# REVIEW ARTICLE

# MicroRNAs are involved in the development and progression of gastric cancer

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MicroRNAs (miRNAs) are recognized as an essential component of the RNA family, exerting multiple and intricate biological functions, particularly in the process of tumorigenesis, proliferation, and metastatic progression. MiRNAs are altered in gastric cancer (GC), showing activity as both tumor suppressors and oncogenes, although their true roles have not been fully understood. This review will focus upon the recent advances of miRNA studies related to the regulatory mechanisms of gastric tumor cell proliferation, apoptosis, and cell cycle. We hope to provide an in-depth insight into the mechanistic role of miRNAs in GC development and progression. In particular, we summarize the latest studies relevant to miRNAs' impact upon the epithelial-mesenchymal transition, tumor microenvironment, and chemoresistance in GC cells. We expect to elucidate the molecular mechanisms involving miRNAs for better understanding the etiology of GC, and facilitating the development of new treatment regimens for the treatment of GC.

**Keywords:** microRNA; gastric cancer; signaling pathway; epithelial-mesenchymal transition (EMT); angiogenesis; tumor microenvironment; chemoresistance

## INTRODUCTION

The World Health Organization has identified cancer as the leading cause of death in 185 countries that were examined [1]. Accordingly, among 36 cancer types, gastric cancer (GC) is the fifth most frequently diagnosed cancer and the third leading cause of cancer death, respectively, and is much more prevalent in Asian countries compared to non-Asian countries [1]. China contributes to more than 50% of all GC cases worldwide, with approximately 680,000 new cases and 500,000 deaths each year [2]. Surgical resection is the preferred method of initial treatment whenever feasible, with adjuvant chemotherapy as a vital addition to the multidisciplinary approach to treatment. For locoregional recurrence of GC, chemotherapy, with or without external beam radiation therapy, appears to be a reasonable approach to treat patients with unresectable disease. However, the response rates to such approaches are marginal at best, leading to a median overall survival of ~8-17 months [3].

Presently, there is a lack of effective treatment options for patients with GC, translating to a uniformly poor overall survival worldwide. As such, the research focus has gradually switched to the discovery of novel and precise biomarkers that can lead to the development of targeted therapeutics. MicroRNAs (miRNAs) are a class of small nucleic acids and function as the master regulators in the control of gene expression [4]. To date, over 2500 human-specific miRNAs have been identified, with their dysregulation associated with tumor cell proliferation, apoptosis, invasion, and metastatic potential. Furthermore, aberrantly expressed miRNAs are potentially useful biomarkers for GC screening, diagnosis, prognosis, and disease monitoring. This review will summarize the most recent literature on miRNAs and the associated target genes that are specific to GC, highlighting their intrinsic mechanistic role in GC development and progression.

## MIRNAS ARE ASSOCIATED WITH GC DEVELOPMENT AND PROGRESSION

Recent studies of miRNAs have shed light on their contributions toward controlling the development and progression of GC. Herein, we will focus on the functional interactions among select miRNAs, their putative target genes, and the relevant signaling pathways that are involved in the key pathophysiological processes of GC.

*Helicobacter pylori* infection-associated tumorigenesis
*Helicobacter pylori* (*H. pylori*) infection is known as a driving cause of significant morbidity in the context of GC. Yang et al. examined the miRNA levels in *H. pylori*-infected patients with GC, and showed that *H. pylori* infection was associated with the specific cancer-related signaling pathways regulated by the miRNA-mRNA interaction network [5]. Of interest, miR-155 was reported to be involved in the differentiation of T helper 17 (Th17) and Th1 cells, which contribute to the immunity against *H. pylori* infection and

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**Table 1.** MiRNAs and their putative targets and signaling pathways that are relevant to GC cell proliferation and apoptosis.

