR. Overexpression of miR-106a was able to reduce the sensitivity of SGC-7901 to anticancer drugs and inhibit cell apoptosis. Conversely, inhibition of miR-106a in SGC-7901/VCR enhanced the sensitivity of SGC-7901/ VCR to chemotherapeutics and decreased their IC_{50} dose[81]. MiR-21 was up-regulated in SGC7901/DDP, a cisplatin resistant cell line and may be partially responsible for resistance of GC cells to cisplatin[80]. MiR-19a/b has also been shown to regulate the resistance of GC cells to anticancer drugs and was found to be up-regulated in MDR cell lines. Furthermore, an increase in miR-19a/b levels reduces the sensitivity of GC cells to drugs by accelerating ADR efflux[79].

In contrast, miR-185 was down-regulated in GC tissues. GC cells with significant overexpression of miR-185 were significantly more sensitive to apoptosis induced by low doses of chemotherapeutic agents compared with their negative controls, a finding which was confirmed in a nude mouse model. Furthermore, reduction of endogenous miR-185 expression in GC cells inhibits cell apoptosis induced by high-dose

chemotherapeutic agents[139]. MiR-218, on the other hand, could increase the sensitivity of GC cells to cisplatin and inhibit cell growth[140], and miR-1271 was found to be down-regulated in the cisplatin resistant cell line SGC7901/DDP. Overexpression of miR-1271 enhanced the response of SGC7901/DDP cells to cisplatin[77]. Finally, miR-200c was also reported to regulate drug resistance in GC cells[141].

Accumulating evidence indicates that miRNAs play an important role in the resistance of cancer cells to chemotherapy treatment; however, the mechanism by which this occurs remains poorly understood. However, the ability of the previously mentioned miRNAs to directly affect drug resistance in tumor lines reveals novel targets for improving the efficacy of chemotherapy in the future. Therefore, chemotherapy in combination with gene therapy might be a new avenue for cancer treatment going forward.

LncRNAs in cell survival: Thousands of lncRNAs were found to be dysregulated in GC tissues compared with adjacent tissues using a microarray analysis, and several lncRNAs from the microarray were confirmed through real-time PCR assays[142,143]. Aberrantly expressed lncRNAs in GC consistently participated in key tumorigenic functions, including growth, drug resistance, and metastasis, and their presence in the tumor indicated a poor prognosis in GC patients[86,95,144,145]. The expression of several of the dysregulated lncRNAs was correlated with tumor size, TNM stage, histologic grade, differentiation, lymphatic metastasis, invasion and other classifications, including SUMO1P3[146], LINC00152[147], FER1L4[98], HMlincRNA717[97], ABHD11-AS1[148], AC138128.1[149], CCAT1[150], HIF1A-AS2[151] and more. In addition to alterations observed in GC tissue, several lncRNAs were found to have a significantly different expression pattern in serum and gastric juice. For example, CUDR, LSINCT-5 and PTENP1 were down-regulated in the serum of GC patients compared with healthy subjects[152], while AA174084 had a high expression level in gastric juice from GC patients compared with healthy controls or patients suffering from other non-cancer diseases, such as minimal gastritis, gastric ulcers and atrophic gastritis[153]. In addition, plasma H19 levels were up-regulated in GC patients compared with healthy controls but were down-regulated in postoperative specimens[154]. Together, these features reveal that lncRNAs play significant roles in the survival of cancer cells.

