

microRNAs in gastric cancer invasion and metastasis

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1. ABSTRACT

microRNAs (miRNAs) are fundamental gene regulators that can control cell proliferation, differentiation, and apoptosis during tumor development. These molecules can function as oncogenes or tumor suppressors in human cancers. In gastric cancer (GC), miRNAs play a dual role of either promoting or inhibiting cancer invasion and metastasis. In addition, some miRNAs are involved in only the invasion or metastasis, while other miRNAs have multiple functions and participate in invasion, migration and metastasis. In this review, we will discuss the role of miRNAs in the invasion and metastasis of GC.

2. INTRODUCTION

microRNAs (miRNAs) are a class of endogenous, small, noncoding regulatory RNAs that regulate target gene expression through specific base-pairing interactions between miRNAs and the untranslated regions of targeted mRNAs. They target a large number of mRNAs and induce mRNA degradation or the inhibition of translation by interacting with the 3' untranslated regions of their targets (1). They are fundamental gene regulators that control proliferation, differentiation, and apoptosis during development (2-4). miRNA expression is temporally and spatially regulated, and the disruption of the physiological

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expression patterns of miRNAs is associated with a number of examples of human tumorigenesis. This observation suggests that miRNAs could function as oncogenes or tumor suppressor genes in human cancers and could potentially be used as novel diagnostic and prognostic biomarkers or therapeutic targets (5).

Gastric cancer (GC) is the second most common cause of cancer death, with a 5-year survival rate of approximately 20% (6). Cancer invasion and metastasis are the primary factors that affect patient survival rate (7). Metastasis is a complex, multi-step process in which cancer cells migrate from the primary neoplasm to a distant location (8). The process begins when primary tumor cells invade adjacent tissues and migrate into the surrounding tissue parenchyma by translocating through the vasculature, initiating micrometastases and finally proliferating to form macroscopic secondary tumors (9). However, the biochemical mechanisms that regulate invasion and metastasis remain poorly understood. Several miRNAs have been found to be downregulated in GC, such as miR-143, -145 (10), -141 (11), -31 (12) and -106a (13), whereas some oncogenic miRNAs, such as miR-21 and miR-27a (14), are upregulated. Thus, miRNAs participate in the development and metastasis of GC. In this review, we will discuss the role of miRNAs in the invasion and metastasis of GC.

3. MICRORNAS IN THE INVASION OF GC

When GC develops to an advanced stage, tumor cells invade the blood vessels and lymphatic vessels near the tumor. This lymphatic and/or blood vessel tumor invasion is the most critical step of tumor cell dissemination and metastasis in various types of cancer (15-17). miRNAs can either promote or inhibit the invasion of GC.

3.1. Promoting cancer invasion

microRNA (miR)-10b could promote the invasion of GC cells. As an miRNA induced by Twist, miR-10b drives metastasis in different types of cancers in which the downstream target gene HOXD10 is the main mediator. Liu and colleagues (18) reported that in gastric tumor species, miR-10b levels were dramatically elevated in lymphoma node metastasis-positive tumor tissues compared with lymphoma node metastasis-free tumor tissues; miR-10b levels were also correlated with HOXD10 expression. Meanwhile, in gastric cell lines with distinct degrees of differentiation, miR-10b was highly expressed in cell lines with strong metastatic properties. They found that through targeting HOXD10, miR-10b stimulates the upregulation of RhoC and AKT phosphorylation, ultimately promoting cell invasion in gastric tumors (18).

3.2. Inhibiting cancer invasion

In addition to promoting cancer invasion, miRNAs have been found to be involved in the inhibition of GC. miR-194 is specifically expressed in the human gastrointestinal tract and is induced during intestinal epithelial cell differentiation (19). Its role in GC was first described by Song and colleagues (20). They found that GC

patients with lower miR-194 expression tended to have larger tumors and more advanced pT stage. The expression of miR-194 was significantly lower in Borrmann IV-type GC than in Borrmann I, II, or III-type GC. Moreover, an *in vitro* invasion assay indicated that the penetrated cell intensity was significantly lower after miR-194 mimic transfection than in the control (20). Thus, miR-194 may play a role in suppressing tumor invasion. These authors also found that the downregulation of miR-194 expression may not be an early event in gastric tumorigenesis, but may rather be a later genetic alteration that contributes to the invasive capability of malignant cells (20). Therefore, miR-194 might be a potential marker of invasion in GC. However, the precise mechanisms underlying the aberrant expression of miR-194 in GC remain to be determined.

