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REVIEW

Role of miRNAs and their potential to be useful as diagnostic and prognostic biomarkers in gastric cancer

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Abstract

Alterations in epigenetic control of gene expression play an important role in many diseases, including gastric cancer. Many studies have identified a large number of upregulated oncogenic miRNAs and downregulated tumour-suppressor miRNAs in this type of cancer. In this review, we provide an overview of the role of miRNAs, pointing to their potential to be useful as diagnostic and/or prognostic biomarkers in gastric cancer. Moreover, we discuss the influence of polymorphisms and epigenetic modifications on miRNA activity.

Key words: Gastric cancer; Epigenetic; Diagnostic biomarkers; miRNAs; Prognostic biomarkers

Core tip: Accumulating evidence indicates that dysregulated miRNAs play important roles in gastric cancer pathogenesis. In this context, we provide an overview of the role of miRNAs, pointing to their potential to be used as diagnostic and prognostic biomarkers in gastric cancer. Moreover, we discuss the influence of polymorphisms and epigenetic modifications on miRNA activity.

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INTRODUCTION

Gastric cancer (GC) is the fifth most frequent cancer, besides being the third leading cause of cancer-related death worldwide[1]. According to Laurén, GC is classified into intestinal and diffuse types[2], which are a consequence of an accumulation of genetic and epigenetic modifications[3].

Epigenetic events refer to alterations that promote gene expression variation without changing the DNA sequence yet leading to transcriptional activation or silencing of the gene[4].

Epigenetic alterations, mainly aberrant DNA methylation, histone modifications and microRNA (miRNA) expression play a central role in many diseases, including GC[5-7].

miRNAs are a class of small non-coding RNAs (19–25 nucleotides) that act as important epigenetic players in many cellular processes, such as differentiation, proliferation and apoptosis, exerting a great influence in cancer pathogenesis[8,9].

In general, miRNA genes are located in intergenic regions, suggesting that most miRNA genes are transcribed as autonomous transcription units[10]. Moreover, these molecules are usually transcribed by RNA polymerase II, generating long primary transcripts (pri-miRNAs). The pri-miRNAs are processed to pre-miRNAs (70 nucleotides) by Drosha. Then, these pre-miRNAs are processed by Dicer and generate a double-stranded RNA, which includes the mature miRNA[8].

The mature miRNAs repress protein translation through binding to the target protein-coding mRNAs by base-pairing to partially complementary regions frequently located at the 3'-untranslated regions (3'-UTR) of the target transcript[8,11-13].

A large number of miRNAs with different biological functions have been found altered in correlation with clinico-pathological features and/or prognosis in GC[5,7]. Ribeiro-dos-Santos *et al*[14] and Moreira *et al*[15] suggested the existence of gastric tissue and organ miRNA expression signatures. Accordingly, Gomes *et al*[16] observed a specific expression signature of let-7b, miR-21, miR-29c, miR-31, miR-192, miR-141, miR-148c and miR-451 in GC.

In this review, we describe the role and clinical significance of miRNAs, highlighting their use as potential prognostic and/or diagnostic biomarkers in GC. Moreover, we discuss the influence of polymorphisms and epigenetic modifications on miRNA activity.

ROLES AND CLINICAL SIGNIFICANCE OF miRNAs IN GASTRIC CANCER

In cancer, miRNAs can function as oncogenes and/or tumour suppressor genes depending on the outcome of the target mRNA (oncomiRNA or tsmiRNA, respectively). Increased activity of an oncomiRNA leads to inhibition of apoptosis and cell proliferation. In contrast, decreased activity of a tsmiRNA leads to increased tumour formation[17].

Because *in vitro* and *in vivo* introduction of tsmiRNAs promotes antitumoural activity by restoring lost tumour suppressor activity[18,19] and the use of antagomirs inhibits the pro-tumourigenic activity of oncomiRNAs[20], improved understanding of miRNAs' role in cancer could be helpful for providing novel insights into the role of miRNAs as molecular targets, whose modulation might hold therapeutic promise.

