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MINIREVIEWS

MiRNA as potential biomarkers and therapeutic targets for gastric cancer

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Abstract

Gastric cancer is one of the leading causes of cancer mortality in the world. Aberrant expression of microRNAs (miRNAs) is the hallmark of this disease. MiRNAs are endogenous non-coding RNAs that are involved in many biological processes (*e.g.*, cell proliferation, differentiation, apoptosis, invasion and development) through gene repression. Deregulation of miRNA expression in gastric tumors and cancer cell lines have been documented to contribute in tumorigenesis, and the expression signature may correlate with different cancer types and clinicopathological features. Here, we summarized the updated gastric cancer-associated miRNAs and the downstream targets in the process of tumorigenesis. Recently, many researchers make use of the miRNA microarray platform to profile miRNA expression in gastric cancer and correlated with different clinical parameters. Its application on cancer diagnosis, prognosis and predicting treatment response rate are still underway and needs further investigation. Emerging roles of miRNAs with oncogenic or tumor suppressive properties in gastric tumorigenesis were discussed. Epigenetic silencing of miRNA by hypermethylation of promoter CpG island was also observed in gastric cancer. However, detailed mechanisms of how miRNAs regulate gene expression in gastric cancer has not been well studied. In this review, we highlight the up-to-date findings on the deregulated miRNAs in gastric cancer, and the potential use of miRNA in the clinical settings, such as diagnostic/prognostic markers and chemotherapeutic tools.

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Key words: MicroRNA; Gastric cancer; Biomarker; Diagnosis; Prognosis; Clinical application

Core tip: This minireview summarized the most up-to-date important microRNAs (miRNAs) involved in tumor progression and development in gastric cancer. The potential use of miRNAs in the different areas of clinical settings is discussed.

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INTRODUCTION

Gastric cancer is the second leading cause of cancer mortality in the world, and has a particularly high incidence in Asian countries including China and Japan. Despite the declining incidence of gastric cancer, there are still over 1 million cases newly diagnosed and 850000 deaths globally each year[1]. The high mortality rate is mainly due to late presentation, since early stage of gastric cancer is either asymptomatic or presents with non-specific symptoms. The survival rate depends on the stage of gastric cancer at the time of diagnosis[2]. In Western countries, the 5-year survival ranged from 5%-20%, whereas in Japan, the survival rate was about 50% due to early diagnosis[3]. Today, surgery remains the mainstay of potentially curative treatment for gastric cancer. Nevertheless, over 50%

of the patients may still develop recurrence after curative resection. A good screening method for early detection is the best way to reduce gastric cancer mortality. Due to the associated side effects with endoscopy, including perforation, aspiration pneumonia or bleeding, thus making endoscopic screening not a common practice in the community. Hence there is an urge for the discovery of biomarkers for non-invasive early detection in gastric cancer patients.

MicroRNAs (miRNAs) are endogenous noncoding regulatory RNAs with 17-25 nucleotides, which play important roles in post-transcriptional gene regulation. The ability to bind complementary sequences in 3'-untranslated regions (3'-UTR) of various target mRNAs leading to direct mRNA degradation or translational repression. MiRNAs regulate gene expression and contribute to development, differentiation, inflammation, and carcinogenesis. At present, over 24500 entries have been listed in the miR Registry Database (release 20, http://www.mirbase.org/), implicating more than 30000 mature miRNA products, and the number of miRNAs is expected to increase exponentially in the future. Studies have shown that over 30% of human genes are regulated by miRNAs, in which a single miRNA controls over hundreds of RNA.

MiRNA plays pivotal role in biological processes including cell proliferation, metastasis, differentiation, development and apoptosis[4,5]. Accumulating evidence showed that the miRNA profiles were differentially expressed in cancerous tissues and normal counterparts[6,7]. The fact that miRNAs are very specific for different types of tissues and even for types of cells within those tissues, many studies profiled the miRNA patterns in various cancer types, which put forward the diagnostic and prognostic values of miRNAs in clinical applications. To date, there are many different platforms to study the expressions of miRNA, for example, northern blots, real-time PCR, primer extension and microarrays. Microarray has been the most widely used for miRNA research, not only it is a more user-friendly platform, its high throughput property makes possible to profile the whole genome of miRNA.

