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Role of microRNAs in gastric cancer

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Abstract

Although gastric cancer (GC) is one of the leading causes of cancer-related death, major therapeutic advances have not been made, and patients with GC still face poor outcomes. The prognosis of GC also remains poor because the molecular mechanisms of GC progression are incompletely understood. MicroRNAs (miRNAs) are noncoding RNAs that are associated with gastric carcinogenesis. Studies investigating the regulation of gene expression by miRNAs have made considerable progress in recent years, and abnormalities in miRNA expression have been shown to be associated with the occurrence and progression of GC. miRNAs contribute to gastric carcinogenesis by altering the expression of oncogenes and tumor suppressors, affecting cell proliferation, apoptosis, motility, and invasion. Moreover, a number of miRNAs have been shown to be associated with tumor type, tumor stage, and patient survival and therefore may be developed as novel diagnostic or prognostic markers. In this review, we discuss the involvement of miRNAs in GC and the mechanisms through which they regulate gene expression and biological functions. Then, we review recent research on the involvement of miR-

NAs in GC prognosis, their potential use in chemotherapy, and their effects on *Helicobacter pylori* infections in GC. A greater understanding of the roles of miRNAs in gastric carcinogenesis could provide insights into the mechanisms of tumor development and could help to identify novel therapeutic targets.

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Key words: MicroRNA; Gastric cancer; Reverse transcription-polymerase chain reaction; Chemosensitivity; *Helicobacter pylori*; Circulating MicroRNA

Core tip: In this review, we discuss the involvement of miRNAs in gastric cancer (GC) and the mechanisms through which they regulate gene expression and biological functions. Then, we review recent research on the involvement of miRNAs in GC prognosis, their potential use in chemotherapy, and their effects on *Helicobacter pylori* infections in GC. A greater understanding of the roles of miRNAs in gastric carcinogenesis could provide insights into the mechanisms of tumor development and could help to identify novel therapeutic targets.

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INTRODUCTION

Despite the decreasing incidence of gastric cancer (GC) in developed countries, GC remains the second leading cause of cancer-related deaths worldwide^[1,2], with 700000 deaths attributed to this malignancy annually^[3]. Therefore, the development of novel therapies to improve the

Table 1 Aberrant expression of miRNAs in gastric cancer

Up-regulated miRNAs
let-7a, miR-9, -10a, -10b, -17, -17-5p, -18a, -18b, -19a, -19b, -20a, -20b, -21, -23a, -23b
miR-25, -26b, -27, -29b-1, -30b, -31, -34a, -34b, -34c, -92, -98, -99a, -100, -103, -106a
miR-106b, -107, -125b, -126, -128a, -130b, -138, -142-3p, -146a, -147, -150, -151-5p
miR-155, 181a, -181a-2, -181b, -181c, -185, -191, -192, -194, -196a, -196b, -199a
miR-199a-3p, -200b, -210, -214, -215, -221, -222, -223, -296-5p
miR-301a, -302f, -337-3p, -340, -370, -421, -520c-3p, -575, -601, -616, -658, -1259
Down-regulated miRNAs
let-7a, -7f, miR-7, -9, -22, -29c, -30a-5p, -31, -34a, -34b, -34c
miR-101, -126, -128b, -129, -129-2, -129-3p, -130b, -133b, -135a, -137, -141, -145
miR-146a, -148, -148b, -149, -152, -155, -181b, -181c, -182, -193b, -195, -195-5p, -197
miR-200, -204, -206, -210, -212, -218, -219-2-3p, -302b, -331-3p, -375
miR-378, -408-3p, -429, -433, -486, -495, -551a, -574-3p, -610, -622, -638, -663, -874

prognosis of patients with GC is critical.