| MiRNA | Target genes | Signaling pathway | References |
|---|---|---|---|
| **Up** | | | |
| miR-21 | 15-PGDH | PGE2/PI3K/Akt/Wnt/β-catenin | [10] |
| | PTEN | PTEN/PI3K/mTOR | [11, 12] |
| miR-27a | SFRP1 | Wnt/β-catenin | [21] |
| miR-103 | KLF4 | | [91] |
| miR-106a | FAS | | [29] |
| miR-107 | NF1 | | [92] |
| | PTEN | PI3K | [16] |
| miR-146a | SMAD4 | | [93] |
| miR-151-5p | P53 | Notch1 | [94] |
| miR-192/215 | APC | Wnt/β-catenin | [22] |
| miR-194 | SUFU | Wnt/β-catenin | [23] |
| miR-200c | P27$^{Kip1}$ | | [95] |
| miR-558 | HPSE | | [96] |
| miR-590-5p | RECK | Akt/ERK; STAT3 | [71] |
| miR-208a-3p | PDCD4 | | [97] |
| miR-423-3p | Bim | | [98] |
| miR-454 | CHD5 | | [99] |
| miR-520c | IRF2 | | [100] |
| miR-3174 | ARHGAP10 | | [24] |
| **Down** | | | |
| miR-15a | Bmi-1 | | [101] |
| miR-15a-3p/miR-16-1-3p | Twist1 | | [102] |
| miR-16-5p | Smad3 | | [103] |
| miR-26b | KPNA2 | KPNA2/c-Jun | [7] |
| miR-29b | KDM2A | RUNX3/miR-29b/KDM2A | [104] |
| miR-29c-3p | KIAA1199 | FGFR4/Wnt/β-catenin; EGFR | [105] |
| miR-31 | HDAC2 | | [106] |
| miR-101 | MCL1/ZEB1 | | [30] |
| miR-127 | MAPK4 | | [107] |
| miR-132-3p | MUC13 | Akt/ ERK | [108] |
| miR-135a | KIFC1 | | [109] |
| miR-143-3p | AKT2 | | [8] |
| miR-154 | DIXDC1 | Wnt | [17] |
| miR-194 | KDM5B | | [110] |
| miR-199a/b-3p | PAK4 | PAK4/MEK/ERK | [111] |
| miR-202-3p | Gli1 | | [112] |
| miR-203a | E2F3 | | [113] |
| miR-203 | Slug | | [114] |
| miR-204 | CKS1B/CXCL1/GPRC5A | | [115] |
| miR-337-3p | MMP-14 | | [116] |
| miR-338-3p | SOX5 | Wnt/β-catenin | [18] |
| miR-375 | YAP1/TEAD4/CTGF | Hippo | [117] |
| miR-495 | Akt; mTOR | PI3K/Akt/mTOR | [13] |
| miR-511 | TRIM24 | PI3K/Akt; Wnt/β-catenin | [15] |
| miR-520f-3p | SOX9 | Wnt/β-catenin | [19] |
| miR-524-5p | MMP-2/MMP-9 | | [118] |

**Table 1.** continued

| MiRNA | Target genes | Signaling pathway | References |
|---|---|---|---|
| miR-584-3p | MMP-14 | | [119] |
| miR-647 | SRF | SRF/MYH9 | [120] |
| miR-873 | STRA6 | Wnt/β-catenin | [20] |
| miR-1284 | EIF4A1 | | [25] |
| miR-3978 | LGMN | | [121] |

the infection-associated immunopathology [6]. *H. pylori* cytotoxin-associated gene A (Cag A) was found to suppress miR-26b, which in turn, upregulated the expression of miR-26b's putative target gene, karyopherin alpha 2 (KPNA2), a promoter for cancer metastasis [7]. MiR-143-3p, which was found to be the most significantly increased miRNA in *H. pylori*-positive GC tissues, hindered tumor growth [8]. In addition, miR-155, miR-16, and miR-146a were reported to be upregulated in gastric epithelial cells infected with *H. pylori*, and increased miR-155 was also found in mucosal tissues from *H. pylori*-positive patients [9]. These studies demonstrate the concurrent influences of miRNAs on *H. pylori*-mediated, inflammation-associated tumorigenesis.

Cell proliferation
Numerous studies have directly examined the role of miRNAs in GC growth by targeting cellular signaling pathways and genes. Table 1 shows the miRNAs and their putative targets that are relevant to the GC proliferation and apoptosis. We will focus on the two major signaling pathways that have been extensively studied in the context of GC cell proliferation.