Deregulation of miRNA in human cancers was a result of impaired miRNA-biogenesis, genomic or epigenetic alterations, leading to the proto-oncogenic or tumor suppressive role of miRNA in tumorigenesis. For oncogenic miRNA, inhibitor of miRNA blocks the function of miRNA; while tumor suppressive miRNA, reconstitute miRNA precursor produce an anti-tumor effect. Hence targeting specific miRNA could be a possible alternative for treating gastric cancer patients.

BIOGENESIS OF MIRNAs

The biogenesis of miRNA involves the transcription of miRNA by RNA polymerase Ⅱ to form large double-stranded precursor (Pri-miRNA) in the nucleus. It appeared in a hairpin structure which was then cleaved by RNase Ⅲ endonuclease Drosha to produce a 60-70 nucleotides hairpin precursor (Pre-miRNA) and exported to the cytoplasm by a nuclear membrane export receptor Expotin-5. Pre-miRNA is then cleaved by another RNase Ⅲ enzyme Dicer to form a mature double-stranded miRNA (about 22 nucleotides) which comprises a mature miRNA guide strand and passenger strand. The guide strand (mature miRNA) is incorporated into RNA-induced silencing complex (RISC) to target mRNA *via* 2 mechanisms: (1) cleavage of mRNA at the miRNA binding site; and (2) repression of translation. Due to the fact that miRNAs are present in the genomic regions that involved in cancers, miRNAs become increasingly recognized as potential marker for diagnosis and prognosis.

GASTRIC CANCER RELATED MIRNAS IN CELL PROLIFERATION AND APOPTOSIS

Microarray is a useful and convenient platform to profile the miRNA expression in human cancers. By comparing the expression in gastric cancerous tissue with non-tumor tissue, the distinct miRNA signatures are associated with progression and perhaps prognosis of gastric cancer[8]. The miRNA signatures have a higher accuracy and reproducibility than mRNA expression profiles, over 80% of the paired gastric samples were classified correctly by the miRNA signatures. Prediction and validation of downstream targets become increasingly important in miRNA research, here; we listed the targets of upregulated and downregulated miRNAs in gastric cancer (Table 1).

Over 92% of the gastric cancer patients demonstrated an upregulation of miR-21 in solid human tumors, including gastric cancer[9]. Currently, it has been reported that miR-21 was upregulated not only in cancerous tissues but also in *Helicobacter pylori* (*H. pylori*)-infected gastric mucosa[10]. Gastric cancer is a result of multistep and long-term interactions between genetic and environmental factors which process from chronic gastritis, atrophic gastritis, intestinal metaplasia, glandular atrophy and dysplasia[11]. The miRNA that was associated with *H. pylori*-induced inflammation was miR-218, overexpression of this miR abrogated nuclear factor-kappa B (NF-κB) activation[12]. It was hypothesized that miR-21 might augment the progression of infected normal mucosa to chronic gastritis with unknown mechanisms. The signal transducer and activator of transcription 3 (STAT3) activated the induction of miR-21[13]. Activation of NF-κB and interleukin (IL)-6 stimulated STAT3 signaling, which may explain the *H. pylori*-mediated upregulation of miR-21. Interestingly, there is a transcription binding site of NF-κB located in miR-21 transcriptional elements, suggesting that miR-21 upregulation is a result of NF-κB activation in gastric cancer[14].

Numerous evidence revealed that miR-21 attributed to gastric cancer through enhanced cell proliferation and inhibited apoptosis. On top of that, miR-21 also has the ability to incite cell invasion and migration. It has been reported that RECK, a tumor suppressor gene, is the target of miR-21. It involves in the process of metastasis