MicroRNAs (miRNAs) are a subset of small non-coding RNA molecules, typically 21-23 nucleotides in length, that are believed to regulate the expression of several genes^[4]. Mature miRNAs are cleaved from 70- to 100-nucleotide hairpin pre-miRNA precursors^[4]. The precursor is cleaved by cytoplasmic RNase III Dicer into a miRNA duplex^[5-7]. One strand of the short-lived duplex is degraded, whereas the other strand serves as the mature miRNA^[8]. Mature miRNAs associate with a cellular complex that is similar to the RNA-induced silencing complex that participates in RNA interference^[9,10]. Recent studies have reported miRNA-mediated regulation of cell growth and apoptosis^[11,12]. Moreover, the measurement of miRNA expression has shown that certain miRNAs are specifically involved in cancer^[12-15]. In the context of GC, the number of publications investigating the relationship between miRNAs and GC has been increasing each year. miRNAs have the unique ability to negatively regulate gene expression, thereby resulting in changes in cell development, proliferation, and apoptosis^[16]. These biological properties of miRNAs may provide the ability to regulate a variety of human diseases, including cancer^[17]. According to recent findings, miRNAs may play important roles in human cancer by acting as potential oncogenes or tumor-suppressor genes^[18-20].

In this review, we introduce and discuss the newest knowledge on the relationship between GC and miRNAs.

Aberrant expression of miRNAs in GC

Although more than 1000 miRNAs are thought to exist, no comprehensive analysis of miRNA expression in GC has been performed to date. Each miRNA modulates the expression of hundreds of genes, and we speculate that miRNAs act in a network-type fashion to mediate the expression of genes.

While several reports have published comprehensive

expression analysis of miRNAs^[21,22], more data, including expression profile analysis by high-throughput real-time reverse transcription-polymerase chain reaction (RT-PCR) or miRNA microarrays, are required. A summary of reported miRNA expression abnormalities in GC is presented in Table 1.

Upregulated miRNAs (oncomirs): Aberrant expression of miRNAs has been observed in many cancers^[19,23]. Oncomirs are oncogenic miRNAs that are up-regulated in cancer cells and have been shown to act as oncogenes in GC. One such oncomir is *miR-21*, which has been widely reported as an oncomir in GC^[24-26].

Overexpression of *miR-21* has been reported in various cancers, such as esophageal cancer^[27], breast cancer^[28], and glioblastoma^[29]. In GC, the expression of *miR-21* is upregulated compared with normal tissues^[22,30,31]. Motoyama *et al*^[31] and Cao *et al*^[32] reported an inverse correlation between *miR-21* and *PDCD4* expression in GC. *PDCD4*, a direct target gene of *miR-21*, encodes a protein that inhibits cell growth and invasion^[33,34]. Moreover, Zhang *et al*^[26] reported that *PTEN*, a well-known tumor-suppressor gene, is a target of *miR-21*. Thus, these data support the idea that *miR-21* acts as a key oncomir in GC by inhibiting the tumor-suppressor genes *PDCD4* and *PTEN*.

In addition to *miR-21*, *miR-106a* expression is also up-regulated in GC (Table 1), as well as in several other human tumors, compared with adjacent normal tissues^[35]. *miR-106a* mimics the function of positive regulators of the G₁-to-S transition^[35]. In several human hematopoietic cell lines, *miR-106a* has been shown to target interleukin (IL) 10^[36], downregulating the expression of this critical cytokine by binding to the 3' untranslated region^[36]. As a further regulatory element, SP1 and EGR1 indirectly downregulate IL10 expression by inducing *miR-106a* expression^[36].

Downregulated miRNAs (tumor-suppressor miRNAs): Down-regulated miRNAs in cancer tissue are referred to as tumor-suppressor miRNAs^[37-39]. The important target gene of a tumor-suppressor miRNA is usually an oncogene. Therefore, decreased expression of the tumor-suppressive miRNA induces the expression of the oncogene. The genomic loss of *miR-101* in cancer leads to overexpression of *EZH2* and concomitant dysregulation of epigenetic pathways, resulting in cancer progression^[40,41]. Because *miR-101* targets cyclooxygenase (COX) 2 in GC, downregulation of *miR-101* induces COX2 expression^[42]. COX2 activates the arachidonic acid/prostaglandin E2 pathway following cell proliferation^[42]. Oncogenic targets of *miR-101* induce cell proliferation in GC. Therefore, *miR-101* may be useful for gene therapy in GC.