*PI3K/Akt/mTOR signaling pathway.* The activation of the phosphoinositide 3-kinases/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling pathway is important for regulating gene expression in a variety of human cancers. This pathway is also involved in cell cycle regulation, apoptosis, transcription, translation, metabolism, and angiogenesis. For instance, elevated miR-21 in GC was reported to target the 15-hydroxyprostaglandin dehydrogenase (15-PGDH) gene and the phosphatase and tensin homolog (PTEN) gene, to promote GC proliferation. In doing so, miR-21 exerts its oncogenic effect through the prostaglandin E2 (PGE2)/PI3K/Akt/Wnt/β-catenin axis, resulting in GC cell proliferation [10–12]. In addition, Akt and mTOR were reported to be targeted by miR-495 directly; the overexpression of miR-495 could inhibit the growth and induce the apoptosis of GC cells, with the blockade of the PI3K/Akt/mTOR signaling, which in turn, altered the expression of Bax, caspase-3/-9, and cyclin D1 [13]. MiR-495 was also shown to accelerate the death of GC cells through noncanonical beclin 1-independent autophagy induced by the Akt/mTOR pathway [14]. Furthermore, tripartite motif-containing 24 (TRIM24) elicited tumor-stimulating effects through the regulation of the PI3K/Akt and Wnt/β-catenin signaling pathways, and these effects seemed to be negated by the overexpression of miR-511 [15] (Fig. 1). A recent study also reported that GC tumor-derived exosomes containing enriched miR-107 could enter myeloid-derived suppressor cells (MDSCs) and downregulate the PTEN gene, leading to the activation of the PI3K pathway in MDSCs [16].

*Wnt/β-catenin signaling pathway.* The Wnt/β-catenin signaling pathway is involved in numerous physiological processes, including cell cycle regulation and tumorigenicity. MiR-154 was reported to inhibit the activation of the Disheveled-Axin domain containing 1 (DIXDC1)/Wnt signaling, which then mitigated the growth of GC cells [17]. It is reported that miR-511 could suppress the PI3K/Akt and Wnt/β-catenin signaling by
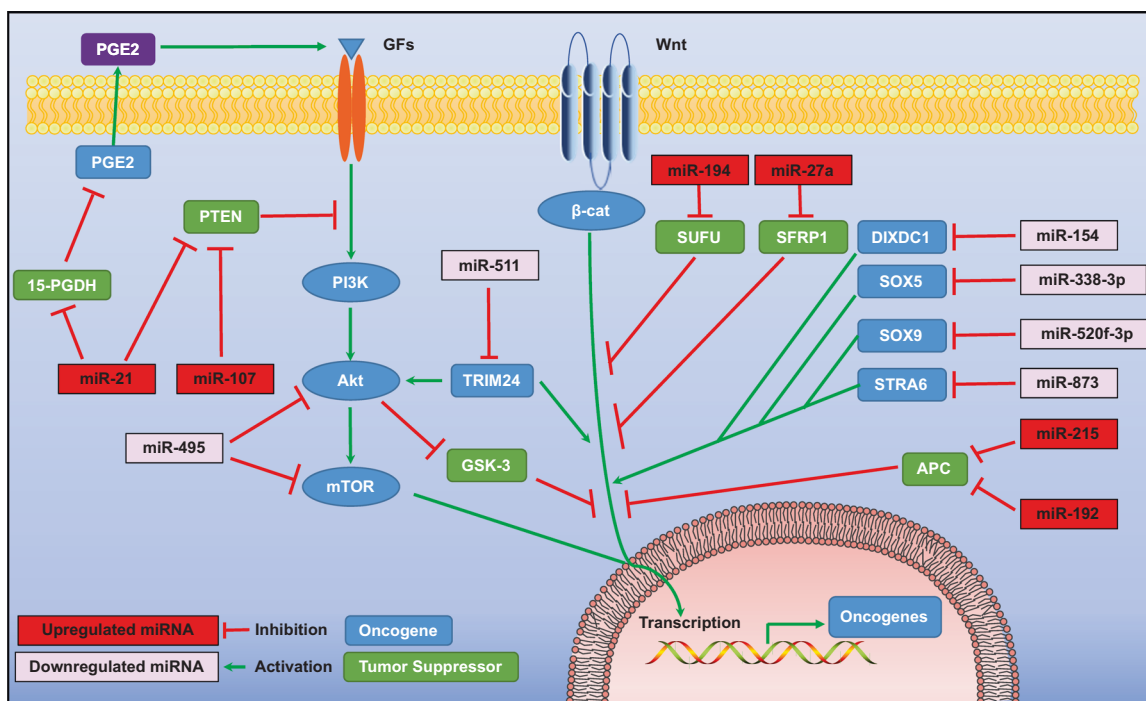
**Fig. 1  MiRNAs are involved in the regulation of gastric cancer cell proliferation by targeting PI3K/Akt/mTOR and Wnt/β-catenin signaling pathways.** 15-PGDH 15-hydroxyprostaglandin dehydrogenase, β-cat β-catenin, Akt protein kinase B, APC adenomatous polyposis coli, DIXDC1 disheveled–axin domain containing 1, GFs growth factors, GSK-3 glycogen synthase kinase-3, mTOR mammalian target of rapamycin, PI3K phosphoinositide 3-kinases, PGE2 prostaglandin E2, PTEN phosphatase and tensin homolog, SFRP1 secreted frizzled-related protein 1, SOX5 SRY-box transcription factor 5, SOX9 SRY-box transcription factor 9, STRA6 stimulated by retinoic acid 6, SUFU suppressor of fused homolog, TRIM24 tripartite motif-containing 24.