Cyclin-dependent kinase 6 (CDK6) is a member of a family of serine-threonine kinases involved in the control of cell cycle progression (21). Recently, CDK6 was found to be upregulated in several types of human tumors, and it has been implicated in cancer initiation and progression (22,23). miR-107 has been identified as a potential regulator of CDK6 expression (24). The ectopic expression of miR-107 reduced both mRNA and protein expression levels of CDK6 and mimicked the effects of CDK6 knockdown in inhibiting proliferation, inducing G1 cell cycle arrest, and blocking the invasion of the GC cells (24). Thus, miR-107 may exert a tumor suppressor function by directly targeting CDK6 to inhibit the proliferation and invasion activities of GC cells (Figure 1).

4. MICRORNAS IN THE METASTASIS OF GC

The metastasis of GC usually leads to a poor prognosis. The five-year survival rate for metastatic GC is nearly 20%, with a median overall survival time of less than 1 year (25,26). Thus, understanding the mechanism of GC metastasis is crucial for reducing mortality. The role of miRNAs in the metastasis of GC has thus attracted much attention. For example, miR-21 has been identified as a promising novel biomarker for lymph node metastasis in patients with GC (27). The expression level of miR-21 was found to be higher in GC patients with lymph node metastasis than in those without lymph node metastasis and was significantly correlated with histologic type, tumor stage, lymph node metastasis and TNM stage. The overall survival rates in GC patients with weakly upregulated miR-21 expression were significantly higher than those with highly upregulated miR-21 (27). These examples demonstrate that miRNAs can play a dual role in the metastasis of GC, both promoting and inhibiting cancer metastasis.

4.1. Promoting cancer metastasis

miR-27 is involved in the metastasis of GC. Zhang and colleagues (28) found that the overexpression of miR-27 promoted the metastasis of AGS cells, whereas its depletion decreased cell metastasis. Furthermore, they demonstrated that miR-27 promoted EMT by activating the Wnt pathway, and the APC gene was identified as the direct functional target of miR-27 (28).

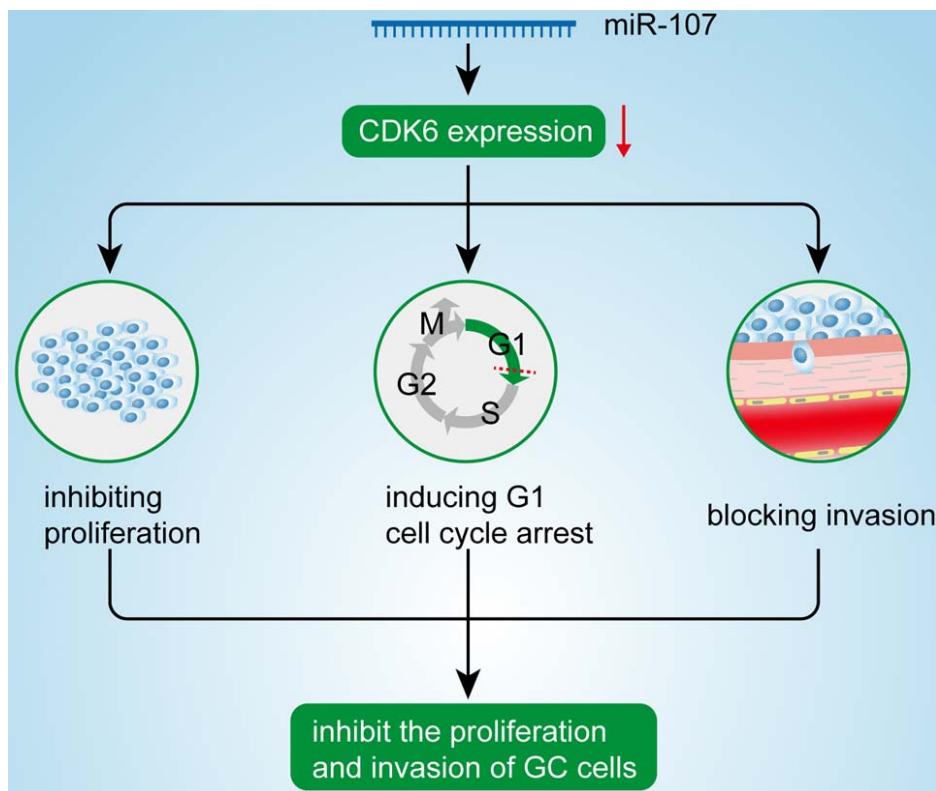


Figure 1. miR-107 functions as a tumor suppressor by directly targeting CDK6 to inhibit the proliferation and invasion activities of GC cells. miR-107 have been identified as a potential regulator of CDK6 expression. Ectopic expression of miR-107 reduced both mRNA and protein expression levels of CDK6 and mimicked the effect of CDK6 knockdown in inhibiting proliferation, inducing G1 cell cycle arrest, and blocking invasion of the GC cells.