Both the overexpression of oncomiRNAs and the decreased expression of tsmiRNAs play pivotal roles in GC, and many studies in the literature have identified a large number of upregulated and downregulated miRNAs and their potential targets in this type of cancer. Therefore, aberrant expression of miRNAs has been significantly related to clinico-pathological features such as tumour stage, size, differentiation, metastasis and *H. pylori* status (Table 1)[21-118].

In GC, studies have consistently reported that miR-106a has oncogenic activity through suppressing the expression of *TIMP2, PTEN, FAS* and *RUNX3* genes[45-50]. Zhu *et al*[50] demonstrated that miR-106a is frequently upregulated in human GC and is closely associated with local tumour invasion and distant spreading by directly regulating its functional target *TIMP2*, a metastasis associated gene. Similarly, Xiao *et al*[45] stated that the level of miR-106a in GC tissues was significantly higher than that in non-tumour tissues, with an average increase of 1.625-fold and was significantly associated with tumour stage, size and differentiation, lymphatic and distant metastasis and invasion.

On the other hand, let-7a is one of the most important tsmiRNAs involved in gastric carcinogenesis,

Table 1 Deregulated miRNA in gastric cancer tumor

miRNA/role	Targets	Clinicopathological features	Ref.
OncomiRNAs			
miR-17	*UBE2C* *FBXO31*	Tumor size Tumor infiltration Clinical grade Prognosis Tumor stage	[21-24]
mir-19a	*MXD1* *SOCS1* *PTEN*	Migration Invasion Metastasis Proliferation Multidrug resistance	[25-28]
miR-20a	*EGR2* *E2F1*	Overall survival Relapse-free survival Self-renewal and proliferation of GC stem cells Chemoresistance of GC cells to cisplatin and docetaxel	[29-31]
miR-21	*PTEN* *PDCD4* *RECK* *SERPINI1*	Differentiation Lymph node metastasis *H. pylori* infection Tumor stage Tumor size	[29,32-37]
miR-25	*FBXW7* *TOB1* *RECK*	Proliferation Invasion Migration Metastasis Aggressive phenotype Poor long-term survival	[38-41]
miR-27a	*PHB* *ZBTB10* *HOXA10* *CCND1*	*H. pylori* infection Proliferation Drug resistance	[42-44]
miR-106a	*TIMP2* *PTEN* *FAS* *RUNX3*	Invasion Differentiation Distant metastasis Lymph node metastasis Tumor stage Tumor size	[45-50]
miR-106b	*P21* *E2F5* *E2F1*	Lymph node metastasis Depth of infiltration	[29,46,51-54]
miR-200b	*ZEB1* *ZEB2* *SUZ12* *DNMT3A* *DNMT3B* *SP1* *WNT-1*	Diffuse-type Poor overall survival *H. pylori* infection Metastasis Tumor size	[55-58]
miR-215	*RB1* *RUNX1*	Tumor stage	[59-61]
miR-222	*PTEN* *RECK*	Shorter metastasis-free survival Proliferation	[38,62-65]
tsmiRNAs			
let-7a	*RAB40C* *CDKN1* *SPHK2* *FN1*	Differentiation Lymph node metastasis Cell cicle arrest Growth suppression Overall survival Relapse-free survival	[66-71]
miR-143	*COX-2*	Invasion Haematogenous metastasis Lymph node metastasis Tumor stage	[69,72-75]
miR-148a	*ROCK1* *MMP7* *p27* *DNMT1* *SMAD4*	Clinical stage Lymph node metastasis Poor clinical outcome Epithelial-mesenchymal transition	[76-80]
miR-200c	*RND3* *DNMT3A* *DNMT3B* *SP1*	Lymph node metastasis Poor overall survival Sensitivity of chemotherapy to cisplatin Clinical stage Invasion	[56,57,81,82]
miR-204	*SIRT1* *BCL-2* *EZR*	Epithelial-mesenchymal transition Anoikis resistance Migration Invasion Colony forming ability	[83-85]
miR-218	*VOPP1* *ROBO1*	Proliferation Migration Metastasis	[86-89]
miR-433	*RAB34* *KRAS*	Tumor stage Overall survival Proliferation Migration Invasion	[90-92]
Controversial			
miR-9	*CCND1* *ETS1* *CDX2* *GRB2* *NF-kappaB1* *RAB34*	Proliferation Invasion Metastasis	[90,93-96]
miR-107	*FOXO1* *DICER1* *CDK6*	Invasion Differentiation Lymph node metastasis Tumor size Tumor stage Overall survival	[97-100]
miR-146a	*EGFR* *IRAK1* *L1CAM* *CARD10* *COPS8* *NASF2* *SMAD4* *WASF2*	Tumor size Poor differentiation Lymph node metastasis Venous invasion Overall survival time Apoptosis	[101-106]
miR-155	*SMAD2* *CDC73* *CYCLIN D1*	Invasion Lymph node metastasis *H. pylori* infection Cell viability Apoptosis	[38,107-111]
miR-181b	*CREB1* *BCL2*	Proliferation Migration Invasion Colony formation Apoptosis Multidrug resistance	[112-115]
miR-223	*EPB41L3* *STMN1* *FBXW7* *HMGA2*	Poor metastasis-free survival Apoptosis Proliferation Invasion Poor clinical prognosis	[116-118]

