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REVIEW

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The role of microRNAs in the gastric cancer tumor microenvironment

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Abstract

Background Gastric cancer (GC) is one of the deadliest malignant tumors with unknown pathogenesis. Due to its treatment resistance, high recurrence rate, and lack of reliable early detection techniques, a majority of patients have a poor prognosis. Therefore, identifying new tumor biomarkers and therapeutic targets is essential. This review aims to provide fresh insights into enhancing the prognosis of patients with GC by summarizing the processes through which microRNAs (miRNAs) regulate the tumor microenvironment (TME) and highlighting their critical role in the TME.

Main text A comprehensive literature review was conducted by focusing on the interactions among tumor cells, extracellular matrix, blood vessels, cancer-associated fibroblasts, and immune cells within the GC TME. The role of noncoding RNAs, known as miRNAs, in modulating the TME through various signaling pathways, cytokines, growth factors, and exosomes was specifically examined. Tumor formation, metastasis, and therapy in GC are significantly influenced by interactions within the TME. miRNAs regulate tumor progression by modulating these interactions through multiple signaling pathways, cytokines, growth factors, and exosomes. Dysregulation of miRNAs affects critical cellular processes such as cell proliferation, differentiation, angiogenesis, metastasis, and treatment resistance, contributing to the pathogenesis of GC.

Conclusions miRNAs play a crucial role in the regulation of the GC TME, influencing tumor progression and patient prognosis. By understanding the mechanisms through which miRNAs control the TME, potential biomarkers and therapeutic targets can be identified to improve the prognosis of patients with GC.

Keywords MicroRNA, Tumor microenvironment, Gastric cancer, Angiogenesis, Exosomes, Immune cells

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Background

Gastric cancer (GC) is the fourth leading cause of cancer-related deaths worldwide and the fifth most prevalent disease globally [1]. This disease is often diagnosed at an advanced stage with metastases, as there are typically no early and accurate diagnostic methods or specific clinical symptoms. As a result, the 5-year survival rate for GC is only approximately 32% [2]. A noticeable process of connective tissue proliferation is present during solid tumor development, including that observed in GC. This process is intimately associated with immune cells, along with other types of mesenchymal stromal cells in the tumor microenvironment (TME) [3]. The TME includes fibroblasts, the extracellular matrix (ECM), blood vessels, endothelial cells, immune cells, and non-cellular elements such as cytokines and exosomes. Thus, the TME plays a significant role in cancer progression [4, 5] (Fig. 1). In this context, the external and internal environments in which the tumor cells are situated considerably affect the onset, development, and metastasis of the tumor, and they are both interdependent and competitive with each other [6]. Growth factors in the TME enhance the viability of tumor cells, reducing the uptake of chemotherapeutic agents or inactivating them. Additionally, the TME produces immunosuppressive factors, thereby promoting resistance to immunotherapy [7]. Therefore, understanding how the GC TME is regulated and applying these insights to clinical treatment is crucial to enhancing the poor prognosis of patients with GC.

In 1993, Ambros et al. discovered the first microRNA (miRNA) in nematodes. This discovery revealed an important part of the noncoding genome that acts as a critical player in post-transcriptional gene regulation [8]. miRNA dysregulation has been identified in several human diseases, including heart disease, diabetes, cancer, and schizophrenia [9]. Dysregulation of miRNA expression levels in cancer has been associated with a range of biological features of human cancer development, including important roles in enhancing tumor cell proliferation, apoptosis, migration, epithelial-mesenchymal transition (EMT), metastasis, angiogenesis, autophagy, and interactions between malignant cells and the TME [10–12]. miRNA expression profiles in normal cells are very different from those in cancer tissues, and different tumor

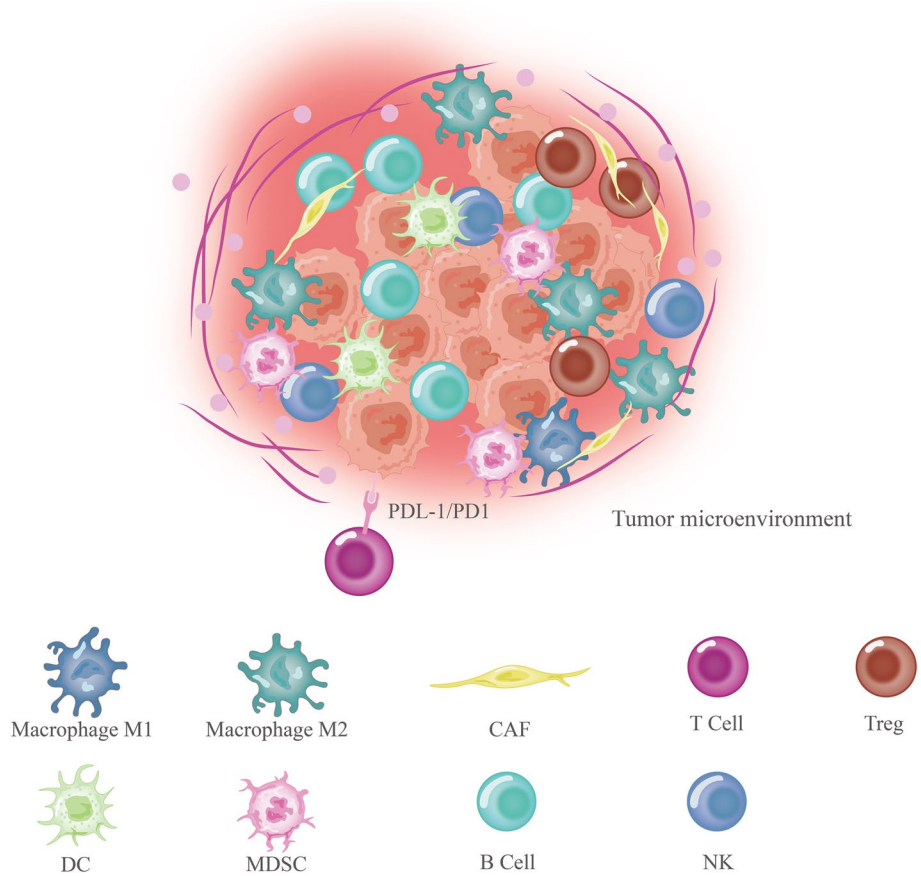

Fig. 1 TME composition in gastric cancer. TME: Tumor microenvironment

types and stages, including tumor development, progression, and metastasis, can be identified based on the expression of specific miRNAs [13, 14]. The regulation of miRNA expression has been associated with the suppression of oncogenic miRNAs and the replacement of tumor suppressor miRNAs [15]. Thus, miRNAs are a particularly important area of cancer research, with relevance to cancer prognosis, pathogenesis, diagnosis, and treatment, and are considered the perfect tool for improving cancer therapy [16].

Dysregulated miRNAs promote cancer-associated fibroblast (CAF) activation, inhibit myeloid-derived suppressor cells (MDSCs), inhibit T-cell differentiation, and facilitate angiogenesis, ultimately remodeling the TME [17]. Particularly, tumor cell-derived miRNAs are strongly associated with the production of an immunosuppressive TME and the loss of effector cells and reduced tumor immunogenicity; moreover, they are key determinants of cancer immune outcomes [18, 19]. Additionally, cancer cells secrete exosomes containing tumor suppressor miRNAs that propagate altered sets of miRNAs to different cellular compartments within the TME [20]. miRNAs may be key to immune-mediated tumor clearance, as miRNAs subtly repress genes and preferentially inhibit dose-sensitive targets [21].

Recently, miRNAs have been considered important potential biomarkers for gastric pathology, as they are frequently dysregulated in gastric tissues in preneoplastic lesions such as *Helicobacter pylori* infection, chronic gastritis, atrophic gastritis, and intestinal metaplasia, as well as in early-stage dysplasia and invasive cancers [22]. Meanwhile, increasing evidence indicates that miRNAs can be considered novel biomarkers; notably, many researchers have analyzed the miRNA profiles in serum and tissue samples from GC to assess their prognostic and diagnostic potential [23, 24] (Table 1). As previously described, miRNAs regulate mesenchymal interactions, immune invasion, and tumor angiogenesis, leading to malignant phenotypes of GC such as tumor growth, metastasis, angiogenesis, and drug resistance [25]. GC cells release extracellular vesicles (EVs) that are enriched in miR-1290. This miRNA enhances the inhibitory impact of GC cells on T-cell activation by targeting grainyhead-like 2 and activating the zinc finger E-box binding homeobox 1/programmed cell death ligand 1 (PD-L1) axis, facilitating GC cell immunological escape [26]. Drug resistance is one of the major challenges facing GC treatment, and manipulating miRNA expression has been shown to alleviate this therapeutic hurdle [27, 28]. Thus, miRNA-targeted GC therapies have great potential to enhance immunotherapy compared to existing therapies [29]. The investigation of microRNAs in GC have entered the clinical settings (Table 2).

A comprehensive understanding of the biological mechanisms facilitated by miRNAs in the TME of GC may, therefore, offer valuable perspectives for the identification of antitumor drugs and the advancement of targeted cancer treatments in the future. This review emphasizes the pivotal role that miRNAs play in the TME and focuses on how control of the TME by miRNAs influences GC development. Increased understanding of these processes may assist in the development of new therapies for patients with GC and the identification of new biomarkers that can improve management and follow-up strategies for patients with GC.

Main text

miRNAs and *H. pylori*/Epstein–Barr virus in the GC TME

H. pylori infection is one of the most significant risk factors for GC [66]. Immune monitoring of the gastric mucosa may be impeded by *H. pylori*-induced activation of signal transducer and activator of transcription 1 (STAT1) and PD-L1 expression, allowing malignant lesions to develop into GC [67]. The *H. pylori* virulence factor CagA affects multiple types of miRNAs in GC cells [68]. CagA inhibits proliferative and antitumor effects of CD8 + T cells and increases PD-L1 levels in GC cell-derived exosomes via suppressing miRNA-34a and P53 [69]. Moreover, CagA promotes miR-543 overexpression, which inhibits autophagy by targeting sirtuin 1, subsequently inducing EMT and triggering cell invasion and migration [70]. The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway is activated by *H. pylori* infection, which results in the TME secreting T regulatory cells (Tregs), suppressing tumor cell death, and enhancing the TME immunosuppressive state. This pathway activation aids in immune evasion, which in turn facilitates the development of tumors [71, 72]. On the contrary, *H. pylori* induces miR-223, which downregulates the expression of interleukin (IL)-6, IL-8, IL-1β, and tumor necrosis factor (TNF)-α and inhibits macrophage activation [73].