Table 1 Gastric cancer-associated microRNAs

	Functions	Targets	Ref.
Upregulated miRNAs			
miR-15b, miR-16	Cell survival	BCL2	[47]
miR-21	Cell proliferation, invasion	PTEN	[49]
		PDCD4	[50]
miR-23a	Cell proliferation	IRF1, IL6R	[51]
miR-27a	Cell proliferation	PROHIBITIN	[52]
miR-43c	Epigenetic regulation	VEZT	[53]
miR-106a	Cell cycle regulation	RB1	[34]
miR-106b-25 cluster	Cell cycle arrest, apoptosis	E2F1	[54]
		p57, p21, p27	[55]
miR-107	Invasion, metastasis	DICER1	[56]
miR-130b	Apoptosis, epigenetic regulation	BIM, RUNX3	[57]
miR-150	Cell proliferation	EGR2	[58]
miR-223	Invasion, metastasis	EPB41L3	[59]
Downregulated miRNAs			
let-7a	Cell proliferation	RAB40C	[60]
miR-9	Cell proliferation	NFkB	[61]
	Cell proliferation, cell cycle regulation	CDX2	[62]
miR-34b	Cell proliferation, transcription, epigenetic regulation	NOTCH1, c-Myc BCL2, SIRT1	[63]
miR-124a	Cell cycle arrest	CDK6	[64]
miR-126	Cell cycle arrest	CRK	[65]
miR-129-2	Cell proliferation, differentiation, epigenetic regulation	SOX4	[66]
miR-143	Cell proliferation	AKT	[17]
miR-145	Cell proliferation	IRS-1	[17]
miR-146a	Invasion, migration	EGFR, IRAK1	[67]
miR-148b	Cell proliferation	CCKBR	[68]
miR-181c	Transcriptional activation	NOTCH4, K-ras	[30]
miR-200 family	Cell proliferation, invasion, migration	ZEB2, E-cadherin	[69]
miR-212	Cell proliferation	MeCP2	[29]
miR-218	Invasion, metastasis	ROBO1 receptor	[70]
	Transcriptional activation	NFκB	[12]
miR-375	Cell survival	PDK1, 14-3-3zeta	[71]
	Cell proliferation	JAK2	[72]
miR-451	Cell proliferation	MIF	[73]

and angiogenesis through regulating metalloproteases (MMPs)[10]. MiR-125b, miR-199a and miR-100 have been shown to be the most important progression-related miRNAs in gastric cancer and pancreatic adenocarcinoma[12,15], implicating that miRNA may have different functions depends upon the tumor site. There are some miRNAs (miR-32, miR-182 and miR-143) that are found to be associated with intestinal-type gastric cancer, this study implicated the usefulness of miRNA expression profiles may serve as diagnostic biomarkers for different subtypes of gastric cancers[16]. Expressions of miR-143, miR-145, miR-9, miR-443, miR-31, and miR-34 have been reported to downregulate in gastric cancer[17-19]. The roles of miR-143 and miR-145 on cell proliferation have also been demonstrated in other gastrointestinal cancers[20]. Ectopic expression of miR-143 and miR-145 showed significant growth retardation and sensitized to 5-fluorouracil treatment in gastric cancer cells[17].

GASTRIC CANCER RELATED MIRNAS IN CELL INVASION AND METASTASIS

There is a strong correlation of elevated expression of high mobility group AT-hook 2 (HMGA2), a nonhistone chromosomal protein that modulate translation, with tumor invasiveness in gastric cancer. HMGA2 was inversely regulated by the let-7 miRNA family. High expression of HMGA2 correlated with tumor invasion and was an independent prognostic factor in gastric cancer[21]. In addition, miR-214 was reported to modulate hedgehog signaling, where activation of hedgehog contributes to gastric cancer[8]. High expression of miR-214 was identified to correlate with unfavorable outcome in gastric cancer. In ovarian cancer, miR-214 regulated the downstream target PTEN to induce cell survival[22]. Furthermore, miR-196b expression has been shown to be significantly higher in gastric cancer tissues than normal counterparts[23]. Silence of ETS2 (a transcriptional modulator) enhanced miR-196b expression which promoted gastric cancer cell migration and invasion by increased vimentin, MMP-2 and MMP-9 expressions and suppressed E-cadherin expression.

Epigenetic alteration of miRNAs

Gastric carcinogenesis is a multistep process with genetic alterations including mutation, activation of oncogenes and suppression of tumor suppressor genes, and overexpression of growth factors. Genetic instability, DNA methylation and mutations are known to participate in the early development of gastric cancer. Epigenetic changes become important areas in gastric cancer research. DNA methylation altered gene expression by methylation of gene promoters at CpG islands which lead to silencing of tumor suppressor genes in cancer cells. Accumulating evidence revealed that abnormal methylation pattern was observed in human diseases, as well as cancer. MiR-9-1, miR-34b/c, miR-148, miR-137, miR-193a, miR-203 and miR-342 were hypermethylated in various human cancers[24,25].

