The Role of miRNAs in Gastric Cancer

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Abstract
Despite promising developments of treatment, the mortality of gastric cancer remains high. MicroRNAs (miRNAs) are non-coding RNA molecules. There are extensive evidences that miRNAs play a dual role, as oncogenes or tumor suppressors through regulating cell proliferation, differentiation, and apoptosis. Additionally, some miRNAs, as promising diagnostic and prognostic biomarkers, are specifically related to gastric cancer. In the current review, we have summarized recent data concerning miRNAs in patient with gastric cancer, allowing us a better understanding miRNA as the prognostic and diagnostic biomarkers and the new targets for clinical therapeutic interventions for gastric cancer.

Keywords: miRNA; Gastric Cancer; Diagnosis; Biomarker

Abbreviations: miRNAs: microRNAs; RISC: RNA-Induced Silencing Complex; AQP3: Aquaporin-3; IRF1: Interferon Regulator Factor 1; DDP: Cisplatin; PTEN: Phosphatase and Tension Homolog; SNP: Single Nucleotide Polymorphism; DGC: Diffuse-type Gastric Cancer; TP53INP1: Tumor Proteins P53-induced Nuclear Protein 1; MMP9: Matrix Metallopeptidase 9

Introduction
Gastric cancer is diagnosed in nearly one million individuals each year and is regarded as the second leading cause of cancer-caused deaths in the world [1]. Gastric cancer is an asymptomatic disease at early stages and is thus often diagnosed late. Surprisingly, the 5-year survival rate is only 20-30%, and even for patients with early stage gastric cancer the 5-year survival rate remains only 61% [2]. The treatment approaches for gastric cancer include systemic chemotherapy and radiotherapy, whereas these methods are limited by their side effects and insensitivity. New approach for diagnosis and treatment are desperately needed for gastric cancer. Recently, miRNAs have been demonstrated to play a critical role in regulating numerous metabolic and cellular pathway, especially controlling cell proliferation and apoptosis underlying various cancer [3,4]. Thus, we focused on the role of miRNA during the occurrence and development of gastric cancer and provided novel insights in the field of miRNA for clinical diagnosis and therapy.

miRNAs
MicroRNAs (miRNAs), are a class of small endogenous and highly conserved non-coding RNAs involved in the regulation of gene expression. The first miRNAs, lin-4, was first discovered in 1993, which inhibit the translation of protein Lin-14 in C. elegans [5]. Currently, over 1000 mammalian miRNAs have been discovered through cloning and sequencing approaches, which include several hundreds miRNAs in humans. miRNAs are composed of 20-22 nucleotides in length, which are processed from larger pri-miRNAs into miRNA duplexes through the cleavage of RNAse III enzyme Dicer [6]. One strand of the duplex is associated with the RNA-induced silencing complex (RISC) while the other strand is universally degraded by cellular nucleases. The complex of miRNA–RISC binds to the 3'or 3' untranslated regions (3'-UTRs) of specific mRNA targets, resulting in translational repression or degradation of these miRNAs [7-9]. It is predicted that miRNAs may control the activities of more than 60% of all protein-coding genes [10,11]. Of note, miRNA-induced mRNA degradation occurs in mammals, whereas the majority of mammalian miRNAs are thought to inhibit target gene expression by a more immediate and low energy-consumption way, translational regulation, which induces rapid changes of protein synthesis without excessive transcriptional activation and subsequent steps in mRNA processing [6,12-14]. In addition, translational modulation form of gene expression possesses the advantage of being readily reversible, thereby providing the cell with great flexibility in response to different cytotoxic stresses [15]. miRNAs have been demonstrated to regulate a variety of biological functions including development, differentiation, metabolism, growth, proliferation and apoptosis [16]. Taken together, miRNAs can regulate protein expression by increasing RNA degradation or preventing mRNA translation. And more biological effects of miRNAs would be discovered in future.

The Involvement of miRNAs as Oncogenes or Tumor Suppressors in Gastric Cancer
The relationship between miRNAs and gastric cancer has been reported (Table 1). miR-19a functions as an oncogenic miRNA in gastric cancer by repressing the expression of tumor suppressor gene SOCS1 (Suppressor of cytokine signaling 1) [17]. miR-296-5p increased cell proliferation in gastric cancer through repression of cedal-related homobox 1 [18]. miR-17-5p/20a was related to gastric cancer not only by promoting cell proliferation but also inhibiting cell apoptosis via post-transcriptional modulation of p21 and TP53INP1 (tumor protein P53-induced nuclear protein 1), indicating the involvement of miRNA as oncogene in gastric cancer [19]. On the other hand, miRNAs can also serve as a tumor suppressor during the development of gastric cancer. MiR-874 in gastric cancer inhibited cell proliferation, migration and invasion through targeting oncogenic gene AQP3 (Aquaporin-3) [20]. MiR-212 inhibited cell growth in gastric cancer through directly down regulating the expression of RBP2 (retinoblastoma binding protein 2), which was a newly found histone demethylase underlying gastric cancer and lung cancer [21,22]. Overexpression of miR-429 markedly promoted gastric cancer cell apoptosis and inhibited gastric cancer cell proliferation while miR-429 inhibitor had opposing effects [23]. Additionally, downregulating MiR-29c conferred a growth advantage on...
The Clinical Application of miRNA in Gastric Cancer