T helper 1 (Th1) and 17 (Th17) cell differentiation are influenced by miR-155 and contribute to immunity against *H. pylori* infection, along with infection-associated immunopathology [74]. However, Tsai et al. [75] noted that GC associated with *H. pylori* significantly increased miR-4286 and miR-18a-3p (5.73-fold and 6.02-fold, respectively). Moreover, invasion and miR-18a-3p, as well as lymph node metastases, tumor size, and tumor stage and miR-4286, have been shown to be significantly associated. Overexpression of miRNA-4286 and miR-18a-3p also inhibits benzodiazepine receptor-associated protein 1 expression while promoting the motility and proliferation of cancer cells. Furthermore, *H.*

Table 1 miRNAs that potentially represent GC biomarkers

Symbol	Materials	Function	Biomarker	sensitivity	specificity	Reference
miR-21	Serum and PBMCs	Promote GC proliferation and invasion	Diagnostic and Prognostic	88.4% (Serum) 79.6% (PBMCs)	60.5% (Serum) 55.9% (PBMCs)	[30]
miR-21 and miR-222	Plasma	Regulate apoptosis, proliferation, and migration	Diagnostic	86.7% (miR-21) 62.5% (miR-222)	72.2% (miR-21) 56.2% (miR-222)	[31]
miR-22	Tissues	Suppress GC cell proliferation and invasion	Prognostic	-	-	[32]
miRNA-22-3p	Plasma	Inhibit GC growth and metastasis	Prognostic	-	-	[33]
miR-200c	Blood	Regulate invasiveness and migration	Diagnostic and prognostic	65.4%	100%	[34]
miR-28-5p	Cell lines	Inhibit GC migration and invasion	Prognostic	-	-	[35]
miR-29c	Tissues	Inhibit GC proliferation, adhesion, invasion, and migration	Diagnostic	-	-	[36]
miR-19b miR-106a	Serum Exosomal	Related to GC lymphatic metastasis	Diagnostic	95%	90%	[37]
miR-21 miR-106a	Gastric Juice	Increase GC proliferation, migration, and invasion	Diagnostic	85.7% (miR-21) 73.8% (miR-106a)	97.8% (miR-21) 89.3% (miR-106a)	[38]
miR-24 and miR-101	Tissues	Promote GC occurrence, development, infiltration and metastasis	Diagnostic and Prognostic	-	-	[39]
miR-124-3p	Tissues and cell lines	Suppressed GC proliferation and induce apoptosis	Prognostic	-	-	[40]
miR-129–1-3p and miR-129–2-3p	Gastric juice	GC suppressor activity	Diagnostic	68.7%	71.9%	[41]
miR-133a	Gastric juice	Inhibit GC proliferation, migration and invasion	Diagnostic	85.9%	84.8%	[42]
miR-140-5p	Tissues	Suppress GC proliferation and invasion	Prognostic	-	-	[43]
miR-181d	Tissues	Promote GC proliferation, migration and invasion	Prognostic	-	-	[44]
miR-187	Tissues	Inhibit GC proliferation and induce cell cycle arrest at the G0/G1 phase	Prognostic	-	-	[45]
miR-196a/b	Plasma	OncomiRs	Monitoring, Diagnostic and Prognostic	69.5% (miR-196a) 62.2% (miR-196b)	97.6% (miR-196a) 96.1% (miR-196b)	[46]
miR-196a	Plasma	Carcinogenesis	Diagnostic	100.00%	75.00%	[47]
miR-203	Serum	Reduce GC EMT phenomena and tumor aggressiveness	Prognostic and Predict metastasis	-	-	[48]
miR-212	Serum	Suppress GC proliferation and induce apoptosis	Prognostic	95.1%	78.7%	[49]
miR-302b	Tissues	Suppressed GC tumorigenesis and metastasis	Prognostic	-	-	[50]
miR-345	Tissues and cell lines	Inhibit GC migration, stem-like cell phenotype, and EMT	Prognostic	-	-	[51]

Table 1 (continued)

Symbol	Materials	Function	Biomarker	sensitivity	specificity	Reference
miR-379	Tissues and cell lines	Inhibit GC migration, invasion and EMT	Prognostic	-	-	[52]
miR-421	Tissues	Promote GC metastasis, inhibit apoptosis, and induce cisplatin resistance	Prognostic	-	-	[53]
miR-421	Plasma		Diagnostic	66.29%	95.56%	[54]
miR-421	Gastric juice	Carcinogenesis	Diagnostic	71.4%	71.7%	[55]
miR-484	Tissues	Inhibit GC proliferation, migration, and invasion	Prognostic	-	-	[56]
miR-520a-3p	Tissues and cells	Inhibit GC proliferation, migration and invasion	Prognostic	-	-	[57]
miR-208a	Tissues	Promote GC proliferation and invasion	Prognostic	-	-	[58]
miR-552	Tissues	Promote GC proliferation, migration, and invasion	Prognostic	-	-	[59]
miR-585	Tissues and cell lines	Inhibit GC growth and migration	Monitoring	-	-	[60]
miR-601	Tissues and cells	Promote GC proliferation, migration, and invasion	Prognostic	-	-	[61]
miR-1225-5p	Tissues	Inhibit GC proliferation, colony formation, migration and invasion	Diagnostic, Prognostic	-	-	[62]
miR-1236-3p	Tissues	Suppress GC migration and invasion	Diagnostic, Prognostic, Monitoring, Recurrences	73.68%	60.53%	[63]
miR-718	Tissues	Promote GC proliferation and invasion	Prognostic	-	-	[64]
miR-4257, miR-6785-5p, miR187-5p, and miR-5739	Serum		Diagnostic	98.3% (discovery set) 99.6% (validation set)	97.7% (discovery set) 95.3% (validation set)	[65]

Abbreviations: *miRNAs* MicroRNAs, *GC* Gastric cancer

pylori infection induces IL-6, which affects STAT3 activity, inhibits miR-520d-5p expression, and activates the STAT3 and Janus kinase (JAK)/STAT pathway, leading to the proliferation of GC cells [76].

In *H. pylori*-infected T cells along with primary macrophages, miR-155 expression is dependent on forkhead box protein 3 (FOX3), indicating a potential functional relationship between the host immune response and miR-155 [77]. Huang et al. [78] indicated that miR-134 directly targets forkhead box protein M1 (FOXM1), and FOXM1 knockdown prevents the EMT induced by *H. pylori* CagA + /P + . Therefore, by targeting FOXM1, miR-134 suppresses invasion, proliferation, and EMT of SGC-7901 cells and may be protective against the GC process caused by *H. pylori* CagA + /P + (Fig. 2).

Besides *H. pylori*, Epstein–Barr virus (EBV) is also a causative factor for GC [79]. EBV has been shown to be the first virus to encode its own miRNA. Immune escape is facilitated by EBV-encoded gene products, it-mediated epigenetic and structural variations, and miRNAs, which all assist in malignant transformation [80]. Furthermore, the EBV-miR-BART cluster, including miRBART-2, -4, -5, -18, and -22, is expressed in GC and linked to a poor prognosis [81]. Moreover, simultaneous infection with EBV also hinders the host response to *H. pylori*. Additionally, EBV synergism may strengthen the oncogenic potential of *H. pylori* CagA [82]. Notably, EMT-inducing transcription factors are induced in EBV-related GC upon downregulation of miR-200b and miR-200a [83]. In EBV-infected GC cells, miR-34a downregulation causes

Table 2 Summary of microRNAs in GC of clinical trials

MicroRNA(s)	Source	Purpose	Enrolled	ClinicalTrials.gov identifier	Status	Organizing Location
miR-20a, miR-21, miR-106b, miR-199a, miR-223	Blood	Diagnostic	280	NCT05901376	Recruiting	Thailand
micro RNAs	Blood	Diagnostic	6862	NCT04329299	Completed	Singapore
miR-215-5p	Tumor Tissues	Predictive	35	NCT01178944	Completed	United States
micro RNAs	Serum	Diagnostic	809	NCT06342427	Completed	United States, Japan
micro RNAs	Blood	Predictive	150	NCT06490055	Recruiting	Japan
micro RNAs	Plasma	Diagnostic	150	NCT06277986	Recruiting	China
micro RNAs	Blood	Predictive	150	NCT06490159	Recruiting	Japan
	Tissue and Blood	Predictive	800	NCT03253107	Recruiting	Korea
micro RNAs	Serum	-	100	NCT05544396	Recruiting	Taiwan
micro RNAs	Blood	Diagnostic	498	NCT05224596	-	China
micro RNAs	Blood	Diagnostic	2430	NCT05431621	Completed	China
micro RNAs	Blood	Diagnostic	15000	NCT05633342	Recruiting	Singapore