and studies in the literature have reported RAB40C, *CDKN1, SPHK2* and *FN1* as its targets[66-71]. Yang *et al*[68] demonstrated that GC tumour and cell lines with lower expression of let-7a tended to have poor differentiation. Furthermore, they demonstrated that induced overexpression of let-7a resulted in a decrease in cell proliferation, G_1 arrest and significant suppression of anchorage-dependent growth *in vitro* and tumourigenicity of GC cells in a nude mouse xenograft model.

Several studies have reported on miRNAs with a controversial role in gastric carcinogenesis such as miR-107 and mir-181b. For example, Guo *et al*[114] stated that the proliferation, migration and invasion of GC cells significantly increased after miR-181b transfection, probably due to downregulation of protein levels of TIMP3. Conversely, Chen *et al*[115] showed that miR-181b is downregulated in human GC cell lines in comparison with gastric epithelial cells. They observed that overexpression of miR-181b suppressed the proliferation and colony formation rate of GC cells, suggesting that miR-181b may function as a tumour suppressor in gastric adenocarcinoma cells through negatively regulating the *CREB1* gene.

The dual role of this and other miRNAs could be explained by the fact that a single miRNA is capable of targeting multiple genes, repressing the production of hundreds of proteins, directly or indirectly. Additionally, each gene can be regulated by multiple miRNAs, so the final effect will depend on these complex interactions[119,120].

Because miRNAs have thousands of predict targets in a complex regulatory cell signalling network, it is important to study multiple target genes simultaneously. Thus, a research group at Federal University of Pará (UFPA) developed the web tool TargetCompare (http://lghm.ufpa.br/targetcompare) to analyse multiple gene targets of pre-selected miRNAs. The described tool is useful for reducing arbitrariness and increasing the chances of selecting target genes having an important role in the analysis[121].

CIRCULATING miRNAs AS POTENTIAL GASTRIC CANCER BIOMARKERS

In cancer, it has been shown that primary tumour cells can release specific cancer miRNAs into the tumour microenvironment as well as into the circulation[122,123]. In recent years, studies have reported that miRNAs detectable in plasma or serum are more stable among individuals of the same species in comparison with other circulating nucleic acids[124].

This finding could be explained by the fact that circulating miRNAs exhibit resistance to endogenous ribonuclease activity by binding certain proteins such as Argonaute2 and high-density lipoproteins, besides being packaged in secretory particles including apoptotic bodies and exosomes, which allow them to be protected from existing ribonucleases[125-127]. Thus, it is plausible to use circulating miRNAs as biomarkers for early detection of various diseases, including GC.