LncRNAs involved in cell proliferation, including HIF1A-AS2[151], MEG3[100], MALAT1[92], CCAT1[155], and LEIGC[101], were identified, however, the mechanisms by which these lncRNAs regulate cell growth are still unclear. In addition, PVT1 was up-regulated in GC tissues, and knockdown of PVT1 resulted in a significant inhibition of cell proliferation. Furthermore, PVT1 regulates the cell cycle by binding to EZH2, an important subunit of the PRC2 complex, and inhibits cyclin-dependent protein kinase inhibitors p15/p16[7]. SPRY4-IT1 was also found to be up-regulated in GC tissues and to control cell growth, colony formation, cell migration and invasion in GC cells partially through regulating the expression of cyclinD1, MMP2 and MMP9[156]. GAS5 is an lncRNA that is down-regulated in GC tissues, and ectopic expression of GAS5 in GC tumors inhibited cell growth and induced apoptosis both *in vitro* and *in vivo* through regulation of the expression of E2F1 and P21 in GC cells[99]. GHET1 physically binds to insulin-like growth factor 2 mRNA binding protein 1 (IGF2BP1), and this process promotes IGF2BP1 binding to c-Myc mRNA, resulting in increased stability of c-Myc mRNA and GC cell growth[157]. HULC, an lncRNA that is up-regulated in GC tissues and cells, is able to reduce cell apoptosis mainly by activating autophagy in the SGC-7901 cell line[158]. In addition to their role in traditional cancer growth, lncRNAs are also heavily involved in the process of drug resistance in GC. The lncRNA PVT1 is not only overexpressed in GC tissues but also in paclitaxel-resistant SGC7901cells, which indicates that it has a role in the process of GC cell resistance to paclitaxel, which so far is poorly understood[86]. In the multidrug-resistant GC cell sublines SGC7901/ADR and SGC7901/VCR, the level of MRUL was increased significantly. Knockdown of MRUL in these two multidrug-resistant sublines enhanced their sensitivity to chemotherapeutic drugs and led to an increased rate of apoptosis induced by adriamycin or vincristine[159]. AK022798 is another lncRNA involved in the resistance of GC cells to cisplatin. This lncRNA was induced by Notch 1 and overexpressed in cisplatin-resistant GC cell lines. The up-regulated AK022798 enhanced the expression of multidrug resistance- associated protein 1 (MRP1) and P-glycoprotein, thereby resulting in a suppression of apoptosis induced by cisplatin and formation of cisplatin-resistant sublines SGC7901/DDP and BGC823/DDP. This evidence suggests that AK022798 plays a significant role in the development of tumor drug resistance[10].

H19 had been demonstrated to play a critical role in GC function. H19 was found to be overexpressed in GC tissues, and it promotes GC cell proliferation[160]. Further studies suggest that c-Myc enhances the expression of H19 in GC cells, which was supported by a positive correlation between H19 and c-Myc in clinical samples[90]. MiR-675 is expressed concurrently with H19 in GC and is a known product of H19. H19/miR-675 promoted significant GC cell growth directly upon binding to RUNX1[91]. However, another mechanism of H19/miR-675 in promoting carcinogenesis has also been uncovered. Although H19 acts in a similar manner to miR-675, it was found that H19 binds to ISM1 and miR-675 also targets CALN1 in GC cells, indicating that H19 has other functions besides generating miR-675[25].

In addition to protein interactions, lncRNAs could also be interacting with miRNAs in GC cells. ANRIL is up-regulated in GC tissues and its expression is

correlated with TNM stage and tumor size in clinical samples. GC cell proliferation was significantly reduced *in vivo* and *in vitro* by reducing ANRIL expression, and the role of ANRIL in regulating cell growth was shown to be partially through inhibition of miR-99a/miR-449a levels[161]. TUSC7 suppressed the growth of GC cells by reducing miR-23b expression, which is a promoter of cell proliferation[94]. Conversely, lncRNAs can also act as targets of some miRNAs. HOTAIR is a target of miR-331-3p and miR-124 and binds with them directly in GC cells. Furthermore, HOTAIR can regulate the expression of HER2 mRNA when induced by miR-331-3p binding similar to a "sponge"[89]. Often the expression of lncRNAs is regulated by miRNAs, and for example, AC130710 is a target of miR-129-5p and is down-regulated *via* ectopic expression of miR-129-5p in GC cells[162].