Aberrant expression of miRNAs has been observed in relation to gastric tumor progression, which may partially be explained by epigenetic modulation. Expressions of miR-34b, miR-127-3p, miR-129-3p and miR-409 have been found to correlate with the methylation status in human gastric cancer tissues, as well as in gastric cancer cell lines[26]. Methylation status of the CpG islands in miR-34b and miR-129 promoters was higher in gastric cancer tissues than normal counterparts. In addition, treatment with 5-aza-2'-deoxycytidine (demethylating agent) and trichostatin A (histone deacetylase inhibitor) significantly restored the expression of these miRNAs in a time-dependent fashion, suggesting low expression of these two miRNAs was due to hypermethylation of CpG islands. In consistent with the findings in gastric cancer, hypermethylation of miR-34b has been implicated in other cancers like ovarian, non-small cell lung and colorectal

cancers[24,27,28]. A recent study revealed that methyl-CpG-binding protein (MeCP2) level was highly expressed in gastric cancer cell lines and primary gastric cancer[29]. Ectopic expression of miR-212 abrogated MeCP2 protein through binding at the MECP2 3'-UTR region leading to cell growth retardation. Notably, there were allelic loss at 3p, 4p, 5q, 8p, 9p, 13q, 17p and 18q in gastric carcinoma, and miR-212 is located at chromosome 17p13.3, which could partly explain the downregulation of miR-212.

In another report, miRNA microarray data showed that miR-181c was upregulated in 5'aza-2'-deoxycitidine-treated cells when compare with untreated gastric cancer cells, and yet the expression was downregulated in primary gastric carcinoma[30]. With the use of cDNA microarray analysis, it revealed that Notch4 and K-ras were the downstream targets of miR-181c. Recent data showed that low expression of miR-181c also involved in the pathogenesis of glioblastoma[31]. Reduced miR-181c expression was observed in a panel of high-grade glioblastoma tumors and cell lines. A highly positively correlated transcript p300/CBP-associated factor modulated by miR-181c inhibited cell growth and increase apoptosis. However, in squamous cell carcinoma, miR-181c expression was found to be upregulated when compare with the normal tissues[32].

Epigenetic modifications plays a crucial role in the control of miRNA expression and linked to cancer phenotype or potentially serve as early detection, disease progression marker for gastric cancer, hence, further mechanistic studies on miR methylation would be an important area to the development of therapeutic strategy in treating against this disease.

CLINICAL APPLICATIONS

Potential miRNA as biomarker

It was found that the expression levels of miRNA correlated with clinical outcome. MiR-421 was overexpressed in 73% (44/60) of gastric cancer tissues when compared with the adjacent normal counterparts, and there is no correlation with poor prognosis of patients, suggesting that miR-421 upregulation could be an early diagnostic marker for gastric cancer[33]. In another study, miR-31 was found to be downregulated in gastric cancer tissues by real-time RT-PCR[19] however, the molecular mechanism is yet to be elucidated. MiR-106a expression was correlated with some clinic-pathological features including tumor stage, size and differentiation, metastasis and invasion[34]. Higher level of miR-106a was observed in gastric carcinoma when compared with non-tumor tissues. Recently, a five-miRNA signature (miR-1, miR-20, miR-27a, miR-34 and miR-423-5p) was identified as a diagnostic marker for gastric cancer with the receiver operating characteristic (ROC) curve over 0.85% in serum samples, which demonstrated a higher sensitivity than conventional marker (CEA or CA19-9)[35].

It was hypothesized that miRNA-derived from tumors would be shredded into the circulation. Indeed, several studies have shown that miRNAs have differential expression in the plasma of gastric cancer patients when compare with the normal controls[36,37]. Most of the studies demonstrated an improved sensitivity and specificity than conventional tumor markers (CEA, CA12-5, CA19-9 and CA72-4)[35,37,38]. These mark a new era for the potential use of circulating miRNA in diagnosis of gastric cancer. Taken together, the deregulated miRNAs could serve as a diagnostic biomarker for gastric cancer, and hopefully detection of miRNA deregulation in plasma might help in early diagnosis of gastric cancer, so that designing individualized treatment to antagonize the action of miR could be done in the early stage to improve survival.