directly targeting TRIM24, while the ectopic expression of miR-511 significantly inhibited GC cell proliferation, with the reduced expression of p-Akt, β-catenin, cyclin D1, and c-Myc [15]. Other studies have shown that miR-338-3p, miR-520f-3p, and miR-873 were downregulated in GC cells, with the forced expression of these miRNAs able to suppress GC progression via the down-regulation of SRY-box transcription factor 5 (SOX5), SRY-box transcription factor 9 (SOX9), and stimulated by retinoic acid 6 (STRA6) to further block Wnt/β-catenin signaling [18–20]. In addition, miR-27a, miR-194, miR-192, and miR-215 were reported to be upregulated in GC cells, and their ectopic expression could promote the tumor cell proliferation and cancer development [21–23]. The mechanistic studies demonstrated that these oncogenic miRNAs could repress the negative regulators of the Wnt signaling cascade, including secreted frizzled-related protein 1 (SFRP1), suppressor of fused homolog (SUFU), and adenomatous polyposis coli (APC), with the translocation of β-catenin into the nucleus, as shown in Fig. 1.

### Apoptosis
Li et al. showed that miR-3174 inhibited mitochondria-dependent apoptosis and autophagic cell death, with the high expression of miR-3174 shown to be related to the resistance of cisplatin (DDP) [24]. Others have shown the effect of miR-1284 in modulating multidrug resistance (MDR) and accelerating drug-induced apoptosis, further preventing cells from entering the S phase of the cell cycle [25]. The mechanistic studies demonstrated that these phenotypes resulted from miR-1284 directly targeting the gene of eukaryotic translation initiation factor 4A1 (EIF4A1), and indirectly suppressing the gene expression of Jun and matrix metallopeptidase 12 (MMP-12) and facilitating the gene expression of Myc [25]. MiR-30a's downregulation was recently identified in DDP-resistant SGC-7901 cells and decreased DDP-induced apoptosis. Of note, the downregulation

**Table 2.**  MiRNAs interfere with GC cell cycle regulation.

| MiRNA | Cell cycle regulation | Target genes | References |
|---|---|---|---|
| **Up** | | | |
| miR-17-5p/-20a | $G_0/G_1$–S acceleration | P21; TP53INP1 | [122] |
| miR-214 | $G_1$–S acceleration | PTEN | [33] |
| miR-215 | $G_0/G_1$–S acceleration | RB1 | [123] |
| **Down** | | | |
| miR-31 | $G_1$–S blockade | E2F2 | [27] |
| MiR-101 | $G_1$ arrest | MCL1/ZEB1 | [30] |
| miR-126 | $G_0/G_1$ arrest | Crk/ADAM9 | [31, 32] |
| miR-143 | $G_0/G_1$ arrest | GATA6 | [124] |
| miR-329 | $G_1$ arrest | KDM1A | [28] |
| miR-375 | $G_1$ arrest | RON | [125] |
| miR-383 | $G_1$ arrest | cyclin E2 | [34] |
| MiR-638 | $G_0/G_1$ arrest | SOX2 | [126] |
| MiR-647 | $G_0/G_1$ arrest | ANK2 | [79] |
| miR-1284 | $G_0/G_1$ arrest | EIF4A1 | [25] |
| miR-4317 | S–$G_2$/M blockade | ZNF322 | [127] |

of LC3-II by miR-30a was able to inhibit chemoresistance-associated autophagy and increase the total apoptotic rate in chemoresistant cells [26].