Metastasis

MiRNAs as oncogenes: MiR-27 promotes GC cell metastasis by inducing EMT[163]. Moreover, single nucleotide polymorphisms (SNPs) of miRNA genes lead to functional losses or disorders of the miRNAs that are generally associated with SNPs. The G/A polymorphism in the miR-27a gene (rs11671784) directly decreases miR-27a expression. MiR-27 is responsible for directly blocking the expression of the tumor suppressor gene APC, and thus, the loss of its function contributes to EMT[164]. MiR-21 is an important oncogene that is involved in many tumorigenic factors, including metastasis and invasion, cell cycle, tumor size, and growth[165,166]. MiRNA-21 promotes tumor invasion in GC by targeting PTEN[167]. Furthermore, high levels of miRNA-21 expression are positively correlated with lymph node metastasis in GC[168]. MiRNA-21 is highly expressed in GC and is negatively correlated with PDCD4 expression, suggesting that PDCD4 is a direct target gene of miRNA-21 that inhibits cell invasion through targeted inhibition. PTEN is a well-known tumor suppressor gene that is also shown to be a direct target of miRNA-21[169]. Up-regulation of the members of miR-106b family (miR-106b, miR-93, and miR-25) in CD44(+) GC cells reduces the expression of smad7, an inhibitor of the TGF-β/Smad signaling pathway. Overexpression of miR-106b family miRNAs in CD44(+) GC cells promotes cancer stem cell-like properties and particularly EMT characteristics by activating the TGF-β/Smad signaling pathway[170]. MiR-210 is often highly overexpressed in GC and is regulated by HIF-1α. Due to this regulation, miRNA-210 expression is significantly increased in hypoxic environments where EMT develops. Unlike previously mentioned miRNAs, miR210 has been associated with *H. pylori* infection[171]. MiRNA-210 up-regulation induces significant migration and invasion of GC cells. Aside from the above-mentioned miRNAs, highly homologous miRNAs play a role in GC cell biology. For example, overexpression of miR-196a/-196b enhances GC cell migration and invasion through inhibitory oligonucleotides or direct targeting of radixin promoters in GC cells[172]. MiR-19a/b is overexpressed in GC tissues and significantly associates with the onset of metastasis. Although MXD1 is a direct target of miR-19a/b, its overexpression reduces both miR-19a/b and c-myc levels[173]. Moreover, some miRNAs directly target genes to regulate metastasis and invasion in GC cells. MiR-214 and miR-21 regulate GC cell migration and invasion by targeting PTEN[79]. In addition, miR-199a-5p acts as an oncogene in GC and functions by targeting klotho[174]. However, these are far from the only miRNA controllers that are involved in metastasis and tumor invasion through the regulation of protein signaling networks in GC cells.

MiRNAs are capable of acting as tumor suppressor genes: The miRNA-200 family suppresses GC cell metastasis by reducing the expression of the transcription factor Zeb, thereby decreasing E-cadherin expression and reducing the occurrence of EMT[175,176]. E-cadherin is a direct target of miRNA-9, and in addition, there are many miRNAs that function by targeting the EMT transcription factors Snail, Snail2, Zeb1 and Zeb2, which regulate signaling pathways controlling tumor metastasis. The tumor suppressor gene p53 can induce the expression of miR-34a and miR-192, which inhibit the expression of Snail-1 and Zeb-2, thus preventing the EMT process[177]. MiRNA-1182 targets the open reading frame of hTERT and serves to lower hTERT expression, inhibiting cell migration in GC[178]. MiRNA-146a inhibits migration and invasion in GC cells by down-regulating EGFR and IRAK gene expression[179]. In addition to these functions, miRNA-146a/b down-regulates UHRF1 by directly targeting its 3'UTR, and this effect in turn reactivates the slit homologue3, cadherin4, and RUNX3 genes *via* promoter demethylation. MiRNA-146a/b plays a key role in regulating the metastatic process in GC cells[180]. MiRNA-328-induced down-regulation of CD44v9 expression occurs in *H. pylori*-infected gastric mucosa adjacent to GC tumors, which decreases the rate at which stem cells transform into GC cells[181]. In summary, abnormal expression of miRNA has been consistently observed in GC tissues. The proteins shown to be dysregulated in GC are actually being driven by a massive miRNA expression imbalance, leading to metastasis and invasion in these tumors.