Several studies have described circulating miRNAs as reproducible and reliable potential biomarkers as well as therapeutic targets in GC (Table 2)[128-137]. Tsujiura *et al*[130] suggested that miR-18a, which is a component of the miR-17-92 cluster, could be considered a novel plasma biomarker in GC patients. In addition to observing that the plasma miR-18a concentrations were significantly higher in GC patients than in healthy controls, they also stated that the plasma miR-18a levels were significantly reduced in postoperative samples compared to preoperative samples.

Recently, Wang *et al*[138] assessed the diagnostic performance of circulating miRNAs for the detection of gastrointestinal cancer in a meta-analysis including 21 GC studies. The majority of the GC studies were of Asian ethnicity, and the most frequent miRNAs found in plasma or serum were miR-106b and miR-21. In Caucasian patients with GC, they described miR-203, miR-146b-5p, miR-192 and miR-200c as potential biomarkers in plasma. However, many of these biomarkers have been tested in very restricted parameters and are highly influenced by ethnic and environmental factors, thus making it even more difficult to find specific biomarkers for GC.

EPIGENETIC FACTORS INFLUENCING miRNA EXPRESSION IN GASTRIC CANCER

Many molecular mechanisms lead to miRNA deregulation such as genetic mutation and epigenetic aberration. Approximately half of miRNA genes are located next to CpG islands, and the expression of these miRNAs is regulated by alterations in DNA methylation and histone modification[139-143].

DNA methylation is involved in silencing expression of tumour suppressor genes by establishing and maintaining a repressive status at gene promoters[5-7,144]. The basic transcription mechanism of miRNAs is fundamentally similar to that of classical protein-coding genes, and aberrant DNA hypermethylation has been shown to silence tsmiRNAs in cancer.

Many miRNAs have been reported to be downregulated due to hypermethylation of the CpG islands in GC, such as miR-9, miR-34b/c, miR-129, miR-137, miR-181c, miR-199a, miR-212, miR-338, miR-512, miR-516, miR-941 and miR-1247[142,143,145-150].

Several studies have shown that the miRNA methylation level was positively associated with the clinicopathological features of GC[147]. Low expression levels of miR-34b and miR-129-3p are associated with a poor clinical outcome in GC patients, and hypermethylation of miR-129-2 and miR-34b CpG islands tends to correlate with poor clinico-pathological features[148].