### Cell cycle
Many oncogenic and tumor suppressor miRNAs have been reported to be involved in cell cycle regulation. Table 2 is the summary of select miRNAs and their putative target genes that

have been reported to contribute to the cell cycle progression in GC cells. For instance, the downregulation of miR-31 has been found in several human cancer cell lines (MGC-803, MKN-45, AGS, and SGC-7901), but not in the N87 cell line. Functionally, miR-31 suppresses tumor cell proliferation, induces apoptosis, blocks $G_1$ transition, and reduces migration and invasion in both SGC-7901 and MGC-803 cells via the inhibition of expression for the E2F transcription factor 2 (E2F2) gene [27]. Clinical and pathological characteristics show that low miR-329 expression, along with high expression of its target gene, histone lysine demethylase 1 A (KDM1A), likely contribute to GC progression. Forced expression of miR-329 showed a comparable phenotype as that of KDM1A silencing in inhibiting BGC-823 cell viability, facilitating $G_1$ arrest, reducing colony formation, and promoting tumor cell apoptosis [28]. The inhibition of miR-106a accelerated GC cell apoptosis with a visible sub-$G_1$ peak as a reliable indicator of apoptosis, which was further confirmed in AGS and N87 cells transfected with miR-106a antisense oligonucleotides [29]. The tumor suppressor miR-101 induced a more significant accumulation of sub-$G_1$ phase cells, with both early and late apoptotic cells after 72 h of miR-101 mimic transfection in MKN-45 cells. The overexpression of miR-101 induced the cleavage of poly(ADP-ribose) polymerase (PARP) and suppressed migratory and invasive abilities, as well as the epithelial-mesenchymal transition (EMT), and directly inhibited the expression of the zinc finger E-box-binding homeobox 1 (ZEB1) gene [30]. Furthermore, miR-126 could function as a putative tumor suppressor in GC, potently inhibiting the cell growth as a result of cell cycle arrest in the $G_0/G_1$ phase by synergistically targeting Crk and a disintegrin and metallopeptidase domain 9 (ADAM9) [31, 32]. The overexpression of miR-214 has been identified in GC cells, and its downregulation can induce $G_1$ cell cycle arrest by upregulating PTEN in BGC-823 and MKN-45 cells [33]. A similar phenotype was observed in SGC-7901 and U87 cells after the transfection of miR-383, which targets cyclin E2 [34].

### EMT

EMT is a process associated with tumor initiation, progression, invasion, metastasis, and resistance to drug therapy [35]. During this process, E-cadherin can sustain key intracellular binding structures, such as desmosomes and claudins, and switch to N-cadherin [36]. The downregulation of E-cadherin can be mediated by putative miRNAs and EMT-inducing TFs, such as snail1 (snail), snail2 (slug), Twist, ZEB1, and ZEB2 [36].

MiR-25 exhibits inhibitory effects on human diffuse-type GC, with the inhibition of miR-25 leading to increased collagen type I alpha 2 chain (COL1A2), as well as the attenuation of E-cadherin gene expression [37]. In addition, miR-25 was shown to suppress p53 gene expression and sensitize c-Src activation, revealing its role in intestinal-type GC [37]. MiR-30a's overexpression increased E-cadherin levels, but decreased N-cadherin levels in SGC-7901 cells, with the activity of mitigating MDR and modulating EMT in GC cells [38]. Moreover, fibroblast-like morphology may be shifted to a more epithelial-like phenotype with miR-30a overexpression in DDP-resistant SGC-7901 cells, increasing DDP sensitivity and inducing a concomitant reduction in both snail and vimentin levels [39]. The restored function of miR-216a resulted in a reduction of GC liver metastatic lesions in nude mice, and was also notable for suppressing EMT via the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling pathway [40]. Furthermore, the alteration of several miRNAs, such as miR-181a-5p [41], miR-302b [42], miR-223 [43], and miR-181b [44], also displayed a variety of effects on EMT, cell proliferation, and migration in GC. A study examining GC stem cells additionally confirmed that miR-196a-5p serves as a regulator of EMT and invasion, with one of the target genes identified as SMAD family member 4 (Smad4) [45].