Abbreviation: *GC* Gastric cancer

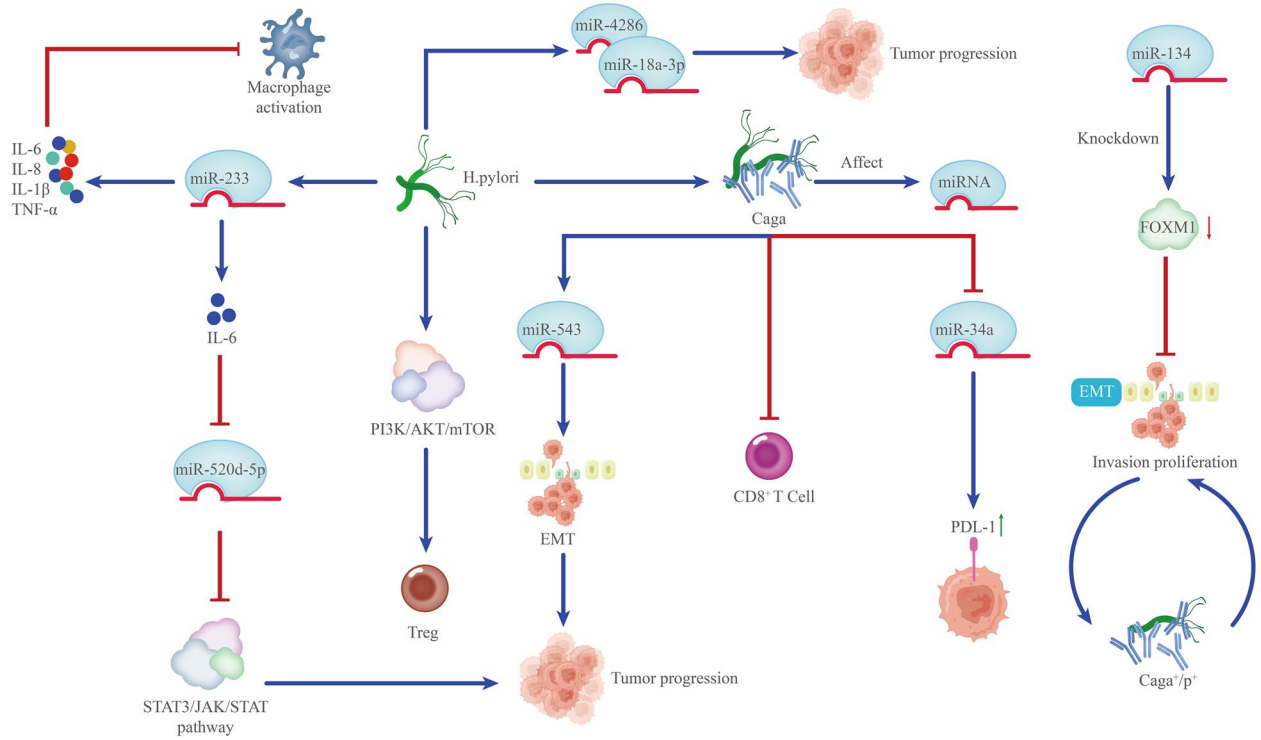

Fig. 2 miRNAs and *Helicobacter pylori* in the gastric cancer TME. miRNAs: MicroRNAs, TME: Tumor microenvironment

NADPH oxidase 2 upregulation, which promotes reactive oxygen species (ROS) generation and improves cell survival [84]. Notably, Choi et al. [85] determined that EBV-infected GC cells secrete miR-BART15-3p via exosomes that target the apoptosis inhibitor BRUCE. Subsequently, polybromo-1 and FOXP1 separately suppress EBV-miR-BART17-3p along with EBV-miR-BART11 and increase PD-L1 transcription, thereby promoting tumor immune escape [86]. Low levels of viral antigen expression help EBV evade the host immune response. Additionally, viral miRNAs directly inhibit the release of the pro-inflammatory cytokine IL-12, thereby modulating the inflammatory response of T cells [87]. Moreover, viral miRNA-BART6-5p targets host cell Dicer and impairs

host cell miRNA expression, thus helping EBV evade the host immune response and achieve chronic infection [88].

miRNAs regulate tumor angiogenesis in the GC TME

Angiogenesis plays a crucial role in cancer progression, as it is associated with immunosuppression and is essential for tumor growth, invasion, and metastasis [89, 90]. Based on the downstream targets of miRNAs, the expression of the most potent regulators of angiogenesis in different tumors has been extensively investigated, and a variety of miRNAs have been found to target angiogenic factors. Additionally to being a significant angiogenic agent, the vascular endothelial growth factor (VEGF) functions as an immunomodulator of the TME, promoting tumor-associated macrophages (TAMs) and Treg activation and preventing antigen presentation [91]. In addition to VEGF, phosphatase and tensin homolog (PTEN), mitogen-activated protein kinase (MAPK), and PI3K/AKT/mTOR are the major signaling pathways through which vascular-regulated miRNAs affect GC, and they are important mechanisms through which aberrant miRNAs regulate the development and progression of GC [92, 93].

Wu et al. [94] observed that miR-616-3p overexpression in GC triggers the downstream AKT/mTOR signaling pathway, targets PTEN, and facilitates EMT and angiogenesis [95]. Furthermore, miR-21 targets the tumor suppressor gene *RECK*, which is linked to tumor metastasis and angiogenesis, to cause cancer [96]. MiR-132 has been demonstrated to activate endothelial cells and targets p120RasGAP to induce pathological angiogenesis [97]. Additionally, exosomes, generated from GC cells that carried miR-23a, induced angiogenesis in a co-culture system by suppressing PTEN [98]. When GC cells overexpressed miR-574-3p and miR-210, VEGF and hypoxia-inducible factor 1-alpha (HIF-1α) were upregulated, leading to increased GC cell proliferation, migration, and invasion along with angiogenesis [99, 100]. Subsequently, reduction of invasion, migration, angiogenesis, and EMT resulting from overexpression of paired box 8 on GC cells is replicated by ectopic expression of miR-612 [101].

Meanwhile, miR-574-5p inhibits the expression of protein tyrosine phosphatase non-receptor type 3 and increases phosphorylation of p44/42 MAPKs in GC cells, which promotes angiogenesis [102]. Through its modulation of cancer stem cells (CSCs) and the EMT, the miR-29c-VEGFA/VEGFR2/extracellular signal-regulated kinases (ERK) signaling axis serves as a significant player in the course of GC metastatic disease, making it a prospective acts for GC clinical interventions [103].

With the rapid development of research on miRNAs, their function in tumor suppression through their anti-angiogenic function offers multifaceted therapeutic potential for these molecules. For example, miR-26a/b can directly act on *VEGFA* in GC, and its overexpression can directly suppress VEGF expression and reduce cell proliferation and angiogenesis, thereby inhibiting GC growth in mice [104]. Besides facilitating GC cell proliferation and migration, a reduction in miR-1 may also trigger pro-angiogenic signaling and encourage endothelial cell migration and proliferation [95]. Moreover, through suppression of *VEGFA* and fibroblast growth factor 1 expression, miR-205-5p inhibits angiogenesis in GC [105].

Furthermore, the PI3K/AKT signaling pathway mediates invasion, metastasis, angiogenesis, and lymphangiogenesis in GC after the downregulation of miR-30b-3p [106]. By suppressing ETS1 expression through a binding site in the 3′-UTR, miR-145 and miR-506 inhibit GC cell invasion, metastasis, and angiogenesis [107, 108]. Through the STAT3/*VEGFA* pathway, downregulation of miR-874 facilitates tumor angiogenesis in GC tissues [109]. In GC, miR-590 can concurrently modulate neuropilin 1 and VEGFR1/2. Furthermore, miR-590 overexpression can suppress GC cell migration, invasion, proliferation, and migration, as well as the release of D-MVA both in vivo and in vitro [110]. Similarly, miR-7 targets Raf-1 to suppress angiogenesis and tumorigenesis in GC cells [111].

Zhang et al. [112] confirmed the anti-angiogenic action of miR-218 in GC and demonstrated that tumor angiogenesis inhibition might be achieved therapeutically by administering miR-218. GC with low expression of miR-200C was markedly enriched for angiogenesis, hypoxia, TGF-β signaling genomes, and EMT, all of which contribute to tumor development and metastasis [113]. Interestingly, miR-29a-low GC is enriched for genes correlated with cell apoptosis, proliferation, angiogenesis, and metastasis; it is linked to less anticancer immune cell infiltration and immune-related scores [114] (Fig. 3).

Peritoneal dissemination is the main cause of patient mortality and the most frequent reason for tumor progression following GC surgery. Notably, GC development and peritoneal dissemination are significantly influenced by angiogenesis [115], and increased expression of VEGF has been found to promote the production of malignant ascites [116]. Additionally, the expression pattern of miRNAs in peritoneal exosomes serves as a valuable diagnostic tool for peritoneal metastasis treatment, reflecting the tumor load within the abdominal cavity [117]. Transitioning from these observations, research into the regulatory mechanisms of miRNAs in tumor angiogenesis has made significant strides. Despite remaining obstacles, these rapidly evolving findings will make way for the future application of miRNAs as predictive biomarkers

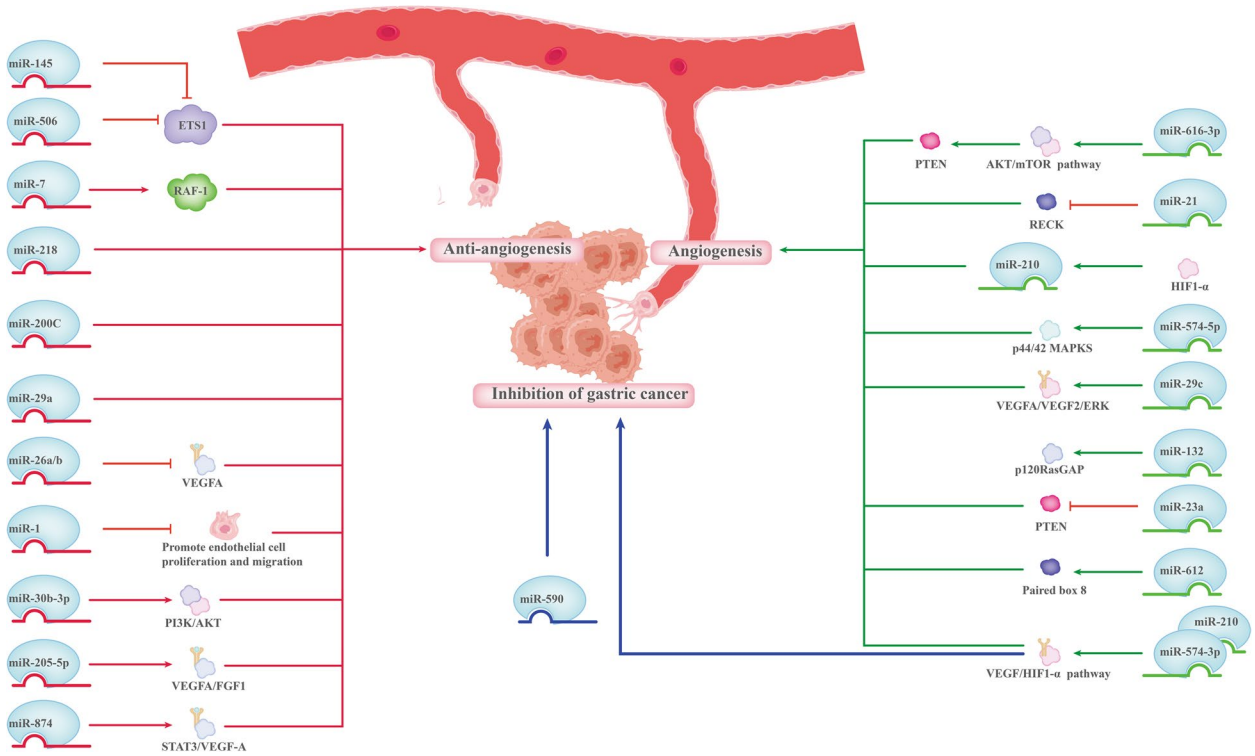

Fig. 3 miRNAs regulate angiogenesis in the development of gastric cancer. miRNAs: MicroRNAs

for anti-angiogenic therapy and miRNA-based antitumor angiogenesis strategies.

miRNAs regulate CAFs in the GC TME

As the major cells in the TME of solid tumors, fibroblasts are controlled by a multitude of factors released by immune or tumor cells [118]. CAFs express a wide range of pro-inflammatory molecules, including chemokines, interleukins, and components of the ECM, which eventually stimulate the growth of tumors by regulating the inflammation associated with the tumor or directing intercellular communication [119]. In the TME, miRNAs are implicated in the whole process of CAF generation and their functional execution, promoting cancer cell proliferation, drug resistance, and immunosuppression via secreting ECM proteins, inflammatory ligands, and growth factors [120].