Dysregulated lncRNA expression: LncRNA HOTAIR plays a role in metastasis in GC cells. LncRNAs PCBP-1 and HOTAIR have an inverse relationship in both expression level and function. PCBP1 has been confirmed to inhibit GC pathogenesis, and overexpression of HOTAIR down-regulates PCBP1 protein levels. HOTAIR expressed in xenograft GC tumors *in vivo* increases metastasis[89,182]. In addition, HOTAIR is a known target of miR-331-3p and miR-124 and may act as a competitive inhibitor of endogenous RNAs[89]. The lncRNA H19 actively binds to ISM1,

but its expression is positively correlated with that of H19, leading to miR-675 targeting of CALN1. While overexpression of H19 directly promotes ISM1 expression and indirectly promotes miR-675 expression in GC, CALN1 is a target of miR-675. H19 mediates this process to promote GC cell metastasis[25]. In addition, lncRNAs are capable of mediating gene expression. For example, SNCG up-regulation by lncRNA AK058003 mediates hypoxia-induced GC cell metastasis. SNCG and AK058003 expression has been shown to be increased by hypoxia[183]. LncRNA HULC positively regulates GC cell migration and invasion, and the deletion of HULC reverses EMT, indicating that HULC plays a role in EMT regulation[158]. FENDRR overexpression suppresses the invasion and metastasis of GC cells by down-regulating FN1 and MMP2/MMP9 expression[96]. High linc-UBC1 expression is correlated with lymph node metastasis, and inhibition of linc-UBC1 suppresses the invasion of GC cells[184]. Silencing of SDMGC or TRIM16 decreases cell invasion and migration rates, while up-regulation of SDMGC or TRIM16 is able to promote invasion and migration[185]. Compared with the comprehensive catalogue of miRNAs uncovered, the majority of lncRNA functions are unknown and those shown to be functional have unclear mechanisms. It is understood that a few lncRNAs can mediate the expression of oncogenes or tumor suppressor genes, and dysfunction of these lncRNAs can result in GC cell metastasis and invasion. Similar to miRNAs, not only can lncRNAs take part in post-transcriptional regulatory activities by binding to the mRNA, but they can also regulate mRNAs indirectly by competitively binding with miRNAs. Currently, lncRNA research remains a small part of the overall GC field, however, we think that lncRNAs represent very important targets for clinical applications in the treatment of this disorder.

Angiogenesis

Angiogenesis is an important step during the development of cancer[186]. MiRNAs, acting as post-transcriptional regulators, are also involved in regulating angiogenesis. MiR-874, which is down-regulated in human GC, could potentially repress the expression of STAT3 by directly targeting the 3' UTR of its mRNA, resulting in a repression of the STAT3/VEGF-A pathway and significantly inhibiting tumor angiogenesis of GC cells[187]. Overexpression of miR-18a inactivated the mTOR pathway and down-regulated HIF1α and VEGF expression in SGC-7901 cells in addition to causing a substantial reduction in the number of microvessels in an SGC-7901 xenograft model[188]. MiRNA-145 also acts as an inhibitor of angiogenesis in GC cells, primarily by directly binding to 3'UTR of the Ets1 mRNA[189]. Hypoxia can induce expression of miRNAs, which may play a role in promoting angiogenesis. MiR-382, which is up-regulated by hypoxia, activates the AKT/mTOR signaling pathway by directly suppressing PTEN and therefore induces angiogenesis *via* VEGF. This evidence indicates that miR-382 is an angiogenic oncogene in GC cells under hypoxic conditions[69]. VEGF-A is a critical factor in the regulation of angiogenesis, so miRNAs that can impact VEGF-A expression should have a function in angiogenesis. For example, miR-126 was found to directly bind to the 3'UTR of VEGF-A in GC cells and therefore could inhibit angiogenesis both *in vitro* and *in vivo*[119]. In addition, lncRNAs also participate in the regulation of tumor angiogenesis. For example, MALAT1 regulates vascular growth in human endothelial cells[190], and hepatocellular carcinoma-related MVIH can activate angiogenesis *in vivo*[191]. However, thus far no lncRNAs that have been shown to impact angiogenic regulation are reported in GC cells or tissues.