## MIRNAS AND THE GC TUMOR MICROENVIRONMENT

The tumor microenvironment (TME) is defined as a complex milieu within the tumor mass itself, surrounded by fibroblasts, blood vessels, immune and inflammatory cells, adipose cells, neuroendocrine cells, and the extracellular matrix [46]. Each component in the TME has a contributing role and function, as it relates to the tumor development and progression. Herein, we will summarize how miRNAs are intimately involved with the regulation of the TME for GC.

### Cancer-associated fibroblasts

Cancer-associated fibroblasts (CAFs) have emerged as one of the key participants involved in the reactive stromal generation that regulates a tumor-promoting environment in cancer [47]. We have progressed our current understanding of CAF's oncogenic functions, learning that the dysregulation of miRNAs in stromal cells has a significant influence on this important tumor milieu, likely contributing to the transformation of CAFs to promote cancer progression. For instance, miR-149 expression negatively regulates CAFs, mediating the crosstalk with tumor cells through the PGE2/interleukin-6 (IL-6) signaling [48]. Another miRNA, miR-106b, has been shown to be upregulated in CAFs, promoting cell migration and invasion by targeting the PTEN gene [49]. The low expression levels of miR-200b and miR-200c have been demonstrated to correlate with an overall poor prognosis for patients with GC [50]. A recent study reported that miR-200b downregulation was associated with the transformation of CAFs in GC. Specifically, miR-200b promoter methylation was observed in GC patients with high expression of alpha-smooth muscle actin (α-SMA), which was one of the specific markers of CAFs [51]. Functional studies further demonstrated that CAFs could promote tumor invasion by epigenetically altering miR-200b expression in GC cells [51]. MiR-141 is a tumor suppressor and a member of the miR-200 family, which was found to be downregulated in GC cells, and associated with cell proliferation in MGC-803, HGC-27, SGC-7901, and BGC-823 cell lines [52]. Recently, miR-141 was also reported to target the STAT4 gene, which is involved in the transformation of CAFs from normal fibroblasts in AGS cells [53].

### Angiogenesis/neovascularization

The process of tumor cell angiogenesis and neovascularization is a well-known mechanism by which tumor cells are able to grow, progress, and eventually develop the means for metastatic spread. The development of newly formed blood vessels by the tumor itself has been clearly established as an important mechanism for tumor cell survival, with antiangiogenic treatment strategies integrated into the current cancer treatment regimens. MiRNAs, such as miR-29c, are stimulated by the treatment with insulin-like growth factor 1 (IGF1) within the endothelium. In turn, direct targeting of miR-29c promotes tube network formation by human umbilical vein endothelial cells (HUVECs) in vitro [54]. The gene expression of vascular endothelial growth factor (VEGF) is upregulated in GC and is directly targeted by miR-29a/c, with its overexpression shown to suppress angiogenesis within the TME. MiR-29a/c delivered by microvesicles (MVs) effectively suppressed the proliferation and ring formation of HUVECs. The blood vessel density was markedly reduced by MV-delivered miR-29a/c in vivo, as clearly indicated by the downregulation of CD31, known as one of the vascular markers [55].

VEGF-C is a putative target of miR-27b, which may function as a tumor suppressor in human GC development by inducing apoptosis. It has been recently reported that the overexpression of miR-27b suppresses GC cell proliferation and inhibits the expression of VEGF-C [56]. In addition, miR-132 was reported to facilitate pathological angiogenesis by targeting p120RasGAP and activating the endothelium [57]. After delivering anti-miR-132 to the tumor endothelium of mice utilizing the nanoparticles targeting integrin αVβ3, Anand et al. found that the tumor

angiogenesis induced by a VEGF-secreting ovarian carcinoma could be ultimately blocked in vivo, which was further validated in a xenograft tumor model of breast cancer with MDA-MB-231 cells. These results support the notion that miRNA modification can regulate pathological neovascularization in vivo [57]. MiR-130a was identified in GC cell-derived exosomes, noted to have the capacity to invade HUVECs and target c-Myb in order to drive angiogenesis [58]. By harnessing the vascular-modulatory functions of miRNAs, we may be able to manipulate the antiangiogenic effect on tumor cells, possibly developing a more effective treatment approach.