Another miRNA that has been suggested to have a role in cancer is *let-7*. Expression of *let-7* reduces the expression of 3 human *RAS* genes, *HRAS*, *KRAS*, and *NRAS*. Moreover, *let-7* expression is lower in lung tumors than in normal lung tissue, whereas expression of

Table 2 miRNAs associated with prognosis in gastric cancer patients

let-7a, -7i
miR-10b, -20a, -20b, -21, -22, -25, -27a, -30a-5p, -34a, -93
miR-103, -106a, -106b, -107, -125a-5p, -126, -130, -142-5p, -144, -146a, -150
miR-155, -181c, -195, -196a, -199a-3p, -200c, -206, -221, -222, -223
miR-335, -338, -372, -375, -451

the RAS proteins is significantly higher in lung tumors, suggesting a possible role of *let-7* in cancer^[43]. The expression of *let-7* miRNA is also reduced in human lung cancer^[44], breast cancer^[45], and hepatocellular carcinomas^[46]. In addition, overexpression of *let-7* inhibits the growth of lung cancer cells *in vitro*^[44]. In GC, RAB40C, a target of *let-7a*, has been reported to play an essential role in gastric tumorigenesis^[47].

MiR-148a has been shown to act as a tumor suppressor in prostate cancer, and its expression is lower in prostate cancer cells compared with normal prostate epithelial cells^[48]. In GC, *miR-148a* is inactivated by hypermethylation of the promoter region^[49]. This may result in the upregulation of DNA methyltransferase, which is a target of *miR-148a*^[49]. Moreover, *miR-148a* suppresses tumor cell invasion by downregulating ROCK1^[50]. In a report from our laboratory, we found that *miR-148a* expression is downregulated in undifferentiated GC^[51].

Roles of miRNAs as prognostic factors

Because many factors affect the prognosis of cancer patients, it is difficult to clarify how miRNAs are involved in the prognosis of patients with GC. However, advances in research on the potential role of miRNAs in patient prognosis may lead to the use of miRNAs as tools in medical treatment or diagnosis in the future. The detection of miRNAs involved in the prognosis of GC patients will not only be useful for predicting prognosis but helpful for developing therapeutic targets in the future. In Table 2, we have summarized the current knowledge on the relationship between miRNAs and prognosis. In particular, *miR-21*, *-93*, and *-125* have been well studied in this context. While we mentioned the usefulness of *miR-21* previously, overexpression of *miR-93* in GC cells has been shown to reduce the cellular response to transforming growth factor (TGF)- β (*TGFB1*) by interfering with the synthesis of p21 (*CDKN1A*) and BIM (*BCL2L11*), the 2 most important downstream effectors of TGF- β -dependent cell cycle arrest and apoptosis, respectively^[52]. High expression of *miR-98* was found to predict poor survival^[53,54]. Interestingly, low expression of *miR-125* in GC has been shown to be an independent prognostic factor for survival^[55,56]. One target gene of *miR-125a-5p* is ERBB2 (*HER2*), which is an important molecular target in chemotherapy^[56].

Notably, many genes act as prognostic factors for patients with GC; miRNAs may regulate these genes, thereby affecting prognosis. Thus, further analysis of candidate miRNAs is necessary.