CLINICAL IMPLICATIONS

MiRNAs as biomarkers

MiRNAs have the potential to be biomarkers for swift GC identification in the clinic. MiRNAs have several large advantages as biomarkers: they are highly specific, with each tissue, including tumor tissue, having its own characteristic miRNA expression profile; miRNAs are very stable and are resistant to RNAse enzymes and changes in their physical state (*i.e.*, temperature, pH and other environmental conditions); miRNAs are easy to detect, with conventional methods such as RT-PCR and gene chip analysis. However, miRNAs still have several major issues that must be addressed before they can be incorporated as cancer biomarkers: miRNA analysis cannot function on a small sample size, and requires a large-scale standardized survey; a reference range detailing the possible miRNAs active in tumors must be created; when looking for cancer metastasis, recurrence and prognosis biomarkers, it is necessary to continue to follow up with more large scale patient data to further define the cancer progression; to be used as biomarkers, detection of peripheral blood miRNAs requires the establishment of a standardized system that includes sample collection, preservation and testing to ensure the accuracy and repeatability of miRNA detection.

At present, because of the high rate of clinical GC, many researchers have opted to select patients with GC to compare their tumor tissues to their own normal tissue samples using microarray analysis. These experiments show significant miRNA increases or decreases in patients with GC. These experiments can then be used to identify key differences between cancer and normal tissue biopsy expression, and real-time PCR validation can be used to determine the accuracy, specificity and sensitivity of those markers.

MiRNAs

Potential biomarkers for GC diagnosis: To detect

differential expression of the miRNAs in GC tissues, researchers usually identify patients with GC tissues and adjacent non-transformed tissues. In addition, some researchers utilize GC tissues and compare those samples to normal tissues of other independent patients. Researchers have found that some patients' non-transformed tissue samples show increased expression of miRNAs such as miR-17, miR-106a, and miR-20a, and others show decreased expression of other miRNAs such as miR-23a, miR-150, and miR-130a[192], indicating a significant difference in miRNA profiles between non-transformed tissue samples. It is found that miR-30b[193], miR-148a[194], miR-143 and miR-195[195] are down-regulated in GC tissues compared with their matched adjacent non-tumor gastric tissues, and tend to be down-regulated in many GC cell lines. MiR-30b has the potential to be a novel tumor suppressor gene, promoting apoptosis and suppressing tumor growth by targeting plasminogen activator inhibitor-1. MiR-148a has an unknown mechanism, but could regulate several different target genes and signaling pathways involved in tumor proliferation, invasion and metastasis. MiR-375 is significantly down-regulated in distal gastric adenocarcinoma tissues and the circulating serum. In addition, this miRNA has been linked to *H. pylori* infections[196,197]. Studies have found that the levels of miR-106a and miR-21 are significantly higher in GC tissues[195,198] and are low in gastric juice[199]. Accordingly, miR-21 is likely a risk factor that could be useful for prognosis evaluation, particularly as it is also found to be similarly increased in plasma[200]. Studies have also found that many other miRNAs are differentially expressed in GC. For example, miR-31 expression is reduced, and miR-421 is overexpressed, among others. These samples have been collected from different races and regions, however, the data require more samples and appropriate statistical treatment to verify the presence of biomarkers. In addition, up-regulation of miR-21 and down-regulation of miR-133b are detectable in both gastric and esophageal cancers[201]. However, because the detection of differential expression in GC tissues is a significantly invasive procedure for patients, these markers are not suitable for initial clinical diagnosis.