miRNAs could be a promising biomarker for the prognosis and diagnosis of gastric cancer with advantage that miRNA have smaller quantity and relative stability compared to mRNA. A recent study showed that plasma miRNA-199a-3p levels in patients with early gastric cancer were significantly higher than those from healthy controls and the patients with gastric precancerous diseases, and that post-operative level of plasma miRNA-199a-3p were significantly reduced as compared to pre-operative level, indicating that plasma miRNA-199a-3p could be novel potential diagnostic biomarkers for early gastric cancer [31]. Another investigation showed that the serum levels of miR-103, miR-107, miR-194 and miR-210 were significantly increased in early and advanced-stage DGC (diffused gastric cancer)-bearing mice that usually exhibit rapid disease progression and a poor prognosis compared with their corresponding controls, indicating the promising specific role to detect the specific subclass of gastric cancer DGC at early stage [32]. Additionally, the serum concentrations of miR-21, miR-146a and miR-148a were closely associated with lymph node metastasis of gastric cancer, suggesting these serum miRNA levels could be biomarker candidates to predict the presence of lymph node metastasis [33]. miR-451, miR-199a-3p, and miR-195 were highly expressed in the gastric cancer patients with early recurrence, whereas low miR-451 expression was related to a better survival [34]. These biomarkers specific to the particular tissue and stage of gastric cancer could provide accurate and effective information to help diagnosis.

Apart from the early diagnosis, drug resistance of chemotherapy is also considered as the driving force to successful treatment of gastric cancer. Recent studies found that miRNA could improve the drug therapeutic effect. Over expressing miR-200c or down regulating miR-21 could enhance the sensitivity of chemotherapy to cisplatin (DDP) in gastric cancer by targeting RhoE and PTEN (phosphatase and tension homolog) [35,36]. Also, MiR-23a have been shown to prevent paclitaxel (mitotic inhibitor used in cancer chemotherapy)-induced apoptosis and promoted cell viability and the colony formation ability of tumor cells via aberrant expression of RCC2 in gastric carcinoma cells [24]. Of note, the SNP (single nucleotide polymorphism) of TNFAIP2 (the key gene in apoptosis) in miRNA binding site, rs8126 T>C, caused high susceptibility to gastric cancer [25], which also indicate the role of miRNA as tumor suppressor. Together, miRNA can serve as oncogenes or tumor suppressors during tumorigenesis of gastric cancer and may be a potential gastric cancer therapeutic target.

With the extensive miRNA studies in gastric cancer, the action of miRNA specific to the particular aspect of gastric cancer, such as invasion and metastasis was found. miR-370 is highly associated with more advanced nodal metastasis and a higher clinical stage of gastric cancer and it can enhance the oncogenic potential of GC cells by inhibiting the expression of transforming growth factor-β receptor II (TGFβ-RII) in gastric cancer [26]. Additionally, miR-301a was significantly up-regulated in both cells and tissues of gastric cancer, and it promoted invasion of gastric cancer cells by directly down-regulating RUNX3 expression post-transcriptionally [27]. In contrast, some miRNAs including miR-22, miR-610 and miR-145 were recently found to be down-regulated in gastric cancer and inhibit invasion and metastasis. Transfection of miR-22 expression plasmid was able to significantly inhibit cell migration and invasion in SGC-7901 and NCL-N87 gastric cancer cell lines by targeting the oncogenic gene Sp1 [28]. miR-610 had been suggested to significantly inhibit the migration and invasion of gastric cancer cells by suppressing actin binding protein vasodilator-stimulated phosphoprotein [29]. miR-145 markedly suppressed gastric cancer metastasis by inhibiting N-cadherin protein translation, and then indirectly down-regulated its downstream effector MMP9 (matrix metalloproteinase 9) [30]. These results reminded us of the specific role of miRNA during invasion and metastasis of gastric cancer.

### Table 1: Dysregulated miRNAs in Gastric Cancer.

<table>
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<tr>
<th>miRNAs</th>
<th>Targets in Gastric Cancer</th>
<th>Reference</th>
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<tbody>
<tr>
<td>miR-19a</td>
<td>SOCS1</td>
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<tr>
<td>miR-296-5p</td>
<td>caudal-related homeobox 1</td>
<td>[18]</td>
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<tr>
<td>miR-17-5p/20a</td>
<td>p21 and TP53/1P1</td>
<td>[19]</td>
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<td>miR-370</td>
<td>TGFβ-RII</td>
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<td>miRNA-199a-3p</td>
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<td>miR-22</td>
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<td>miR-145</td>
<td>N-cadherin and MMP9</td>
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</tbody>
</table>

### Conclusions

miRNAs expression differs for the specific stages and types of gastric cancer, suggesting miRNAs may function as novel and potential targets for prevention and treatment of gastric cancer, and also have broad applications in early diagnosis, prognosis, and improving sensitivity in radiotherapy and chemotherapy of gastric cancer. However, it is still under investigation that the altered expression of miRNAs is the direct or indirect cause of gastric cancer in most studies. Additionally, single miRNA can regulate multiple targets and various miRNA target one gene, making the regulatory mechanism of miRNAs complicated. Thus, studies based on the clinical application of miRNAs for gastric cancer still lack extensive and precise data from large multi-center studies. With the improvement of techniques and the development of new antagonir and mimic approaches, the detailed knowledge of miRNAs in gastric cancer will be discovered in future.

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