Table 3 MiRNAs involved in chemosensitivity

5FU sensitivity
let-7g
miR-10b, -22, -30c, -31, -32,
miR-133b, -143, -144, -145, -181b, -190, -197, -200c, -204, -210
miR-335, -501, -501-5p, -532, -615, -615-5p, -766, -877
miR-1224-3p, -1229, -3131, -3149, -3162-3p, -4763-3p
CPT sensitivity
let-7g
miR-7, -31, -98, -126, -196a, -200, -338
CDDP, CF sensitivity
let-7g
miR-1, -16, -21, -34, -181, -181b, -342, -497

MiRNAs involved in chemosensitivity

Chemotherapy is an important tool for the treatment of GC. However, with currently available tools, it is impossible to predict whether GC patients will respond to chemotherapeutic approaches. The ability to predict the effects of chemotherapy may help reduce the unnecessary use of chemotherapeutics in GC. Current chemotherapeutic agents used in the treatment of GC include 5FU, CDDP, taxan, and irinotecan. Many studies have reported that miRNAs may affect the efficacy of chemotherapy. Wang *et al*^[57] identified 9 upregulated miRNAs and 18 downregulated miRNAs involved in 5FU sensitivity by microarray and RT-PCR (Table 3). Moreover, *miR-143*, *miR-145*, and *miR-144* have been reported to be involved in 5FU sensitivity^[58,59]. In Table 3, we summarize the involvement of miRNAs in CPT, CDDP, and CF sensitivity. In the near future, we will be able to use miRNA expression as a predictor of chemotherapeutic efficacy. Additionally, gene therapy with miRNAs may be able to induce chemosensitivity in patients with GC.

MiRNAs involved in *Helicobacter pylori* infection

Helicobacter pylori (*H. pylori*) selectively colonize the gastric epithelium and typically persist for the lifetime of the host. Among colonized individuals, however, only a fraction develop gastric adenocarcinoma, emphasizing the importance of understanding the pathogenic mechanisms through which *H. pylori* promote chronic inflammation and the progression to GC^[60]. miRNAs involved in *H. pylori* infections have been reported in several papers. *Let-7* expression has been shown to be downregulated by Cag A after *H. pylori* infection, and Ras, a target of *let-7*, is overexpressed in GC^[61]. Additionally, *miR-17/92*, the *miR-106b-93-25* cluster, *miR-21*, *miR-194*, *miR-196*, *miR155*, *miR-222*, and *miR-223* are upregulated in gastric mucosa infected by *H. pylori*^[62,64]. Among these miRNAs, Li *et al*^[64] revealed that *miR-222* targets RECK, which inhibits the tumorigenicity of GC^[64-66]. Further analysis of miRNAs and target genes may clarify the complicated mechanism of GC that occurs in the context of *H. pylori* infections.

Circulating miRNAs as biomarkers

Presently, circulating miRNAs found in the blood of pa-

Table 4 Circulating miRNAs as biomarkers

Up-regulated miRNAs
miR-1, -17, -17-5p, -20a, -21, -27a, -31, -34, -103, -106a, -106b, -107, -194, -200c
miR-210, -221, -223, -370, -376a, -378, 421, 423-5p, 451, -486, 744
Down-regulated miRNAs
miR-218, -375

tients constitute the most promising type of miRNA for clinical use, because these are concise for blood collecting. We summarized the circulating miRNAs in the blood of GC patients in Table 4.

There are a number of reports describing the use of miR-106^[67,69], miR-17^[67,70], miR-21^[67,71], and miR-221 as potential biomarkers^[72]. The detection of miRNA in peripheral blood may be a novel tool for monitoring circulating tumor cells in patients with gastric cancers. Moreover, circulating miRNA may be a promising, non-invasive molecular marker for tracking pathological progression, predicting prognosis and monitoring chemotherapeutic effects in gastric cancer.

Finally, the precise mechanism of each miRNA is not well known. Further reports about miRNA are expected to help us better understand cancer mechanisms. This research will be useful for clinical diagnosis or treatment for GC patients.

CONCLUSION

In this review, we presented and discussed the newest knowledge on miRNAs in gastric cancer and their potential usefulness as future medical treatments and diagnostic tools. Although the molecular biology of GC has been well characterized, research on miRNAs in GC is still in its infancy. Thus, in the near future, we anticipate that advances in miRNA research in GC may help to develop novel medical treatments or diagnostic tools, thereby improving the prognosis of GC patients.

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