The high levels of miR-27a observed in GC cell exosomes stimulate the metastasis, motility, and proliferation of cancer cells both in vitro and in vivo, as well as the reprogramming of fibroblasts into CAFs [121]. Meanwhile, another study reported that transformation of CAFs in GC was linked to miR-200b downregulation. Particularly, methylation of the miR-200b promoter was detected in GC cases exhibiting elevated expression of the CAF-specific marker α-smooth muscle actin [122]. However, in contrast to normal fibroblasts, the expression of miR-224-3p was lower in CAFs from patients with squamous GC, and miR-224-3p mimics were found to attenuate CAF migration and invasion [123]. miR-214 in CAFs directly modulates fibroblast growth factor 9 expression, which facilitates cell invasion and GC migration in vitro [124]. Likewise, miR-496 upregulates IL-33, which amplifies CAFs' tumor-promoting properties by improving GC cell proliferation, EMT, migration, and invasion [125].

It has been confirmed that CAFs elevate miR-106b levels, targeting PTEN to facilitate cell invasion and migration [126]. Zhang et al. [127] demonstrated that the heterogeneous nuclear ribonucleoprotein A1 axis and ubiquitin-specific protease 7 are activated by paclitaxel and cisplatin, which makes it easier for miR-522 to be secreted from CAFs through the de-ubiquitination pathway. Furthermore, miR-522 targets arachidonic acid lipoxygenase 15, which also prevents ROS accumulation. This suppresses ferroptosis in GC cells, causing GC cells to become resistant to chemotherapy [127]. Moreover, by targeting the STAT4/Wnt/β-catenin axis, miR-141-3p suppresses normal fibroblasts from transforming into CAFs, which in turn inhibits GC invasion and migration [128] (Fig. 4). Overall, the activation and creation of CAFs are intimately linked to miRNA dysregulation,

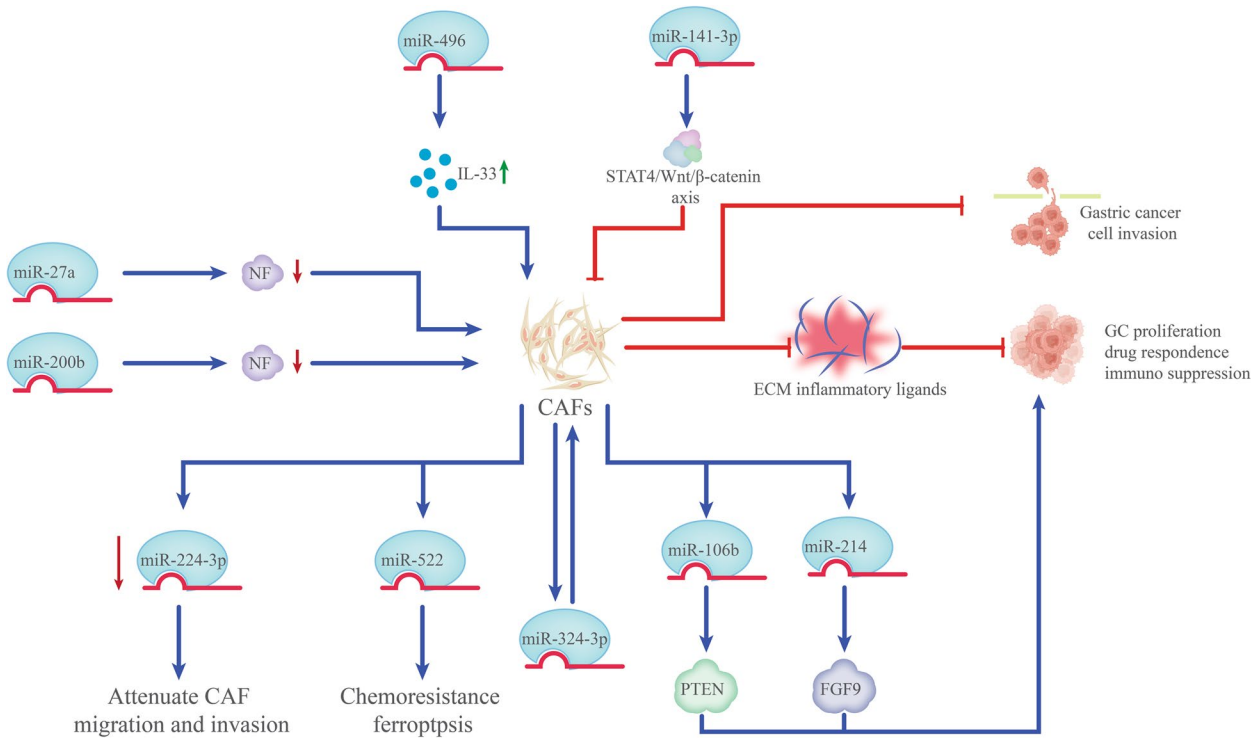

Fig. 4 miRNAs regulate CAFs in the development of gastric cancer. miRNAs: MicroRNAs

which plays a role in both executive function and CAF generation. These results offer fresh perspectives on the relationship between GC cells and CAFs.

miRNAs regulate immunosuppressive cells in the GC TME

The TME consists of various stromal cells such as macrophages, T cells, MDSCs, Tregs, and the ECM; furthermore, blood vessels, lymphatic vessels, cytokines, mediators, and other non-cellular components are vital in defending the human body against pathogen invasion. These cells also impact GC through the modulation of immune responses and the elimination of mutated or damaged cells [129, 130]. miRNAs are implicated in the function and maintenance of Tregs and macrophage polarization, maintaining homeostasis in vivo under physiological conditions and driving immune tolerance or immunosuppression under pathological conditions [131].

Macrophages are a crucial component of both the innate and adaptive immune systems, playing key roles in pathogen defense and the regulation of body homeostasis [132]. The polarization of macrophages is influenced by the PI3K/AKT and JAK/STAT pathways, along with critical regulators such as the STAT family, peroxisome proliferation-activated receptor-g (PPARg), and interferon modulator [133, 134]. This process can lead to the development of TAMs in response to chemokines, cytokines, and other growth factors secreted by tumor cells, as well as tumor-associated conditions. TAMs may adopt the M1 phenotype, which exhibits antitumor activity, or the M2 phenotype, which supports tumor growth [135]. Predominantly, TAMs align with the M2 phenotype and are more likely to promote tumor progression [136]. In GC tissues and ascites, TAMs are abundant and may enhance GC cell migration and invasion through the secretion of EVs [137]. Moreover, dysregulation of miRNAs in tumors facilitates the shift of macrophage polarization from M1 to M2, adversely impacting TAM phenotypes and suppressing the immune response [138]. The involvement of TAMs in GC underscores their complex role, suggesting that miRNA-based reprogramming of TAM polarization could advance tumor immunotherapy.

According to Yun et al. [139], downregulating miR-30c under hypoxic environments decreased mTOR and glycolysis activity in TAMs in GC and further suppressed M1 macrophage differentiation and antitumor effects. With PTEN and IFN-γ/STAT1, miR-21 modulates TAMs, enhancing tumor cell motility and M2 polarization while lowering the expression of PD-L1 and M1 polarization to promote cancer progression [140]. Interestingly, TAMs deficient in miR-21 had an inflammatory gene signature, and antagonism of miR-21 increased the level of granzyme B, which enhanced the cytotoxicity of CD8 + T cells in immune TME [141].

Additionally, exosomes derived from M2 macrophages may transfer miR-487a into GC cells, possibly facilitating GC progression through the downregulation of T-cell intracellular antigen [142]. Exosomes derived from M2 macrophages produce miR-588, which targets cylindromatosis and enhances resistance to cisplatin in GC cells [143]. Moreover, exosome miR-21 translocates directly from TAMs to GC cells and modulates GC resistance to cisplatin by targeting PTEN, suppressing apoptosis, and activating the PI3K/AKT signaling pathway [144]. These studies highlight the importance of miRNA regulation of macrophages through key signaling pathways.

Compared with other intra-abdominal tumors, GC is more prone to peritoneal metastases, and the peritoneal immune microenvironment is critical for GC progression [145, 146]. Notably, TAM in malignant ascites of GC showed a significant M2-like phenotype, which promotes peritoneal metastasis of GC [147, 148]. Microarray analysis revealed a significant connection in GC tissue between the expression of miR-210 and CD204 + M2-like TAM infiltration. TNF-α, released by CD204 + M2-like TAMs, upregulates miR-210 through NF-κB/HIF-1α signaling to facilitate GC progression [149]. In summary, these candidate preclinical and clinical miRNAs underscore their roles as TME immune modulators and their therapeutic potential. A deeper understanding of how different miRNAs influence the M1/M2 balance could aid in developing targeted therapies to re-educate macrophages toward the M1 phenotype.