Clinically, detecting differences in the serum or plasma of patients is more useful than tissue sample analysis because blood work is relatively non- invasive and easy to obtain. With more insight into blood miRNA expression during GC, it is possible to identify markers that are not only suitable for diagnosis but also can guide treatment and prognosis. In serum samples, miR-233, miR-16, and miR-100 have increased expression in patients with GC. These markers correlated significantly with clinical characteristics of GC patients, such as their TNM stages[202]. In addition, plasma miR-222 was significantly up-regulated in GC patients compared with chronic atrophic gastritis patients and healthy controls and also correlated with patients' clinical stages and lymph node metastasis status[203]. Some miRNAs that are abnormally expressed in other tumors have a similar expression pattern in GC. Circulating miR-18a is one such miRNA, which shows altered expression in both GC and bladder cancer[204]. MiR-let-7 regulation is sabotaged in GC, breast cancer[205], oropharyngeal cancer[206], and lung cancer[207]. These markers represent the potential for an extensive screening test that may be able to identify a variety of nascent cancers in patients. In plasma samples, miR-16-5p and miR-19b-3p are down-regulated, and can be used to distinguish healthy patients from GC patients with a variety of different TNM stages and differentiation grades, including the early stages of the cancer[208]. Several miRNAs found in serum samples are predictively consistent with GC standards in the industry, including mic-RNA-421, which has been shown to have a higher sensitivity and specificity than carcinoembryonic antigen and cancer antigen 125 in GC[209,210]. In addition to these markers, certain miRNAs in the blood showed altered levels unrelated to the presence of cancer, most likely due to the occurrence of hemolysis in the patient samples.

In addition to the patient's blood and stomach tissue, their gastric juice can also be used to detect increased risk of GC. Samples of gastric juice are usually collected from normal gastric mucosa, gastritis, and GC, therefore a wealth of potential biomarkers await investigation. For example, investigators found that miR-129-1-3p and miR-129-2-3p are decreased in GC[211]. In addition, miR-21 and miR-106a are decreased in GC, which also correlates with patients' TNM stage. High expression of miR-21 and miR-106a occurs in intestinal GC types compared with diffuse GC types[199]. Furthermore, miR-21 and miR-106a are also up-regulated in gastric carcinoma tissue.

Potential biomarkers of prognosis: In addition to their potential as diagnostic markers, the expression levels of specific miRNAs can also be used as prognostic markers, as several miRNA expression changes appear to suggest poor prognosis. These include the down-regulation of miR-451, which is associated with poor prognosis. Furthermore, the overexpression of miR-451 increased tumor sensitivity to radiotherapy[212]. MiRNAs can be combined with other proteins as part of a comprehensive combination marker. An example of this is miR-200c, which forms a complex with GDF15 and is indicative of poor outcomes in GC patients[213]. Many diagnostic markers may also have prognostic value; however, significant work will need to be conducted to confirm their role in prognosis.

Certain miRNAs act as key regulatory hubs, controlling a significant portion of the cancer cell's signaling network, and the reregulation of any one of them may be a marker for growth and metastasis. MiR-214 is one example of these key miRNAs[214]. Some miRNAs, such as miR-133a[123] and miR-29c[215], are known to function as tumor suppressors.