Immune cells
The TME consists of a variety of immune cells, which have a dominant influence on and control of tumorigenesis, immune tolerance, and immune escape. Multiple immune cell types, including neutrophils, macrophages, dendritic cells, natural killer (NK) cells, and T and B lymphocytes, have been shown to infiltrate the tumor and actively participate in the modulation of the TME [59]. MiRNAs are recognized as dynamic regulators of immune cell functions in human cancers, and tumor-derived miRNAs can significantly influence the TME and specifically target immune cells to facilitate immune surveillance [60]. There has been a scarcity of publications that have detailed the true impact of miRNAs upon immune cells in GC.

Various levels of miRNA expression will have differential effects on NK cell and invariant NKT (iNKT) cell development. In the thymus and peripheral lymphoid organs, miR-150 negatively regulates iNKT cells [61]. Exosomal miR-451 was associated with increased Th17 cell differentiation and the redistribution of miR-451 from GC cells to infiltrating T cells [62]. MiR-155 regulates interferon γ (IFN-γ) production in NK cells by IL-12, IL-18, or CD16 stimulation [63]. In the GC TME, a novel mechanism was identified by which the downregulation of the miR-155-5p drives the switch of bone marrow mesenchymal stem cells (MSCs) to a more aggressive GC tissue-derived MSC-like phenotype. The mechanism was dependent upon the activation of nuclear factor kappa B (NF-κB) p65, revealing a potential meaningful approach for GC therapy within the TME [64].

## MIRNAS AND GC CHEMORESISTANCE
It is readily apparent that miRNA expression contributes to tumor growth by modulating the functional expression of critical genes and signaling pathways that are important for tumor cell proliferation or survival. In addition, we have discussed a number of specific miRNAs related to the regulation of GC growth, as well as their responses to chemotherapy and targeted therapy. Although the molecular mechanisms accounting for the chemoresistance in GC cells are not fully understood yet, miR-21 [65, 66], miR-99a and miR-491 [67], miR-132 [68], miR-147 [69], miR-214 [70], miR-590-5p [71], and miR-3174 [24], have been identified as contributing to the resistance to chemotherapy in GC cells. For example, miR-99a and miR-491 were identified to be upregulated in GC cell lines with resistance to the DDP treatment, the gene calpain small subunit 1 (CAPNS1) was demonstrated to be targeted by both miRNAs. Inhibiting miR-99a and miR-491, or overexpressing CAPNS1 could robustly improve the sensitivity of these resistant GC cells to DDP [67]. In addition, anti-miR-21 combined with 5-fluorouracil (5-FU) can induce the sensitivity of receptor tyrosine-protein kinase erbB-2 (HER2)-positive GC cells to the anti-HER2 antibody trastuzumab, repressing GC cell proliferation and slowing disease progression [66].

Furthermore, the sensitivity of GC cells to chemotherapy drugs can be enhanced by the overexpression of miR-7 [72], miR-23b-3p
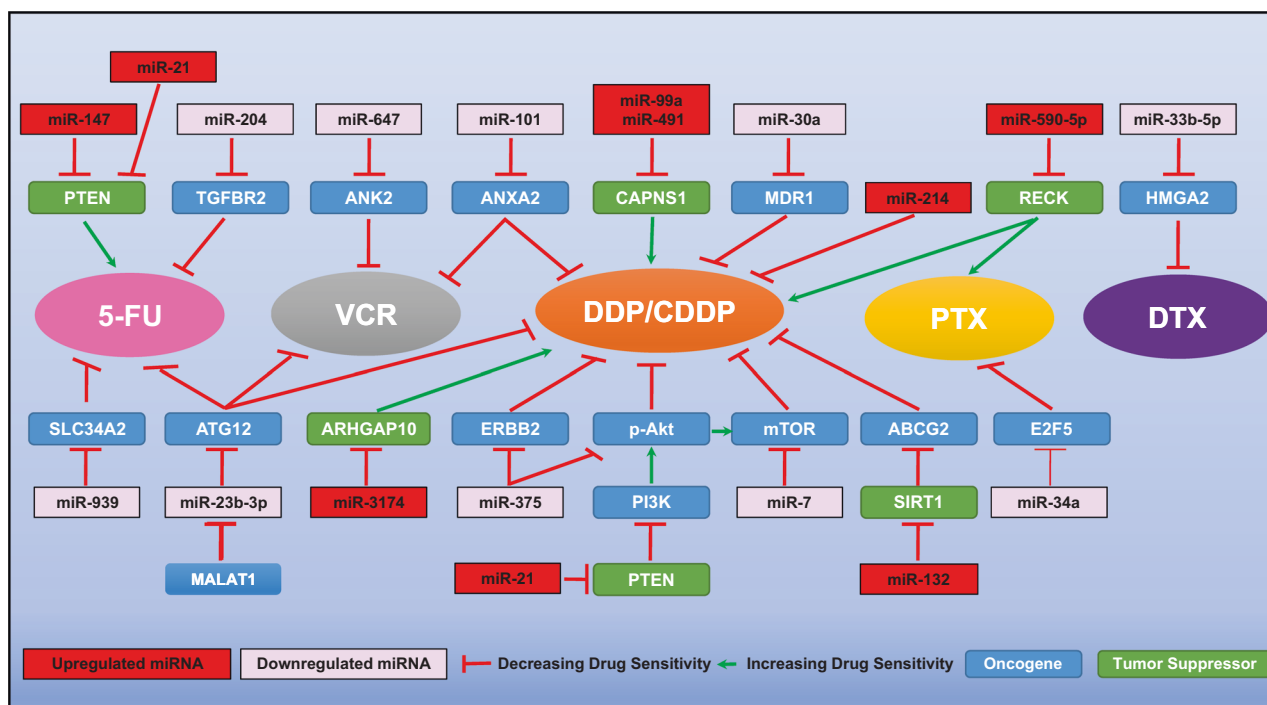