After antigenic stimulation, naive CD4 + T cells differentiate into multiple effector Th subpopulations with distinct phenotypes, such as Th1, Th2, Treg, and IL-17-producing Th17 [150]. Certain miRNAs have been shown to regulate T-cell differentiation. For example, the differentiation of Treg/Th17 and Th1 cells is inhibited by miR-23 and -27, whereas miR-24 facilitates their differentiation, creating an immunosuppressive microenvironment conducive to GC progression and metastasis [151]. Furthermore, the miR-192-5p/Rb1/NF-κBp65 signaling axis stimulates Treg differentiation by modulating IL-10 production in GC while also facilitating EMT in tumor cells [152]. Importantly, exosomes promote the differentiation of primary neoplastic Treg cells at the expense of antitumor Th1/Th17 differentiation, suggesting that tumor miRNAs can orchestrate immune evasion through multiple simultaneous mechanisms [153, 154]. Furthermore, the secretion of exosomal miR-451, which escalates under low-glycemic conditions and is subsequently transferred to T cells, supports the differentiation of T cells into Th17 cells by diminishing AMP-activated protein kinase and enhancing mTOR activity, marking a potential indicator of poor prognosis [155]. Additionally, a hypoxic TME reduces miR-34a expression, resulting in elevated lactate levels in GC tumor-infiltrating lymphocytes and a reduction in Th1 cells and cytotoxic T lymphocytes (CTLs), thereby compromising the immune efficacy of GCs [156].

Moreover, MDSCs, a heterogeneous group of myeloid-derived cells, facilitate tumor invasion and metastasis through diverse mechanisms, with tumor miRNAs directly governing the recruitment and functionality of MDSCs [157]. Notably, MDSCs characterized by the expression of the myeloid differentiation factor schlafen4 +, a regulator of myeloid differentiation, have been identified in GC, particularly in preneoplastic lesions infected with *H. pylori* [158]. miR-130b is increased in Schlafen4 + GC cells and promotes gastric epithelial cell proliferation, which is essential for MDSCs to suppress T-cell functions [159]. Exosomes secreted by GC deliver miR-107 to host MDSCs and induce their amplification and activation by targeting *DICER1* and *PTEN* genes, thus providing new cancer therapeutic targets for GC [160]. Furthermore, miR-200C reduces PTEN and friend of Gata 2 expression, induces the PI3K/Akt cascade, promotes MDSCs amplification, and suppresses immune response in TME [161] (Fig. 5).

The miRNAs can also directly affect immunosuppressive signaling, thereby altering the TME. Meanwhile, miR-4510 inhibits GC cell metastasis by altering immunosuppressive signals in the TME through the downregulation of glypican-3 [162]. miR-148b-5p deficiency results in immunological tolerance and GC development via the CSF1 and miR-148b-5p/ATPIF1/TNFa + IL6 axis [163].

These studies suggest that many miRNAs play essential roles in regulating TME-mediated immunosuppressive mechanisms. However, this area of research still needs to be further explored.

miRNAs modulate immunoreactive cells in the TME of GC

T cells are vital to maintaining health and preventing disease and are divided into two main subpopulations: CD4 + and CD8 + T-cell subpopulations [164]. Longer survival from cancer is linked to infiltration of CD8 + T cells; however, low immunogenicity of tumor cells in the TME inhibits T lymphocyte immunological activity, which reduces their antitumor capacity [165]. Post-transcriptional gene regulation via miRNAs has emerged as a major control mechanism for a variety of biological processes, including T-cell development and function [166]. Given that T cells can perform both pro-inflammatory and pro-absorptive tasks, identification and characterization of miRNAs associated with T-cell function will reveal miRNA-mediated mechanisms as therapeutic targets for immunotherapy against a wide range of diseases with inflammatory and immunosuppressive environments [167].

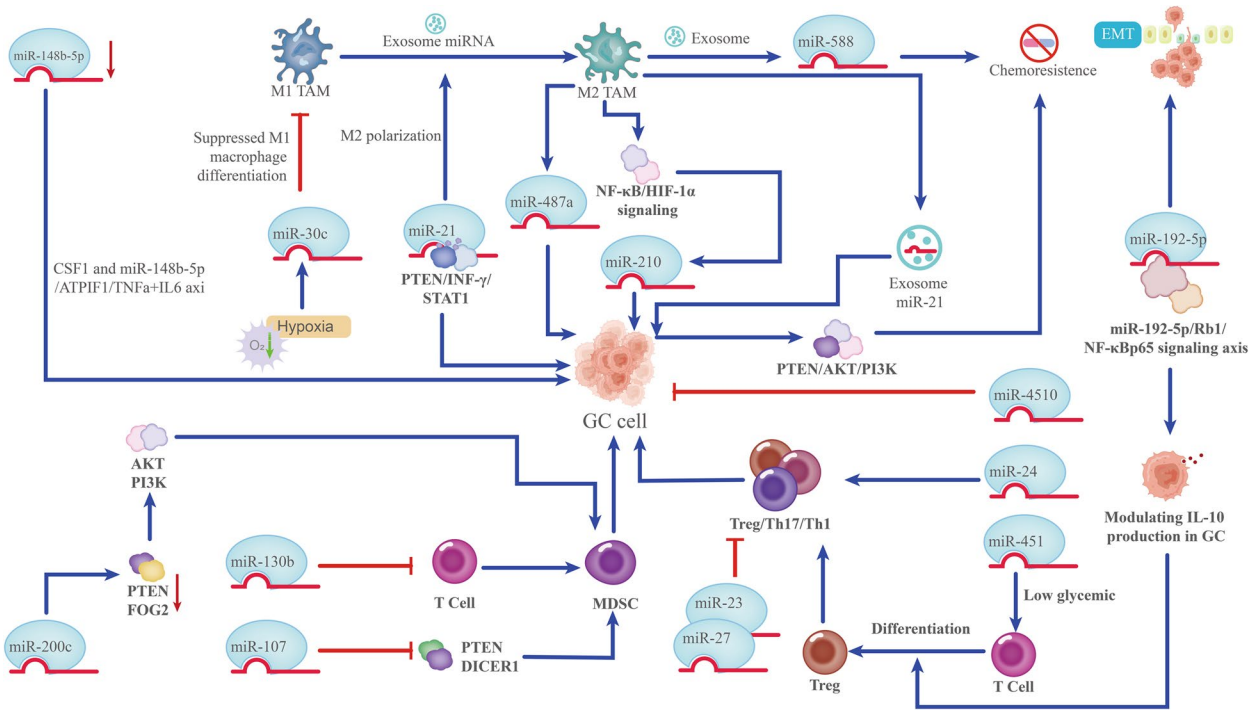

Fig. 5 miRNAs regulate immunosuppressive cells in the development of gastric cancer. miRNAs: MicroRNAs, CAFs: Cancer-associated fibroblasts

miRNAs regulate the expression of immune checkpoint ligands and protect tumors from T-cell-mediated lysis [168]. For instance, miR-105-5p, serving as a key player in the post-transcriptional suppression of PD-L1 in GC, prevents immunological escape resulting from upregulation of PD-L1 in cancer cells [169]. Furthermore, miR-424 has been identified as a potential inhibitor of the PD-L1/PD-1 pathway, and restoration of miR-424 expression reverses chemotherapy resistance [170].

miR-138 mainly modulates the immune system by interacting with CTLA-4 and PD-1 to repress tumor-infiltrating Tregs, thereby mitigating damage to immune-disordered cells in the TME [171]. Notably, *H. pylori*-positive GC has considerably higher PD-L1 expression levels, and miR-140 overexpression suppresses the proliferation and tumor growth of GC cells by blocking PD-L1 and mTOR activity [172]. Additionally, by repressing the expression of miR-513, reducing the translational repression of PD-L1, activating the pathway of JAK2/STAT1/IFR-1, and augmenting PD-L1 expression, INF-γ induces GC immune escape [173]. Notably, in vitro silencing of PD-1 enhances miR-21 expression, increases the proportion of Th17 cells, and decreases that of Treg cells [174]. miRNAs play an essential role in regulating the immune response, and miRNAs can interact with immune checkpoint inhibitors.

Additionally, elevated miR-152 levels improve immune responses by facilitating effector cytokine production and T-cell proliferation through the suppression of the B7-H1/PD-1 pathway. MiR-152 may be a potential therapeutic approach for GC [175]. Notably, manipulation of immune checkpoint protein expression by miRNA-based therapies combined with anti-immune checkpoint drugs may be an improved approach to GC treatment.

Dendritic cells (DCs) are the most potent antigen-presenting cells, capable of efficiently cross-presenting antigens. DCs contribute significantly to antitumor immunity by modulating the TME and attracting and activating anticancer T cells [176]. Thus, by impairing DC activation, antigen presentation, maturation, recruitment, and differentiation, TME and GC cells evade immune control [177]. Many miRNAs are implicated in the development and differentiation of DCs and in the regulation of inflammatory responses in DCs. Tumor miRNAs can directly or indirectly control DCs maturation and induce a tolerant state [178]. miR-17-5p decreased the secretion of TNF-α and IL-12 while increasing the production of IL-10. This shift inhibits the stimulation of T cells by DCs and promotes the expansion of Tregs. Furthermore, it can be utilized as a biomarker for GC originating from GC cells [179]. Additionally, in gastric TME, *H. pylori* can suppress miRNA-375 expression. This triggers the JAK2-STAT3 pathway, consequently promoting the

release of VEGF, IL-10, and IL-6. These released factors promote DCs to differentiate immaturely and contribute to the induction of GC [180] (Fig. 6). These studies have demonstrated that miRNAs regulate the development, differentiation, and function of DCs, establishing them as pivotal regulators of the immune response. Another critical cellular component of innate immunity is the natural killer (NK) cells, which are essential in the immune response against cancer by killing tumor cells and secreting immunostimulatory cytokines [181]. Variations in miRNA expression influence the progression of NK and invariant NKT cells differently. For example, invariant NKT cells in the peripheral and thymus lymphoid organs are negatively regulated by miR-150 [182]. Conversely, miR-155 enhances NK cell function by increasing NKG2D, IFN-γ, and granzyme B production [183]. Furthermore, lncRNA-GAS5 enhances IFN-γ secretion by targeting miR-18a, thus promoting NK cell responses against GC cells [184]. In addition to modulating receptor signaling, miRNAs directly affect the production of effector molecules that determine NK cell activity.