The expression of these miRNAs was significantly decreased in GC, and their deregulation was associated with lymph node metastasis in GC patients. MiR-133a suppresses TAGLN2 at the transcriptional and translational levels, while MiR-29c directly targets ITGB1. Overexpression of miR-133a inhibits cell growth and invasion and induces cell apoptosis and cycle arrest through the repression of the TAGLN2 gene, which makes it a candidate as a biomarker or a therapeutic target. Loss of miR-29c expression is an early event in the initiation of gastric carcinogenesis, which makes it attractive as a diagnostic and therapeutic biomarker for patients with GC. MiR-29c also plays a role in the efficacy of chemotherapy, and suppresses metastasis in GC[75].

Cancer stem cells are characterized by their strong tumorigenicity. In GC stem cells that express CD44, miR-106b expression is increased, activating TGF-β/Smad signaling in GC cells. This phenomenon leads to a strong invasion and migration impetus for the stem cell population. In an miRNA microarray, the miR-106b family composed of miR-106b, miR-93, and miR-25 is significantly up-regulated in CD44(+) cells compared to CD44(-) cells[170], which also significantly correlates with tumor size, borrmann type and TNM stage in GC patients[216].

LncRNAs and prognosis

In addition to miRNAs, lncRNAs can promote tumor cell expression of CD44, causing those tumor cells to exhibit stem cell properties. One example is the lncRNA GAPLINC (gastric adenocarcinoma predictive long intergenic noncoding RNA)[217]. Typically, these non-coding RNAs promote high tumor aggressiveness, and lead to a poor prognosis. GAPLINC overexpression currently defines a subgroup of GC patients with very poor survival outcomes. Mechanistic investigations show that GAPLINC regulates CD44 as a molecular decoy for miR211-3p, an miRNA that targets both molecules. Another lncRNA, ANRIL, recruits and binds to PRC2, and is up-regulated in GC tissues. Knockdown of ANRIL can repress the proliferation of GC cells both *in vitro* and *in vivo*. E2F1 induces ANRIL and ANRIL-mediated growth promotion by epigenetically silencing miR-99a/miR-449a. Like GAPLINC, the presence of ANRIL indicates a poor prognosis for patients[161]. Overexpression of the lncRNA HOTAIR is characteristic of poor prognosis in GC, and may confer an as of yet unknown malignant phenotype to tumor cells. It functions as a competing endogenous RNA to regulate HER2 expression by sponging miR-331-3p in GC[89]. HER (human epidermal growth factor receptor) based cancers, such as HER2-positive breast cancer and GC, often show miR-337 and miR-302f overexpression, and miR-139 and miR-129 underexpression[218].

In tumor cells, the regulatory interactions between lncRNAs, miRNAs and proteins are complicated and unknown. It is important not just to look at statistical markers but also to attempt to identify the mechanisms by which these molecules interact with each other to understand the full scope of the regulatory network altered by tumorigenic mutations. For now, technology is limited, but it is also important to obtain more samples for comprehensive studies.

CONCLUSION

Recently, accumulating evidence is revealing that ncRNAs play a more critical role in cancer than has been thought for decades. As we have summarized and discussed in this review, ncRNAs participate in every stage of cancer, including tumorigenesis, growth, apoptosis, cell cycle regulation, metastasis, angiogenesis, and drug resistance. Hundreds of ncRNAs have been shown to be dysregulated in tissues and cell lines, often with each sequence functioning as a tumor promoter or inhibitor. However, the mechanism driving aberrant expression has been unclear until now. We described factors that can regulate miRNA expression in GC, such as *H. pylori* infection, DNA methylation, cytokine exposure, and hypoxia. NcRNAs act as key regulators in cell processes, and their levels vary to regulate the expression levels of their targets, leading to normal growth and differentiation. Once cells suffer from carcinogenic alterations, the regulation of ncRNA levels become dysregulated, leading to cell survival in cancer lines. If the process of the cells' tumorigenesis cannot be stopped, the gene expression of these malignant cells will fundamentally change and a new ncRNA profile will emerge. This new profile often involves the down-regulation of anti-tumor ncRNAs and up-regulation of ncRNAs that promote the survival of malignant cells and the initial formation of the tumor. However, some miRNAs that are up-regulated in GC tissues and cells also act as tumor suppressors. This may be explained by the presence of a negative feedback loop, such as the case with miR-146a. It is difficult to explain the mechanism of ncRNAs in the process of malignant transformation because it is unclear whether ncRNAs are a driving force behind the transformation or a result of it. Regardless of this, the abnormal expression of ncRNAs indicates a novel method to diagnose cancer, especially in its early stages. Some ncRNAs are secreted into blood, gastric juice, or urine and this facilitates the acquisition of samples for biomarker analysis with little discomfort to the patient. Some ncRNAs can also indicate a different prognosis for patients based on their presence or their expression level in clinical testing. In addition to use as biomarkers, abnormally expressed ncRNAs may be potential candidates for cancer therapy.