miRNAs can also be decontrolled as a consequence

Table 2 Circulating miRNA as diagnostic and prognostic biomarkers

miRNA	Samples	Potential biomarker type	Method	Clinical implication	Ref.
miR-1	164 GC/127 C Serum	Diagnostic	Solexa sequencing qRT-PCR	GC detection	[128]
miR-16	40 GNCA/40 C Plasma	Diagnostic	Taqman low-density array qRT-PCR	Early detection of GNCA	[122]
miR-17-5p	79 GC/30 C Plasma	Diagnostic	qRT-PCR	GC detection	[46]
	79 pre-operative GC/30 post-operative GC/6 relapse Plasma	Prognostic	qRT-PCR	Prediction of prognosis and monitoring of chemotherapeutic effects	[129]
miR-18a	104 GC/65 C Plasma	Diagnostic Prognostic	qRT-PCR	Screening GC and monitoring tumor dynamics	[130]
miR-20a	164 GC/127 C Serum	Diagnostic	Solexa sequencing qRT-PCR	GC detection	[128]
	90 GC/90 C Plasma	Diagnostic	qRT-PCR	Early detection of GC	[131]
	79 pre-operative GC/30 post-operative GC/6 relapse Plasma	Prognostic	qRT-PCR	Prediction of prognosis and monitoring of chemotherapeutic effects	[129]
miR-21	69 GC Plasma	Prognostic	qRT-PCR	Prognostic marker	[132]
	16 LN-metastasis positive/15 LN-metastasis negative/10 C Serum	Prognostic	qRT-PCR	Predicting LN metastasis	[133]
	79 GC/30 C Plasma	Diagnostic	qRT-PCR	GC detection	[46]
	70 GC/70 C Plasma	Diagnostic	qRT-PCR	GC detection	[134]
miR-25	40 GNCA/40 C Plasma	Diagnostic	Taqman low-density array qRT-PCR	Early detection of GNCA	[122]
miR-34	164 GC/127 C Serum	Diagnostic	Solexa sequencing qRT-PCR	GC detection	[128]
miR-92a	40 GNCA/40 C Plasma	Diagnostic	Taqman low-density array qRT-PCR	Early detection of GNCA	[122]
miR-106a	79 GC/30 C Plasma	Diagnostic	qRT-PCR	GC detection	[46]
miR-106b	79 GC/30 C Plasma	Diagnostic	qRT-PCR	GC detection	[46]
	90 GC/90 C Plasma	Diagnostic	qRT-PCR	Early detection of GC	[131]
miR-191	57 GC/58 C Serum	Diagnostic	qRT-PCR	GC detection	[135]
miR-218	70 GC/70 C Plasma	Diagnostic	qRT-PCR	GC detection	[134]
miR-221	90 GC/90 C Plasma	Diagnostic	qRT-PCR	Early detection of GC	[131]
miR-223	70GC/70C Plasma	Diagnostic	qRT-PCR	GC detection	[134]
miR-378	61GC/61C Serum	Diagnostic	miRNA microarray qRT-PCR	Early detection of GC	[136]
miR-423-5p	164GC/127C Serum	Diagnostic	Solexa sequencing qRT-PCR	GC detection	[128]
miR-451	56GC/30C Plasma	Diagnostic	miRNA microarray qRT-PCR	Screening GC	[137]
	40GNCA/40C Plasma	Diagnostic	Taqman low-density array qRT-PCR	Early detection of GNCA	[122]
miR-486	56GC/30C Plasma	Diagnostic	miRNA microarray qRT-PCR	GC Screening	[137]
miR-486-5p	40GNCA/40C Plasma	Diagnostic	Taqman low-density array qRT-PCR	Early detection of GNCA	[122]
let-7a	79GC/30C Plasma	Diagnostic	qRT-PCR	GC detection	[46]

C: Control; GC: Gastric cancer; LN: Lymph node; GNCA: Gastric non-cardia adenocarcinoma; qRT-PCR: Quantitative real time polymerase chain reaction.

of aberrant expression of specific epigenetic regulators such as polycomb repressor complexes and histone deacetylases (HDACs). Wisnieski *et al*[151] demonstrated HDAC1 downregulation in gastric tumours compared with adjacent non-tumour samples. According to Scott *et al*[152], inhibition of HDACs results in transcriptional changes in approximately 40% of miRNAs expressed in a breast cancer cell line (SKBr3).

In 2009, Saito *et al*[153] analysed the miRNA expression profile in human GC cells treated with 5-aza-2′-deoxycytidine (5-Aza-CdR) and 4-phenylbutyric acid (PBA), and they suggested that chromatin remodelling at Alu repeats by DNA demethylation and HDAC inhibition can induce expression of silenced *miR-512-5p*. Moreover, activation of *miR-512-5p* can lead to suppression of *Mcl-1*, resulting in apoptosis of gastric cancer cells. Thus, epigenetic treatment, by using synthetic miRNAs, can serve as an "endogenous silencer" of target oncogenes in GC cells, blocking their activity as tumour enhancers.