Exosome-derived miRNAs regulate the GC TME

The discovery of exosomes and their multiple functions in cancer biology is undoubtedly one of the most exciting discoveries in recent years. Exosomes are nanoscale (30–150 nm in diameter) EVs that can transport a broad range of substances, including metabolites, proteins, lipids, and nucleic acids [185]. miRNAs in cancer-derived exosomes promote intercellular communication, targeting themselves and contributing to the regulation of multiple components of the immune system, ultimately modulating the TME to regulate GC development, metastasis, invasion, drug resistance, and angiogenesis [186, 187]. They are very valuable for the prognosis and early GC diagnosis and, to some extent, reflect the malignant

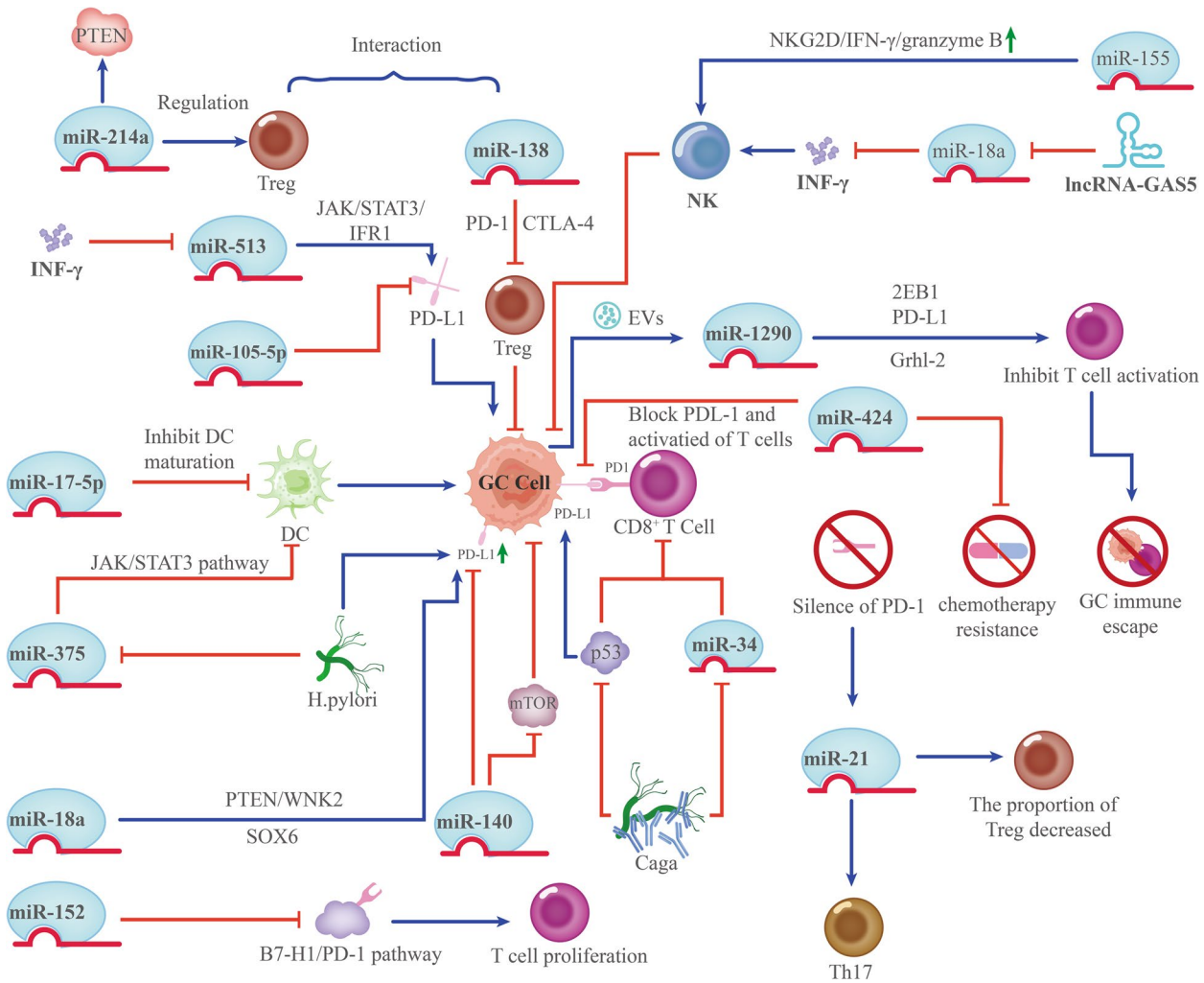

Fig. 6 miRNAs modulate immunoreactive cells in gastric cancer. miRNAs: MicroRNAs

characteristics of the tumor [188, 189]. Meanwhile, miRNAs play a role in the communication between tumor cells and TME through exosomal secretion and transport [190].

GC cells release exosomes containing miR-582-3p, which targets VEGF to stimulate cell invasion and proliferation [191]. Exosomes produced from GC cells carrying miR-135b have been found by Bai et al. [192] to lower FOXO1 protein levels and stimulate angiogenesis. GC cells can give rise to exosomes enriched in miR-301a-3p in hypoxic TMEs, which contribute to EMT, GC proliferation, invasion, and migration, along with HIF-1α accumulation [193]. Additionally, individuals with GC hepatic metastases demonstrate serum exosomes exhibiting considerably higher miR-519a-3p levels compared to individuals without liver metastases. Moreover, by targeting DUSP2, exosomal miR-519a-3p promotes the MAPK/ERK pathway, leading to M2-like polarization of macrophages, resulting in angiogenesis, facilitating the development of pre-metastatic niches in the liver, and accelerating the process of liver metastasis [194].

Exosomal miR-106a and miR-21-5p activates the TGF-β pathway by targeting TIMP2 and SMAD7, disrupts the mesothelial barrier, and promotes the peritoneal spread of GC by integrating into peritoneal mesothelial cells [195, 196]. Moreover, serum exosomes from patients with GC were enriched in miR-423-5p, and a significant correlation existed between lymph node metastasis and extracellular miR-423-5p levels, which facilitated cancer growth and metastasis [197].

Macrophages produce exosomes containing miR-16-5p that translocate to GC cells and target PD-L1 to activate T cells, thereby suppressing GC development [198]. Exosomes containing miR-21 are produced in tumors when the EMT transcription factor Snail activates miR-21. These exosomes are taken up by CD14 + human monocytes, which then cause a rise in M2 marker expression and ultimately accelerate tumor progression [199]. Furthermore, exosomal miR-15b-3p suppresses apoptosis in vivo and in vitro by inhibiting the expression of DYNLT1, cleaved caspase-3, and caspase-9. This promotes the proliferation, invasion, and migration of

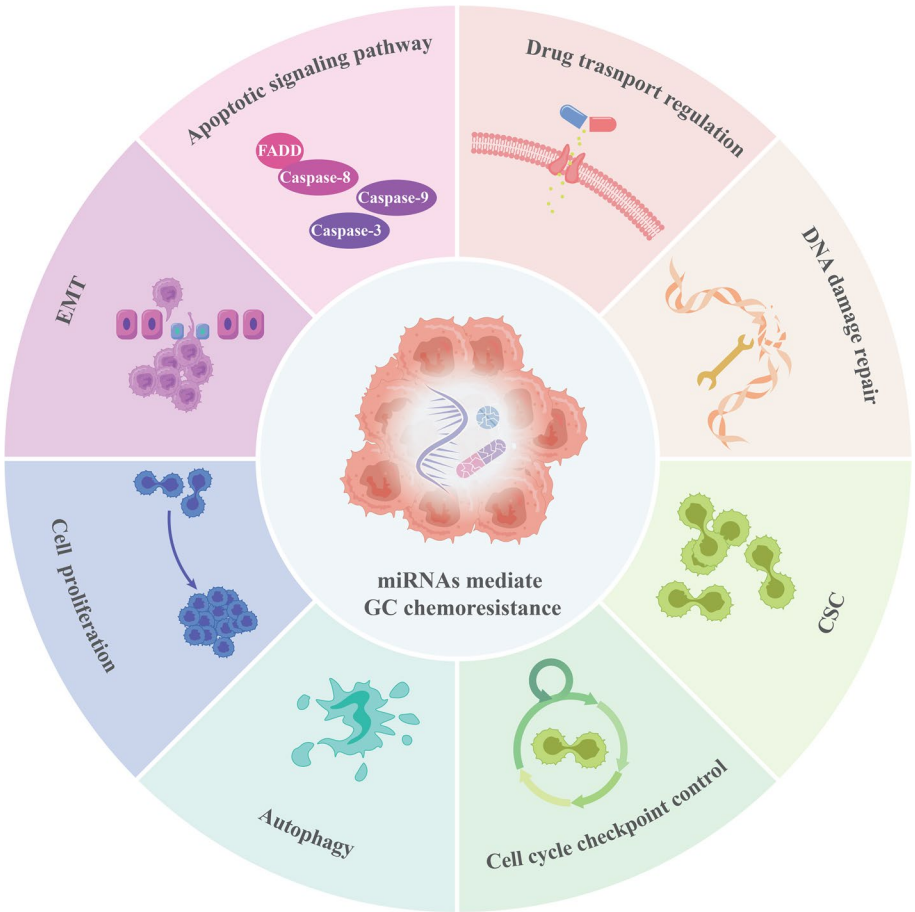

Fig. 7 miRNAs modulate GC chemoresistance through several mechanisms. miRNAs: MicroRNAs, GC: Gastric cancer