4.2. Inhibiting cancer metastasis

Antimetastatic miRNAs (antimetastamirs) have potential therapeutic applications in blocking metastatic dissemination of GCs. The role and targets of several miRNAs in the inhibition of GC have been reported. Takei and colleagues (29) identified several miRNAs involved in cancer metastasis using an established mouse model for the peritoneal dissemination of human scirrhous gastric carcinoma cells and focused on miR-516a-3p as a candidate antimetastamir. These authors identified sulfatase 1 as a direct target of the miRNA in cells with stable ectopic overexpression of 44As3-miR-516a-3p (29). Thus, these findings define the miRNA miR-516-3p as an antimetastamir with potential therapeutic applications in blocking the metastatic dissemination of GCs.

The insulin-like growth factor-1 receptor (IGF1R) can stimulate cell proliferation, cell differentiation, and changes in cell size, as well as protect cells from apoptosis. In tumor cells, the overexpression of IGF1R, often in concert with the overexpression of insulin-like growth factor (IGF) ligands, leads to the potentiation of these signals, and as a result, enhanced cell proliferation and survival. miR-7 blocks GC metastasis by targeting IGF1R, and a novel miR-7/IGF1R/Snail axis has been proposed in the mechanism of inhibiting metastasis (30). The overexpression of miR-7 markedly inhibited GC metastasis in vivo, and the IGF1R oncogene, which is often mutated

or amplified in human cancers and functions as an important regulator of cell growth and tumor invasion, was identified as a direct target of miR-7. Furthermore, the suppression of Snail by miR-7 targeting of IGF1R increased E-cadherin expression and partially reversed the epithelial-mesenchymal transition phenotype (30). Thus, targeting the miR-7/IGF1R/Snail axis would be helpful as a therapeutic approach to block GC metastasis.

5. MICRORNAS WITH MULTIPLE FUNCTIONS IN GC METASTASIS

For most solid malignancies, metastasis is the predominant cause of cancer death (31,32,8). The elucidation of the molecular mechanisms that regulate each sequential step of metastasis is thus critical for the reduction of cancer mortality in GC patients. miRNAs that are involved GC could not only play specific role in invasion or metastasis as we mentioned above but could also have multiple functions in invasion, migration and metastasis.

5.1. Promoting GC metastasis

Invasion, migration and metastasis, the most important steps in cancer metastasis, are the leading events in malignant cancer that lead to lethality, especially for GC. miR-107 has been reported to be an oncogenic microRNA that regulates tumor invasion and metastasis (33). Silencing

