Mechanisms of MicroRNA Deregulation and MicroRNA Targets in Gastric Cancer

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Reduced or increased levels of mature microRNAs (miRNAs) in tumors are often the result of deregulated transcription, epigenetic silencing, genetic loss, or defects in their biogenesis pathway in gastric cancer. Among these, *Helicobacter pylori* infection, epigenetic regulation and defects in the pathway of miRNA biogenesis predominate in gastric cancer [1].

The miRNA profile seen in gastric cancer tissues, when compared to that of healthy controls, reveals several reasons for this. *H. pylori* is an etiological factor for gastric carcinogenesis. Upon infection with *H. pylori*, miR-21 is up-regulated while miR-218 is down-regulated in gastric epithelial tissues and AGS cells. CagA is a virulence factor of this bacteria and prevents expression of Let-7 by promoting methylation of its promoter. Tumor-associated miR-7 and miR-146a are deregulated by inflammation factors that are produced through the interaction between CagA and the host cell (fig. 1) [2–6].

Epigenetic regulation of miRNAs is also important for deregulation of miRNAs in gastric cancer. DNA hypomethylation and promoter methylation change the miRNA expression profile; the former causes miR-196b overexpression and the latter results in down-regulation of miR-124a [7–8]. The miR-17–92 cluster is located at a fragile site in the genome [9], and has been found to be overexpressed in many cancers including gastric cancer [10]. miR-449 inhibits cell proliferation and is down-regulated in gastric cancer cells [11]. E2F1 overexpression is a biomarker for gastric cancer and E2F1 transcriptionally targets and up-regulates the miR-106b/25 cluster, and up-regulated miR-106b/25 and miR-93 repress E2F1 transcription within a negative feedback loop in gastric cancer cells (fig. 2) [12].

Defects in the miRNA biogenesis pathway also contribute to miRNA deregulation. Loss of Ago2 causes a blockage of miRNA synthesis at a premature step [13]. Genes harboring microsatellite instability are targets of frameshift mutations, and in microsatellite instability-positive gastric cancers, the miRNA processing gene in the biogenesis pathway, TARBP2, has been found to be mutated. In that

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**Summary**
Gastric cancer is a genetically heterogeneous disease that causes cancer-related deaths worldwide. Although many studies on this disease have been performed, the molecular mechanisms of gastric tumorigenesis, invasion, and metastasis have still not been identified. MicroRNAs (miRNAs) are endogenously coded small RNA molecules, 18–25 nucleotides in length, that regulate gene expression at the post-transcriptional level. They are required for physiological activities in the cell, including development, proliferation, differentiation, and apoptosis. Research has now indicated their importance in carcinogenesis, with miRNA profiling revealing differences in the tumor and the normal tissue in several cancers. This difference in the expression pattern might lead to disrupted regulation of genes such as tumor suppressor genes and proto-oncogenes that are involved in cell cycle control, proliferative pathways, apoptosis, and metastasis in gastric carcinogenesis. Genes encoding miRNAs have been characterized as novel proto-oncogenes and tumor-suppressor genes based on findings that these miRNAs control malignant phenotypes. miRNA deregulation promotes cell-cycle progression, confers resistance to apoptosis, and enhances invasiveness and metastasis. Deregulated miRNAs affect the regulation of their target genes. Knowing the targets of miRNAs is of great importance for identifying the molecular mechanisms behind gastric carcinogenesis and forms the focus of this review.

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Deregulated miRNAs in cancers can be classified as tumor suppressors that prevent cell proliferation and oncopgenes that stimulate growth and cell proliferation (tables 1 and 2). miR-212 is a tumor suppressor for gastric cancer and acts through down-regulating a novel histone demethylase, RBP2 [16]. miR-874 targets an oncogenic gene AQP3, thereby inhibiting gastric cancer cell migration and invasion [17]. Moreover, a growth advantage is conferred to miR-29c-down-regulated gastric cancer cells that exhibit aberrant RCC2 expression [18]. Down-regulation of miR-145 inhibited invasion and metastasis in gastric cancers by directly targeting N-cadherin translation and indirectly MMP-9 [19]. miR-610 is also repressed, and suppresses invasion and metastasis in gastric cancer cells by down-regulating an acting binding protein called vasodilator-stimulated phosphoprotein in gastric cancer [20]. miR-22 down-regulation in gastric cancer cell lines also blocked cell invasion and metastasis by targeting Sp-1 [21]. On the other hand, miR-19a has an oncogenic role by suppressing SOCS1 in gastric cancer [22]. miR-296–5p increased cell proliferation, while miR-17–5p/20a both increased proliferation and inhibited apoptosis in gastric cancer cells, the former down-regulating cdkal-related homeobox1, and the latter modulating p21 and TP53INP1 post-transcriptionally [23–24]. miR-370 enhances tumorigenic potential of gastric cancers by inhibiting TGFβ-RII (transforming growth factor-β receptor II) [25]. miR-301a up-regulation has been associated with gastric cancer cell invasion and targeted RUNX expression post-transcriptionally [26]. Both miR-370 and miR-370a were shown to be up-regulated in gastric cancer tissues and associated with higher clinical stages. miR-223 can directly inhibit synthesis of the EPB41L3 protein, in turn causing cell migration and invasion showing oncogenic character [27].