Table 3 miRNAs that play roles in GC chemoresistance

Symbol	Status	Signaling Pathway/ Targets	Function	Effects on chemosensitivity	Resistance	Reference
miR-1	Downregulated	Sorcin	Promote the accumulation of intracellular drugs and enhance apoptosis	Increasing	Adriamycin, Vincristine	[210]
miR-7	Downregulated	LDH-A	Increase apoptosis and caspase-3 activation	Increasing	Cisplatin	[211]
miR-16–1	Downregulated	FUBP1	Inhibit GC proliferation and invasion, and advanced apoptosis	Increasing	Adriamycin	[212]
miR-17	Upregulated	EMT, DEDD	Inhibit apoptosis	Decreasing	Cisplatin, 5-Fluorouracil	[213]
miR-17-5p	Downregulated	P21	Inhibit apoptosis	Decreasing	Cisplatin	[214]
mir-15b or miR-16	Downregulated	Bcl-2	Induce apoptosis	Increasing	Doxorubicin, Etoposide, Vincristine, Cisplatin	[215]
miR-19a/b	Upregulated	PI3K-Akt/ PTEN	Accelerate drug efflux and inhibit apoptosis	Decreasing	Cisplatin, 5-Fluorouracil, Adriamycin	[216]
miR-20a	Upregulated	NFκB/CYLD	Inhibit apoptosis	Decreasing	Cisplatin	[217]
miR-20a	-	PI3K-AKT and MAPK-ERK/ LRIG1	Reduce apoptosis	Decreasing	Adriamycin, Vincristine	[218]
miR-21	Upregulated	PTEN-PI3K-Akt/PTEN	Reduce antiproliferative effects and apoptosis	Decreasing	Cisplatin	[219]
miR-23b-3p	Downregulated	ATG12 and HMGB2	Inhibit autophagy	Increasing	Vincristine, 5-Fluorouracil and Cisplatin	[220]
miR-25	Upregulated	FOXO3a	Promote GC cycle progression	Decreasing	Cisplatin	[221]
miR-27a and miR-155	Upregulated	RKIP	Inhibit apoptosis	Decreasing	5-Fluorouracil and Oxaliplatin	[209]
miR-30a	Upregulated	beclin 1	Suppress autophagy, induce apoptosis and G2/M cell cycle arrest	Increasing	Cisplatin	[222]
miR-31	Downregulated	RhoA	Enhance apoptosis, inhibit cell cycle	Increasing	5-Fluorouracil	[223]
miR-34	-	Bcl-2, Notch, and HMGA2	Induce GC apoptosis, Caspase-3 activation, and accumulate in G1 phase	Increasing	Docetaxel, Gemcitabine, Cisplatin, Doxorubicin	[224]
miR-34a	Upregulated	MET	Inhibit GC proliferation and induct apoptosis	Increasing	Cisplatin	[225]
miR-34c	Downregulated		Promote GC apoptosis and inhibit proliferation	Increasing	Paclitaxel, Cisplatin	[226]
miR-34c-5p	Downregulated	MAPT	Regulate DNA methylation, inhibit GC proliferation and promote apoptosis	Increasing	Paclitaxel	[227]
miR-96	Upregulated	FOXO1	Promote GC proliferation	Decreasing	Cisplatin, Doxorubicin	[228]
miR-99a and miR-491	Upregulated	AKT-FOX3A/ CAPNS1	Induced GC apoptosis	Increasing	Cisplatin	[229]
miR-101	Downregulated	p38MAPK and AKT / ANXA2	Promote GC apoptosis	Increasing	Cisplatin, Vincristine	[230]
miR-106a	Upregulated	RUNX3	Accelerate ADR efflux, and suppress apoptosis	Decreasing	Adriamycin, Vincristine	[231]
miR-106a	Upregulated	PI3K-AKT/ PTEN	Regulate GC apoptosis	Decreasing	Cisplatin	[232]
miR-126	Downregulated	EZH2	Promote GC proliferation and migration	Increasing	Vincristine, Adriamycin	[233]
miR-128	Downregulated	HMGA2	Increase GC apoptosis	Decreasing	Cisplatin	[234]

Table 3 (continued)

Symbol	Status	Signaling Pathway/ Targets	Function	Effects on chemosensitivity	Resistance	Reference
miR-129	Downregulated	P-gp	Activate apoptotic pathway via upregulating caspase-9 and caspase-3	Increasing	Cisplatin	[235]
miR-130b	Upregulated	CMPK1	Reduce sensitivity and DNA damage	Increasing	5-Fluorouracil	[236]
miR-132	Upregulated	SIRT1-CREB-ABCG2/ SIRT1	Regulate CSC	Decreasing	Cisplatin	[237]
miR-135a-5p	Upregulated	AP-2α/ BCL-2	Enhance cell resistance to apoptosis	Increasing	Adriamycin	[238]
miR-135b	Upregulated	MAPK/ MST1	Inhibit apoptosis, and induce proliferation	Decreasing	Cisplatin	[239]
miR-145	Downregulated	CD44	Regulate CSC	Decreasing	5-Fluorouracil, Cisplatin	[240]
miR-148a-3p	Downregulated	AKAP1, RAB12	Activate mitochondrial fission and apoptosis	Increasing	Cisplatin	[241]
miR-138-5p	Downregulated	ERCC	Regulate DNA damage repair	Increasing	Cisplatin	[242]
miR-155	Upregulated	STAT3 and NF-κB	Inhibit GC apoptosis, promote proliferation	Decreasing	Cisplatin and 5-Fluorouracil	[243]
miR-155-5p	Upregulated	GATA3 TP53INP1	Regulate EMT	Decreasing	Paclitaxel	[244]
miR-181a	Upregulated	MTMR3	Attenuate GC apoptosis and autophagy	Decreasing	Cisplatin	[245]
miR-181a-2-3p	Upregulated		Inhibit GC apoptosis	Increasing	Cisplatin	[246]
miR-181b	Downregulated	BCL2	Induce apoptosis	Increasing	Vincristine, Cisplatin, Adriamycin, Etoposide, 5-Fluorouracil	[247]
miR-185	Upregulated	ARC	Induce apoptosis	Increasing	Cisplatin, Doxorubicin	[248]
miR-193a-3p	Upregulated	Mitochondrial apoptosis/ SRSF2	Inhibit apoptosis	Decreasing	Cisplatin	[249]
miR-195-5p	Downregulated	ZNF139	Regulate MDR	Increasing	5-Fluorouracil, Oxaliplatin	[250]
miR-200bc/429	Downregulated	BCL2, XIAP	Induce apoptosis	Increasing	Vincristine, Cisplatin, Adriamycin, Etoposide, 5-Fluorouracil	[251]
miR-200c	Downregulated	Zinc finger E-box binding homeobox 2	Induce apoptosis	Increasing	Cisplatin	[252]
miR-204	Downregulated	Bcl-2	Promote GC apoptosis	Increasing	5-Fluorouracil; Oxaliplatin	[253]
miR-204	Downregulated	TGFBR2	Regulate EMT	Increasing	5-Fluorouracil	[254]
miR-218	Upregulated	mTOR	Induce apoptosis	Increasing	Cisplatin	[255]
miR-223	Upregulated	FBXW7	Regulate cell cycle and apoptosis	Decreasing	Cisplatin	[256]
miR-223	Upregulated	FBXW7	Regulate EMT	Decreasing	Doxorubicin	[257]
miR-193-3p	Upregulated	PTEN	Promote GC proliferation migration	Decreasing	5Ffluorouracil	[258]
miR-301b-3p	Upregulated	TXNIP	Promote MDR	Decreasing	Cisplatin, Vincristine	[259]
miR-361-5p	-	PI3K-AKT-mTOR/ FOXM1	Inhibit autophagy	Increasing	Docetaxel	[260]
miR-363	Upregulated	FBW7	Promote GC proliferation	Decreasing	docetaxel + cisplatin + 5-FU	[261]
miR-375	Upregulated	PI3K-AKT/ ERBB2	Anti-proliferative and apoptosis-inducing	Increasing	Cisplatin	[262]
miR-421	Upregulated	E-cadherin and caspase-3	Promote metastasis, inhibit apoptosis	Decreasing	Cisplatin	[53]

Table 3 (continued)

Symbol	Status	Signaling Pathway/ Targets	Function	Effects on chemosensitivity	Resistance	Reference
miR-424-3p	Downregulated	ABCC2	Promote GC proliferation	Decreasing	Cisplatin	[263]
miR-429	Downregulated	PI3K-AKT-mTOR/ SOX2	Inhibit apoptosis	Decreasing	Cisplatin	[264]
miR-492	Upregulated	DNMT3B	Induce GC proliferation	Decreasing	Cisplatin	[265]
miR-493		MAD2L1	Regulate chemosensitivity	Decreasing	Paclitaxel	[266]
miR-495-3p	Downregulated	GRP78-mTOR/ GRP78	Inhibit autophagy	Increasing	Vincristine, Adriamycin	[267]
miR-497	Upregulated	Bcl-2	Induce apoptosis	Increasing	Vincristine; Cisplatin; Etoposide; Adriamycin	[268]
miR-500a-3p	Upregulated	FBXW7	Induce CSCs properties	Decreasing	Cisplatin	[269]
miR-503	Downregulated	IGF1R, BCL2	Inhibit GC proliferation, induce apoptosis	Increasing	Cisplatin	[270]
miR-508-5p	Downregulated	ZNRD1,ABCB1	Induce apoptosis	Increasing	Vincristine; Adriamycin; 5-Fluorouracil; Cisplatin	[271]
miR-524-5p	Upregulated	SOX9	Inhibit GC proliferation and invasion	Increasing	Cisplatin	[272]
miR-590-5p	Upregulated	AKT-ERK and STAT3/ RECK	Promote GC proliferation and invasion	Decreasing	Cisplatin and Paclitaxel	[273]
miR-623	Downregulated	Cyclin D1	Inhibit GC proliferation	Increasing	5-Fluorouracil	[274]
miR-647	Downregulated	ANK2-CD44-SNAIL1/ Ankyrins	Induce GC apoptosis and prevent cells from entering S phase of the cell cycle	Increasing	Vincristine	[275]
miR-648	Downregulated	ET-1	Induct apoptosis	Increasing	5-Fluorouracil	[276]
miR-708-3p	Upregulated	ETNK1	Promote GC proliferation and migration, inhibit apoptosis, and facilitate the transition from the G0/G1 to the G2/M phase	Decreasing		[277]
miR-873-5p	Downregulated	THUMPD1	Regulate migration, invasion, and chemoresistance	Increasing	Doxorubicin, 5-Fluorouracil, Cisplatin	[278]
miR-874	Downregulated	ATG16L1	Inhibit autophagy	Increasing	Cisplatin	[279]
miR-1229-3p	Upregulated	SLC22A7	Induce chemoresistance	Decreasing	5-Fluorouracil	[280]
miR-1284	Downregulated	EIF4A1-JUN-MYC/ EIF4F	Promote cell cycle arrested at the G0/G1 phase, induce apoptosis	Increasing	Vincristine	[281]
miR-4295	Upregulated	EGFR-PI3K-AKT/ LRIG1	Induce apoptosis	Decreasing	Cisplatin	[282]

Abbreviations: *miRNAs* MicroRNAs, *GC* Gastric cancer

GC cells [200]. Additionally, GC cells secrete exosomes capable of delivering miR-107 to MDSCs, which causes the activation and amplification in MDSCs by targeting PTEN and DICER1 [160].