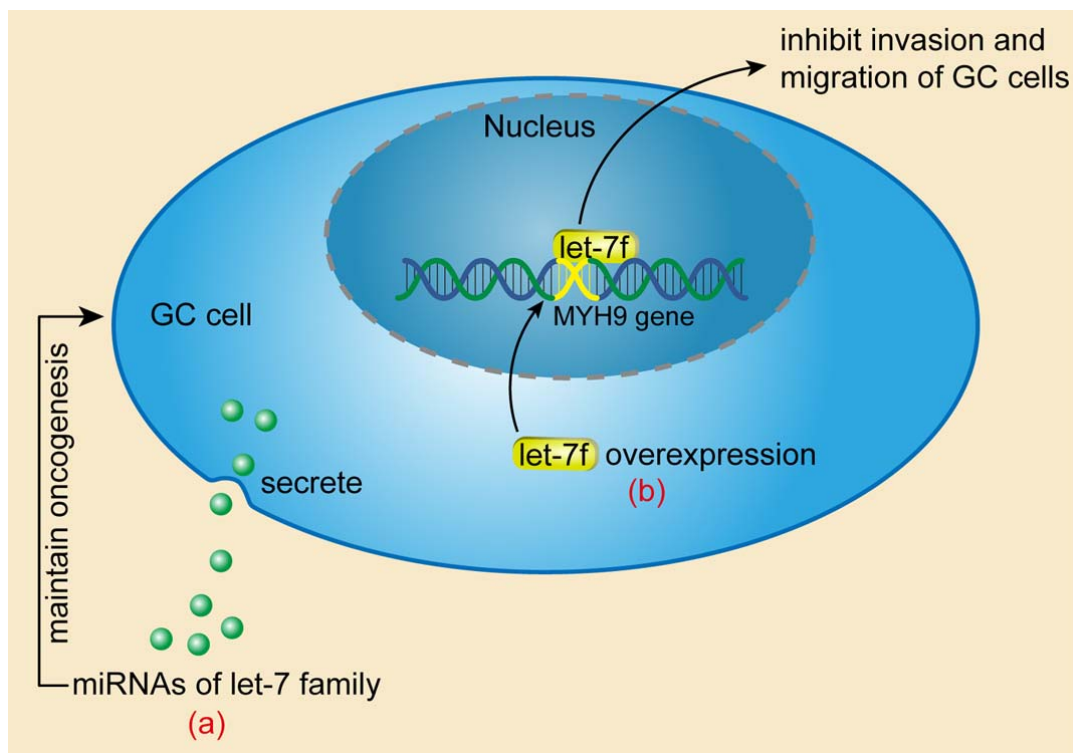


Figure 2. let-7 family in GC. In GC, miRNAs of let-7 family, including let-7f, are selectively secreted into the extracellular environment via exosomes in a metastatic GC cell line to maintain the oncogenic status of the cells. The overexpression of let-7f in GC could inhibit invasion and migration of GC cells through directly targeting the tumor metastasis-associated gene MYH9.

miR-107 expression inhibits GC cell migration and invasion in vitro and in vivo, and further, miR-107 promotes GC metastasis through the downregulation of DICER1 (33). In addition to functions in both invasion and migration, miRNAs could also participate in both invasion and metastasis. miR-622 is involved in differentiation and lymphatic metastasis in human GC. The ectopic expression of miR-622 promoted the invasion, tumorigenesis and metastasis of GC cells both in vitro and in vivo by directly targeting ING1 (34).

Because miR-21 has been identified as a novel potential biomarker of GC (35), its function in the metastasis of GC has been studied. Li and colleagues (36) found that miRNA-21 expression was upregulated in GC tissues and was significantly associated with the degree of tumor tissue differentiation, local invasion and lymph node metastasis. Moreover, the overexpression of miR-21 promoted BGC-823 cell growth, invasion and cell migration in vitro, whereas the downregulation of miR-21 exerted a stronger inhibitory effect on the biological behavior of GC cells. Additionally, miR-21 inhibition may upregulate the PTEN expression level, which indicates that PTEN may be a target gene for GC initiation and development (36). Thus, miR-21 could simultaneously promote invasion, migration and metastasis in GC.

5.2. Function in inhibiting GC metastasis

Although some miRNAs have been found to promote GC metastasis, mRNAs with multiple cancer-

inhibitory functions have attracted greater attention. miRNAs that inhibit both invasion and migration in GC have been reported. Members of the miR-29 family have been found to obviously inhibit the proliferation, migration, and invasion of GC cells by targeting Cdc42 (37). Similar functions were also reported in miR-101. Wang and colleagues found that miR-101 may function as a tumor suppressor in GC; it inhibits not only cellular proliferation, migration and invasion in vitro but also tumor growth in vivo (38). Another in vivo study found that the overexpression of miR-155 in SGC-7901 and MKN-45 GC cells dramatically suppressed cell invasion, migration and adhesion (39). Furthermore, in the regulation of GC metastasis, miR-155 directly targets SMAD2, and its downregulation in GC cells may be partly ascribed to changes in DNA methylation (39). miR-610 was also found to inhibit the migration and invasion of GC cells. Moreover, miR-610 was identified as a novel miRNA that is regulated by epidermal growth factor, which targets VASP in GC cells (40).

Let-7 miRNA family members have been found to act as tumor suppressors in many cancers, such as prostate cancer, lung cancer and breast cancer (41-43). Let-7 family miRNAs, including let-7f, are selectively secreted into the extracellular environment via exosomes in a metastatic GC cell line to maintain the oncogenic status of the cells (44). The overexpression of let-7f in GC could inhibit the invasion and migration of GC cells by directly

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targeting the tumor metastasis-associated gene MYH9 (45) (Figure 2).

miRNAs with multiple functions, i.e., inhibiting both invasion and metastasis, have also been found. miR-218 inhibits GC invasion and metastasis both in vitro and in vivo by targeting the Robo1 receptor (46). Both in vitro and in vivo studies have shown that miR-625 (47) and miR-146a (48) also inhibit the invasion and metastasis of GC. The target of miR-625 is ILK (47), and the inhibitory function of miR-146a may be attributed, at least in part, to the downregulation of L1CAM (48). miR-335 was found to have a similar function; it can act as a metastasis suppressor in GC by targeting SP1 directly and indirectly through the Bel-w-induced phosphoinositide 3-kinase-Akt-Sp1 pathway (49). Xu and colleagues (49) also found that low expression of miR-335 was significantly associated with lymph-node metastasis, poor pT stage, poor pN stage and lymphatic vessel invasion.