**Fig. 2  MiRNAs modulate the chemoresistance in gastric cancer cells.** 5-FU 5-fluorouracil, DTX docetaxel, DDP/CDDP cisplatin, PTX paclitaxel, VCR vincristine, ABCG2 ATP binding cassette subfamily G member 2, Akt protein kinase B, ANK2 ankyrin 2, ANXA2 annexin A2, ARHGAP10 rho GTPase activating protein 10, ATG12 autophagy-related 12, CAPNS1 calpain small subunit 1, E2F5 E2F transcription factor 5, ERBB2 erb-b2 receptor tyrosine kinase 2, HMGA2 high mobility group AT-Hook 2, MALAT1 metastasis-associated lung adenocarcinoma transcript 1, MDR1 multidrug resistance mutation 1, mTOR mammalian target of rapamycin, PI3K phosphoinositide 3-kinases, PTEN phosphatase and tensin homolog, RECK reversion-inducing cysteine-rich protein with Kazal motifs, SIRT1 sirtuin 1, SLC34A2 solute carrier family 34 member 2, TGFBR2 transforming growth factor beta receptor 2.

[73], miR-30a [26], miR-33b-5p [74], miR-34a [75], miR-101 [76], miR-204 [77], miR-375 [78], miR-647 [79], and miR-939 [80]. For example, miR-101 was identified to be downregulated in GC tissues and chemoresistant GC cells, showing an inverse correlation to the gene expression of annexin A2 (ANXA2). Forced expression of miR-101 could enhance the response of GC cells to DDP and vincristine (VCR) [76]. In addition, the GC chemoresistant cell line, SGC-7901/VCR, not only showed the resistance to VCR, but also to 5-FU and DDP. Of significance, the mechanistic studies demonstrated that a long noncoding RNA, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), was involved in the development of chemoresistance in SGC-7901/VCR cells, interacting with autophagy-related 12 (ATG12). Intriguingly, miR-23b-3p was identified as the "linker" between MALAT1 and ATG12, because it could suppress the expression of ATG12 and was also targeted by MALAT1 directly. In the in vivo studies, the drug resistance caused by MALAT1 overexpression could be compromised by the ectopic expression of miR-23b-3p [73]. Figure 2 illustrates the mechanistic involvement of these miRNAs and their putative target genes in GC chemoresistance.

## CONCLUSION

Our group has been focused on researching the central importance of the interactions of miRNAs with several human cancers for well over a decade [81–90]. We have learned quite a bit about the role of miRNAs, with much more to understand about their involvement with the TME and the host immune system. In this review, we have summarized the latest literature on this topic, focusing on GC and the related genes involved in tumor development, progression, and chemoresistance. In doing so, we expect to identify homologous target genes and the associated signaling pathways involved in the clinically aggressive behavior of GC. Although the effects of particular miRNAs on GC have been identified, the true function of miRNA remains quite enigmatic, with further research needed examining the specific impact on GC development and progression.

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## ADDITIONAL INFORMATION

**Competing interests:** The authors declare no competing interests

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