MIRNA AS PROGNOSTIC MARKER

Recently, many researchers are looking into the potential use of miRNAs as prognostic tools other than diagnostic application, however, this specific marker needs to correlate closely with clinical outcomes and metastatic potential. Profiling of miRNAs seems to be advantageous over mRNAs in terms of cancer phenotypes differentiation. A current report suggested a prognostic signature for gastric cancer which consist of four risk miRNAs (miR-10b, miR-21, miR-223 and miR-338; with hazard ratio > 1) and three protective miRNAs (miR-30a-5p, miR-126 and let-7a; hazard ratio < 1), and was associated with clinical outcomes[39]. Another study showed that low expressions of miR-21 and miR-181b are associated with overall survival in patients treated with S-1 and doxifluridine[40]. Low expression of miR-125a-3p is correlated with tumor size, invasion, metastasis and advanced clinical stage, and an independent prognostic marker for gastric cancer[41]. Ectopic expression of miR-125a-3p showed remarkable retardation of gastric cancer growth *in vitro*, illustrating the tumor suppressive property and potential clinical use of miR-125a-3p. On the other hand, the other strand of miR-125a, miR-125-5p also showed similar tumor suppressive effect in gastric cancer, and low expression was associated with poor prognosis[42]. Other study showed that HMGA2 expression was directly correlated with tumor invasiveness and prognosis, which is modulated by let-7 family[21]. A similar observation was also seen in pituitary adenomas, in which low expression of let-7 induced HGMA2 and related to tumor proliferation and invasion[43].

MIRNA AND CHEMOTHERAPY

Though surgery is a promising treatment for gastric cancer, however, over 50% of patients will have recurrence or systemic metastasis. Chemotherapy has been widely used in the management of patients with advanced disease to prolong survival. However, multidrug resistance (MDR) often hinders successful chemotherapeutic treatment. And there are the two mechanisms exist in tumor cells towards cytostatic drugs: intrinsic or acquired drug

resistance.

MiR-138 was found to be highly expressed in MDR variant when compared with its parental leukemia cells[44]. Increased accumulation of adriamycin inside the cells resulted in apoptosis through the repression of P-glycoprotein (P-gp) and Bcl2 expressions. Multidrug resistance-associated protein (MRP-1) is another transporter, other than P-gp, that expels cytostatic drugs out of the cell. Transfection with miR-326 reduced expression of MRP-1 and sensitized the cells to VP-16 and doxorubicin in resistance cells[45]. Similar approach by using miR-27a and miR-451 antagomirs decreased P-gp and multidrug resistance-1 (MDR1) mRNA expression which increased the intracellular concentration of cytotoxic drugs in the cells[46]. When the miRNA expression profiles in MDR variant were compared with its parental gastric cell line, a small subset of miRs has been excavated. Downregulation of miR-15b and miR-16 in MDR cells restrained the cells from apoptosis by modulation of Bcl2[47]. Ectopic expression of miR-15b and miR-16 sensitized MDR cells to chemotherapeutic agent, which lead to cell apoptosis[48]. These findings are of great impact on the functions of miRNAs, and notably improve/sensitize the efficacy of chemotherapeutic agent in gastric cancer.

CONCLUSION

The important roles of miRNAs in cancer biology have been extensively studied in recent years. Ideally, miRNA could be a better therapeutic tool over single gene therapy, due to its ability to target multiple genes. However, several problems were encountered when translated into clinical applications. Firstly, as agreed by most of the researchers, identification of the downstream targets of miRNA is intricating. Despite several target prediction algorithms (*e.g.*, TargetScan, miRTar and miRecords *etc.*) currently available to envisage miRNA targets, however, the complication is that various miRNA could target the same mRNA, hence, justification from results algorithms are inevitable. Microarray and real-time RT-PCR are the analyzing techniques that are commonly used for screening and validation. With the use of locked nucleic acid oligos for *in situ* hybridization, knockdown or PCR studies, these enhance the sensitivity and specificity for the analysis of miRNAs. Detailed studies on the mechanism of miRNA biogenesis and interaction with RISC in gastric carcinogenesis would favor the manipulation of miRNA expression which might help in designing a more specific chemotherapeutic agent.

There are increasing demand on miRNA profiling with the expansion of its application into differentiating subtypes and predict treatment response in gastric cancers. The stability of miRNAs in the circulation makes it suitable as diagnostic and prognostic markers in various cancers. Also, it is likely to acquire a miRNA signature, instead of a single miRNA, to provide useful information for the clinicians to make decision on personalized management of the disease. With a better understanding of these miRNAs and their target genes, it would open up new perspectives for more sophisticated and effective therapeutic agents for treating gastric cancer.

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