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Review

Unraveling the Role of microRNAs in the Metastatic Landscape of Gastric Cancer

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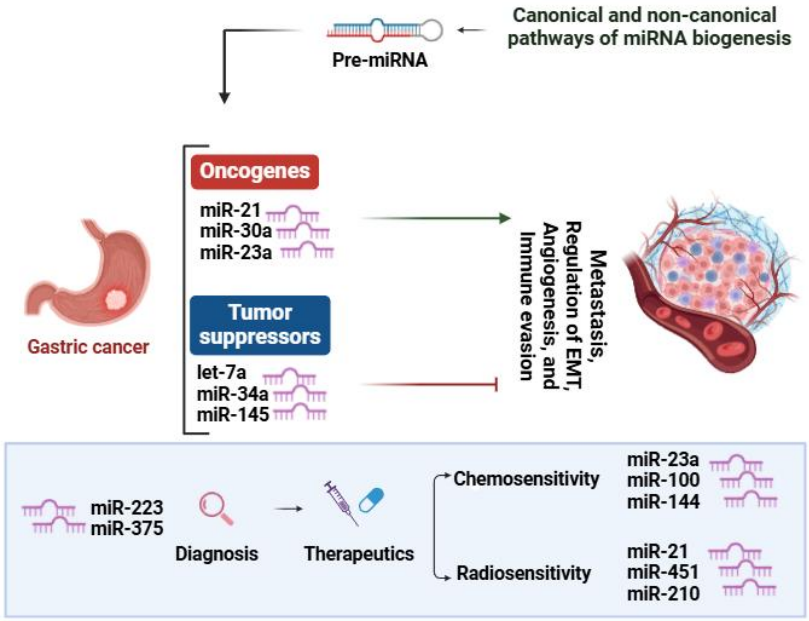
Abstract

Gastric cancer (GC) continues to pose a major health issue worldwide, and diagnoses made at advanced stages frequently result in unfavorable outcomes. The metastatic spread of GC presents substantial therapeutic challenges, necessitating a deeper understanding of the tumor microenvironment (TME) and its interactions with cancer cells. MicroRNAs (miRNAs) are small non-coding RNA molecules that regulate gene expression and have been identified as key factors in the metastasis of GC. This review explores the biogenesis and functional mechanisms of miRNAs, highlighting their dual roles as oncogenes and tumor suppressors in GC metastasis. We discuss specific miRNAs that facilitate metastatic progression by influencing key pathways related to invasion, angiogenesis, and immune evasion. Furthermore, we examine the potential of miRNAs as diagnostic and prognostic biomarkers, offering insights into their utility in timely identification and tailored therapeutic approaches. By elucidating the complex regulatory networks involving miRNAs, this review underscores their significance as both therapeutic targets and biomarkers in the management of gastric cancer.

Graphical Abstract



1. Introduction

Gastric cancer (GC) ranks among the most prevalent cancers worldwide and is a leading contributor to cancer-related fatalities. Its late diagnosis, often at an advanced stage with metastases, results in a poor five-year survival rate [1,2]. The metastatic spread is the primary challenge in GC treatment. Understanding the tumor microenvironment (TME) and its interactions with cancer cells is crucial for improving the prognosis of GC patients. The TME plays a significant function in tumorigenesis, growth, and metastasis by influencing tumor cell survival, chemoresistance, and immune evasion [3-5].

MicroRNAs (miRNAs) are small non-coding RNA molecules that are vital in controlling gene expression across diverse biological functions, including cancer progression. Their dysregulation in cancer cells has been

widely documented, making them potential targets for cancer therapy [6-8]. This review seeks to investigate the function of miRNAs in the metastatic process of GC and their potential as diagnostic and therapeutic tools.

MiRNAs are typically 21–23 nucleotides long, and regulate gene expression post-transcriptionally. They are transcribed as primary miRNAs (pri-miRNAs) and processed by RNase III enzymes into precursor miRNAs (pre-miRNAs) and mature miRNA duplexes. The mature strand becomes part of the RNA-induced silencing complex (RISC), which binds to target mRNAs to either degrade them or suppress their translation [9-11].