In addition to the miRNAs that inhibit both invasion and migration or invasion and metastasis, some miRNAs inhibit all three steps of GC progression invasion, migration and metastasis. miR-148a was identified as a tumor metastasis suppressor in GC (50). miR-148a was suppressed by more than 4-fold in GC tissues compared with the corresponding nontumorous tissues, and the downregulation of miR-148a was significantly associated with TNM stage and lymph node metastasis. The overexpression of miR-148a suppressed GC cell migration in vitro, suppressed lung metastasis formation in vivo, and reduced the mRNA and protein levels of ROCK1, whereas miR-148a silencing significantly increased ROCK1 expression. The knockdown of ROCK1 significantly inhibited GC cell migration and invasion, similar to miR-148a overexpression. Therefore, miR-148a suppresses GC cell invasion, migration and metastasis by downregulating ROCK1 in GC (50). miR-145 has a function similar to that of miR-148, but with a different target, N-cadherin (CDH2). A stepwise decrease in miR-145 expression can be observed in nontumorous gastric mucosa, primary GCs and their secondary metastases. An in vitro analysis of ectopic miR-145 expression and loss-of-function suggests that this molecule suppresses GC cell migration and invasion. Furthermore, miR-145 was found to suppress metastasis through a novel mechanism. miR-145 suppresses tumor metastasis by inhibiting N-cadherin protein translation, which indirectly downregulates the downstream effector MMP9 (51).

In summary, miRNAs participate in several different steps of GC metastasis and regulate GC metastasis at multiple different steps. miRNAs with multiple functions in the inhibition of GC metastasis are especially promising as therapies for GC because they can simultaneously block several steps in the process of metastasis.

6. ARTIFICIAL MICRORNAS IN GC METASTASIS

miRNAs can play important regulatory roles via the RNA-interference pathway by targeting mRNA for cleavage (52) or translation repression (53-55). Target

cleavage can be induced artificially by altering the targets or the miRNA sequences to achieve complete hybridization (55-57). Furthermore, miRNA-based shRNAs inhibit gene expression more potently than traditional stem-loop shRNAs (58). Thus, artificial miRNAs are commonly used tools in studies of GC metastasis. Artificial miRNA can depress the expression of PRL-3, which might be a potential therapeutic target to prevent peritoneal metastasis in GC (59). Artificial microRNA interference has been used to investigate the molecular mechanism of PRL-3 in lymph node metastasis of GC (60). By using a plasmid containing newly synthesized artificial miRNAs, the GC cells were transfected to block Snail expression, leading to significantly decreased migration and invasion potential (61). RNA interference mediated by recombinant lentivirus vectors expressing artificial CDH17 miRNA was applied to induce a long-lasting downregulation of CDH17 gene expression in human stomach cancer BGC823 cells. The CDH17-miRNA-transfected cells exhibited a significant decrease in cell proliferation, cell motility, and migration in comparison with the control cells (62).

7. CONCLUSIONS

The mechanisms of GC invasion and metastasis are crucial for the treatment and prognosis of gastric cancer patients. miRNAs participate in the process of GC invasion and metastasis. miRNAs play a dual role in this process; they can both promote and inhibit cancer invasion and metastasis. Although some miRNAs are involved only in invasion or metastasis, other miRNAs have multiple functions and may participate in more than one aspect of invasion, migration and metastasis. Therefore, miRNAs could not only be studied to help clarify the mechanism of GC invasion and metastasis, but also could be exploited as practical biomarkers or therapy targets for GC invasion and metastasis in GC patients.

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Xiaoning Zhao and Yuan Huqin are both the corresponding author.

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Abbreviations: miRNAs, microRNAs; miR, microRNA; GC, gastric cancer; CDK6, Cyclin-dependent kinase 6; antimetastamirs, antimetastatic miRNAs; IGF1R, insulin-like growth factor-1 receptor; IGF, insulin-like growth factor; CDH2, N-cadherin

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