Gene regulation by epigenetic mechanisms is important for gastric carcinogenesis, and miRNAs are often down-regulated by hypermethylation of the CpG islands in their promoters in gastric cancers. Myc is a proto-oncoprotein that is potentially regulated by miR-212 which shows decreased levels subsequent to promoter hypermethylation in gastric cancer cell lines [28]. miR-137 is related to CDC42 inactivation and inhibition of cell growth and induction of apoptosis in gastric cancer cells [29]. In gastric cancers, miR-155 is methylated and down-regulated and conversely, overexpression of miR-155 can inhibit cell migration, invasion, and adhesion by targeting 3' UTR of SMAD2 in TGF-β pathway [30]. CDK4, CCNF2, and CCNA2 are cell cycle-related genes that are targeted by miR-34b and miR-34c, which are also silenced epigenetically by methylation in gastric cancers [31]. miR-129 is methylated and down-regulated in primary gastric tumors, leading to SOX4 gene being up-regulated in gastric cancers. In these patients, these biomarkers are associated with poor differentiation and metastasis. Inhibition of SOX4 in SGC-7901 cells together with pre-miR-129–2 expression results in apoptosis [32]. Epigenetic silencing of miR-181c targets and activates oncogenic molecules, namely, NOTCH2/4 and KRAS, while pre-miR-181c overexpression reduces gastric cancer cell growth [33]. Promoter hypermethylation remarkably decreases miR-137 expression, and this is inversely correlated with CDC42 expression in gastric cancer tissues compared with normal gastric tissues [33]. miR-10b is located in the promoter of the HOXD4 gene and in clinical cases, HOXD4 expression is inversely regulated with the methylation of miR-10b [34]. MAPRE1 is a positive regulator of cell growth and a negative regulator of apoptosis. MAPRE1 targets the β-catenin/TCF pathway and itself is directly down-regulated by miR-10b. As expected, methylated miR-10b results in increased MAPRE1 levels [35]. miR-375 appears to be silenced by DNA methylation and histone deacetylation in NUGC3 cells. When miR-375 is expressed in gastric cancer cells, growth of these cells is
reduced and the survival molecule PDK1/AKT and anti-apoptotic molecules, cIAP and 14–3-3-ζ are also targeted [36]. Epigenetically regulated miR-941 and miR-1247 are transcriptionally silenced by DNA hypermethylation. Their target mRNAs include KDM6B, TAOK1, PRDM16, RARA, STX1B, and RCC2 in gastric cancer cell lines [37]. miR-34c-5p targets 3' UTR of MAPT and the expression of miR-34c-5p is highly reduced by promoter methylation in the multidrug-resistant gastric cancer cell line, SGC-7901/VCR, and paclitaxel-resistant gastric tissues [38]. Histone deacetylation and CpG island methylation down-regulate miR-219–2-3p in gastric cancer cell lines and gastric cancer tissues. Expression of miR-219–2-3p inhibits survival, migration, and invasion of gastric cancer cells by affecting the ERK/2 pathway. In addition, potential targets of miR-219–2-3p seems to be ERB3, MAPK8, SCL7A11, YOD1, TBK1, and SOX4 [39]. Remarkably, mimics of miR-195 and miR-378 cause cell cycle arrest at G0/G1 and G2/M phases and inhibit gastric cancer cell growth by targeting CDK6 and VEGF, respectively. miR-195 and miR-378 are down-regulated most probably through promoter methylation in gastric cancers since 5'-aza-2'-deoxycytidine treatment reverses this effect [40].

Conclusions

During the past decade, miRNAs, which are known for their importance in post-transcriptional gene regulation, have attracted the attention in the ongoing search to understand the development and progression of gastric cancer. Knowing not only the differential expression pattern of miRNAs in tumor and normal gastric tissues, but also identifying miRNA-target genes have been extremely significant for revealing the post-transcriptional gene regulation defects directed by miRNAs in gastric cancers. Although there have been many reports relating to this issue over the past 5 years, further research is required to understand the roles of miRNAs in gastric carcinogenesis.

Disclosure Statement

There is no competing financial interest in relation to the work to declare.
References