SINGLE-NUCLEOTIDE miRNA POLYMORPHISMS IN GASTRIC CANCER

Single-nucleotide polymorphisms (SNPs) in miRNA have also been associated with alteration of GC susceptibility

Table 3 miRNA related to the risk of gastric cancer

miRNA	SNP	Country	Population	Number of cases/ controls	Ref.
miR-27a	rs895819	China	Asian	304/304	[43]
		China	Asian	295/413	[154]
		China	Asian	278/278	[155]
	rs11671784	China	Asian	892 /978	[156]
		China	Asian	278/278	[155]
miR-146a	rs2910164	China	Asian	304/304	[157]
		Japan	Asian	583/1637	[158]
		Japan	Asian	90/90	[101]
		China	Asian	1686/1895	[159]
		South Korea	Asian	461/447	[160]
		Japan	Asian	552/697	[161]
miR-196a	rs11614913	Japan	Asian	552/697	[161]
		China	Asian	213/213	[162]
		South Korea	Asian	461/447	[160]
		Greece	Greak	163/480	[163]
miR-499	rs3746444	Japan	Asian	697/552	[161]
		South Korea	Asian	461/447	[160]
		China	Asian	363/969	[164]
miR-149	rs2292832	China	Asian	274/269	[165]
		South Korea	Asian	461/447	[160]
		Greece	Greak	163/480	[163]
miR-24	rs4819388	China	Asian	183/348	[166]
miR-570	rs4143815	China	Asian	205/393	[167]
miR-200c	rs12904	China	Asian	522/501	[168]
miR-505	rs111638916	China	Asian	857/748	[169]
Pre-miR-30c	rs928508	China	Asian	240/240	[170]
Pri-let-7a-2	rs629367	China	Asian	107/124	[171]

and modification of target gene expression. However, the role of these genetic variants in GC susceptibility remains essentially unidentified[7]. Table 3[154-171] summarizes described SNPs in miRNA in GC.

One of the most described miRNA SNPs associated with elevated risk in GC is SNP rs2910164 of miR-146a. Ahn *et al*[160] demonstrated that the C/G polymorphism in miR-146a decreases miR-146a expression and subsequently leads to reduced regulation of the target genes *TRAF6*, *IRAK1* and *PTC1* by the C allele. Moreover, some studies reported that miR-146a rs2910164 also affects susceptibility to gastric lesions. Song *et al*[172] found that the G/C polymorphism in miR-146a rs2910164 may play a role in the evolution of *H. pylori*-associated gastric lesions. Thus, SNP rs2910164 may be used as a genetic biomarker to predict GC risk.

SNPs in pri-miRNAs and pre-miRNAs could affect the maturation process and function of the miRNA, which may affect the expression of many proteins in the interaction pathway. Recently, Xu *et al*[171] found that upregulation of pri-let-7a-2 expression by the rs629367 C/C genotype was associated with increased risk and low survival in GC, probably by affecting the expression of mature let-7a.

The binding capacity of a miRNA with its target can be modified by SNPs affecting the miRNA TAG sequence. Additionally, a SNP in an mRNA sequence could influence the complementarity between the miRNA and the target mRNA. This could result in alteration of susceptibility to tumorigenesis. Wang *et al*[167] described that a SNP in the *PDL1* (rs4143815) could affect its protein expression by interfering with miR-570 negative regulation. Furthermore, this SNP was significantly related to the risk of GC and depth of tumour infiltration, differentiation grade, lymph node metastasis, tumour size and staging.

Hence, SNP data could be useful to improve our understanding of the contribution of individual susceptibility to GC pathogenesis.

FUTURE PERSPECTIVES

Accumulating evidence indicates that the dysregulation of miRNAs plays important roles in GC pathogenesis. In this context, miRNA expression profiles have been shown to correlate with GC development, progression and response to therapy[173,174], suggesting their possible use as diagnostic, prognostic and predictive biomarkers.

Moreover, miRNA-based anticancer therapies have recently been explored, either alone or in combination with current targeted therapies[175,176]. However, a big challenge in using miRNAs in cancer therapeutics is the considerable number of genes that a single miRNA can target, leading to a pleiotropic effect that may limit their manipulation at the systemic level. Nevertheless, the increasing capability of producing synthetic interfering miRNAs with higher affinity to the desired target is minimizing this barrier.

Thus, the strategy of using miRNAs for targeted therapy in the near future is probably over-optimistic, considering that the studies of miRNA-based the-

rapeutics are still premature; however, the number of discoveries, increasing so fast in the past few years, is surely extremely promising.

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