Moreover, some miRNAs directly target genes to regulate metastasis and invasion in GC cells. MiR-214 and miR-21 regulate GC cell migration and invasion by targeting PTEN. MiR-199a-5p acts as an oncogene in GC and functions by targeting klotho. Some miRNAs control metastasis and invasion through the

regulation of signaling networks in GC cells. MiRNAs regulate gene expression through post-transcriptional repression and can act to control multiple cellular pathways. Based on the literature, abnormal expression of miRNA has been observed in GC tissues. The proteins that are dysregulated due to aberrant miRNA expression in GC often drive metastasis and invasion in tumor cells. The ideal time for a tumor to invade and metastasize is when the original cancer cells transform into malignancies, as that generally leads to local invasion and distant metastasis. During this process, cancer cells often undergo morphological changes and reduce their contacts to the extracellular matrix. The process by which the cancer cell undergoes metastasis and invasion is very complex. Between continuous signaling, expression of transcription factors, the reduction of cell-cell adhesion proteins such as cadherin, tumor growth, the changing tumor microenvironment, the tumor stem cells as well as indirect stimulation, it can often result in multiple mutant tumor cell genomes that compete and can accelerate metastasis and invasion of cancer cells. Of course, cancer cells grown in continuous culture do not model natural tumors without exposure to the blood vessels. These vessels function to supply oxygen to tumor cells that have limited nutritional capability, leaving hypoxic conditions within the tumor core and thus promoting tumor cell migration to the blood vessels and lymphatic areas. During metastasis and invasion, cells will detect a more suitable location to grow, although new colonies will often form at the first viable point rather than at optimal points.

Cisplatin resistance is the most common cause of treatment failure in GC patients. Many cancer chemotherapy treatments fail because of drug resistance, and miRNAs serve as modulators that can adjust the sensitivity of cells to drugs. For example, the miR-223/FBXW7 signaling pathway contributes significantly to DDP resistance of GC cells[82].

From a novel methodology in which the system is capable of identifying more screening markers and more reliable markers[219], fourteen total biomarkers have been found to be associated with GC. Additionally, three miRNAs (miR-211, let-7b, and miR-708) were reported for the first time to differentiate patients with GC and represent possible diagnostic biomarkers for GC.

Polymorphisms of miRNAs primarily occur *via* a change in their precursor molecule. Mutations of some sites can interfere the expression of mature miRNAs, which in turn impacts their function and can macroscopically affect tumor malignancy. Specific miRNA polymorphism sites can be used as tumor markers for prognosis. For example, the pri-let-7a-2 rs629367 CC genotype, which may increase the risk of GC, possibly affects mature let-7a expression and could therefore serve as a predictive biomarker for high risk and poor prognosis of GC[220]. LncRNAs are also known for their potential polymorphisms, although specific lncRNA polymorphisms are rarely studied[221]. However, research of this type is gaining more attention[222]. These biomarkers are diverse and complex and could provide the basis for future individualized treatment of GC.

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