Notably, exosomal miR-122-5p inhibits both tumor development in vivo and GC cell migration and proliferation in vitro [201]. Furthermore, exosomal miR-139 produced by CAFs suppresses GC cell metastasis and tumor growth by decreasing the expression of matrix metalloproteinase 11 both in vitro and in vivo [202]. Moreover, exosomal miR-29b-1-5p generated from CAFs inhibits GC cell survival, invasion, and migration, as well as vascular mimicry development; however, it also stimulates apoptosis [203]. Additionally, CAF-derived EVs containing miR-199a-5p downregulate FKBP5, resulting in elevated AKT1 phosphorylation and mammalian target of rapamycin complex 1 activation, thereby promoting GC [204].

Chemotherapy is the cornerstone of cancer treatment; however, some individuals develop resistance to the drugs administered. GC has the highest rate of drug-resistant recurrence among all cancer types; this

phenomenon considerably restricts the long-term prospects of patients with cancer, with 5-year survival rates dropping as low as 30% [205]. An increasing number of miRNAs have been found to be aberrantly expressed in drug-resistant GC tissues and are involved in the process of chemoresistance. These miRNAs function through complex mechanisms, including inactivation of apoptotic signaling pathways, loss of cell cycle checkpoint control, accelerated cell proliferation and autophagy flux, enhanced DNA damage repair, and drug transport and regulation. Furthermore, they activate CSCs and EMT [206–208] (Fig. 7). These correlations suggest that miRNA analysis will be a valuable tool for accurately assessing cellular sensitivity to chemotherapy and can be used to develop novel therapeutic approaches capable of overcoming resistance to GC chemotherapy [209] (Table 3).

This phenomenon of chemoresistance is also linked to miRNAs in exosomes. For example, patients with GC who have elevated miR-500a-3p levels in their plasma exosomes are more likely to be resistant to cisplatin, which lowers their progression-free survival rate [269]. Additionally, exosomes allow miR-21 to be transported from macrophages to GC cells, which significantly lowers the sensitivity of GC cells to cisplatin treatment both in vitro and in vivo, partly through modulation of the PTEN/PI3K/AKT signaling pathway [144].

Clinically, GC tissues display markedly elevated levels of miR-223 expression. Moreover, a strong correlation between high expression levels of plasma exosomal miR-223 and doxorubicin resistance is observed in patients with GC [257]. For example, biologically active miR-769-5p spreads cisplatin resistance by integrating into exosomes and infiltrating sensitive cells. Furthermore, by targeting CASP9, miR-769-5p enables the ubiquitin–proteasome pathway to degrade p53, an apoptosis-associated protein, while suppressing the downstream caspase pathway [283]. Furthermore, by modulating the high mobility group A2/mTOR/P-GP axis, exosome-secreted miR-107 dramatically increases the sensitivity of drug-resistant GC cells to chemotherapeutic drugs [284]. Finally, in paclitaxel-resistant GC cells, exosomal

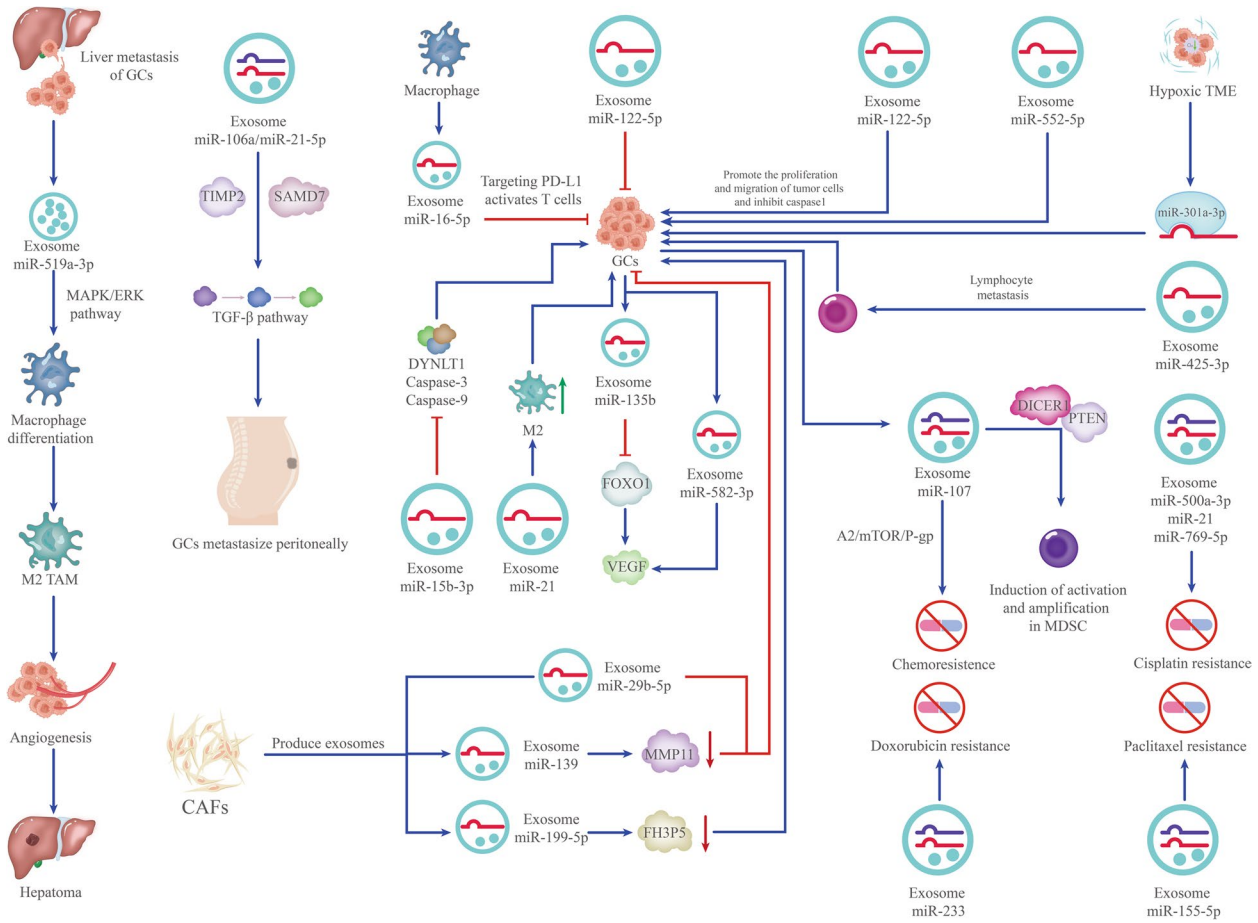

Fig. 8 Exosome-derived miRNAs regulate TME and participate in the development of gastric cancer. miRNAs: MicroRNAs, TME: Tumor microenvironment

administration of miR-155-5p promotes chemoresistant phenotypes and EMT, which may be mediated by suppression of TP53INP1 and GATA3 [244] (Fig. 8). Overall, these findings imply that exosomal-derived miRNAs are essential for the development of medication resistance.

Conclusions

Despite treatment efforts, GC remains one of the deadliest tumors. Over the past years, growing research has indicated the significant role of the TME in the development, advancement, invasion, and metastasis of GC. Recent studies have shown a strong correlation between GC and miRNA dysregulation, which has a significant impact on TME-related activities and provides new insights into the relationship between immune cells, mesenchymal stromal cells, malignant cells, and non-cellular components of the TME, promoting tumor proliferation, angiogenesis, and metastasis.

Particularly, malignant and drug-resistant tumor cells secrete exosomes containing specific miRNAs. Therefore, exosomes are crucial for material exchange, energy flow, and signaling between the different cellular components of the TME. An in-depth study of the effect of miRNAs on TME is of great significance in furthering our understanding of the biology of GC. Based on the role of miRNAs in TME, the development of miRNAs as synergistic tumor immunotherapeutics is of great significance to improve the efficacy of monotherapy and reduce tumor survival.

Notably, several challenges remain to be addressed before these studies can be translated into clinical applications. Firstly, due to the complexity of the TME, the exact mechanisms of different miRNAs in different cell types in the TME remain largely unknown [285]. To select the optimal targets, a deeper understanding of the role of each specific miRNA in all immune cell subpopulations and their complete regulatory networks is essential. Additionally, given that naked miRNAs have a short half-life in vivo and are easily degraded, there is an urgent need to identify a safe, effective, and targeted vector to protect the miRNAs and ensure their delivery to the intended sites [286].

In conclusion, this review describes the communication mechanisms of miRNAs between the TME and GC tumor cells. Dysregulated miRNAs are found in both non-tumor and tumor cells within the TME, emphasizing the key role played by the TME and miRNAs in the development and metastasis of cancer. While their exact mechanism of action is still being investigated, several miRNAs have emerged as potential therapeutic targets and GC biomarkers. Exploring and studying the regulatory effects of naturally derived drugs on the TME at the miRNA level holds promise, especially considering the polygenic targeting of miRNAs and the anticancer effects of natural drugs on various types of mesenchymal stromal cells within the TME.

Abbreviations

GC	Gastric cancer
TME	Tumor microenvironment
CAFs	Cancer-associated fibroblasts
miRNAs	MicroRNAs
ECM	Extracellular matrix
DC	Dendritic cells
Tregs	Regulatory T cells
MDSCs	Myeloid-derived suppressor cells
EVs	Extracellular vesicles
VEGF	Vascular endothelial growth factor
IL	Interleukin
JAK2-STAT3	Janus kinase 2
MAPK/ERK	Mitogen-activated protein kinase/extracellular signal-regulated kinases
EMT	Epithelial-mesenchymal transition
PI3K/AKT/mTOR	Phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin
FOXM1	Forkhead box M1
PD-L1	Programmed death ligand 1
HIF-1α	Hypoxia-inducible factor 1-alpha
TAMs	Tumor-associated macrophages
PTEN	Phosphatase and tensin homolog
Th1	T helper 1 cells
Th17	T helper 17 cells
CTLs	Cytotoxic T lymphocytes
NKs	Natural killer cells
ROS	Reactive oxygen species
EBV	Epstein–Barr virus
ZEB1	Zinc finger E-box-binding homeobox 1
TNF	Tumor necrosis factor
CSCs	Cancer stem cells

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Authors' contributions

XZ Y and Y Z conceptualized the manuscript. XZ Y wrote the first draft. QH Z, FM L and LL Z contributed substantially by revising the manuscript. All authors approved the submitted version and are fully accountable for every aspect of the work.

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Availability of data and materials

Not applicable.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
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Competing interests
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