Non-canonical miRNA biogenesis pathways deviate from the classical Drosha-Dicer processing route. These pathways can be further categorized based on their dependence on Drosha and Dicer [12]. Some miRNAs, such as miR-451, bypass Drosha processing. In this non-canonical pathway, the miRNA is directly processed by Dicer-independent mechanisms. For example, miR-451 is processed by AGO2 instead of Dicer, with Drosha serving as the key enzyme in cleaving the pri-miRNA. A notable example of Dicer-independent pathway involves mirtrons, where pre-miRNAs originate from the intronc regions of protein-coding genes and bypass Drosha processing [13]. These mirtrons are spliced out as part of the mRNA splicing process and are directly folded into pre-miRNA hairpins, which are then transported to the cytoplasm and processed via Dicer. Another subset involves miRNAs like pre-miR-320, which contain a 7-methylguanosine (m7G) cap and are exported to the cytoplasm through Exportin 1, completely bypassing Drosha processing altogether [14,15].

These non-canonical pathways provide flexibility in miRNA biogenesis, enabling cells to adapt miRNA production under varying physiological or pathological conditions, including stress, inflammation, or cancer [16] (Figure 1).

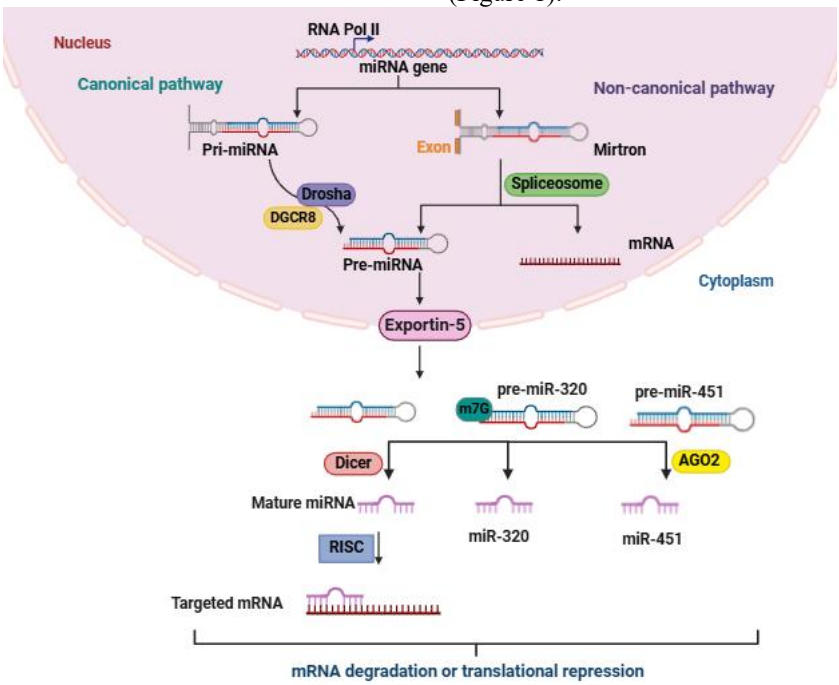


Figure 1. The biogenesis of miRNAs, highlighting both canonical and non-canonical pathways, and their role in cancer regulation.

MiRNA dysregulation is a hallmark of many cancers, including GC. MiRNAs can function as either oncogenes (oncomiRs) or tumor suppressors, depending on the context and target genes. For instance, miRNAs such as miR-100, miR-34a, miR-23a, miR-27a, and miR-30a are engaged in the controlling of stemness, metastatic spread, and treatment resistance [17-19].

2. miRNAs in Gastric Cancer Metastasis

Metastasis refers to the mechanism by which cancer cells migrate from their original location to other organs. This process encompasses several stages: local invasion, entry into the bloodstream, survival in circulation, exit from blood vessels, and establishment at a new site. In GC, typical metastatic locations include the peritoneum, liver, lungs, and bones. MiRNAs are crucial in modulating the genes that participate in these stages of metastasis [20,21].

2.1 miRNAs as Oncogenes in Gastric Cancer Metastasis

Several miRNAs function as oncogenes in GC by promoting metastasis and contributing to tumor progression. One prominent example is miR-23a, which is overexpressed in GC and enhances metastasis by inhibiting autophagy-related genes such as ATG12 and HMGB2. This miRNA also promotes epithelial-mesenchymal transition (EMT) and activates the PI3K/Akt pathway, linking it to malignancies across various cancer types, including GC, where it is linked with tumor-advanced and chemotherapy resistance [22,23].

Another significant miRNA in this context is miR-30a, which promotes cell growth and metastasis by influencing the P53-related mitochondrial apoptosis pathway. While miR-30a has been detected as an EMT suppressor in other cancers, in GC, it acts as an oncomiR that contributes to multidrug resistance and tumor growth [24].

MiR-21 is well-known for its role in targeting tumor suppressor genes such as PTEN and RECK (reversion-inducing cysteine-rich protein with Kazal motifs). It facilitates metastasis, angiogenesis, and EMT in gastric cancer, while also regulating the PI3K/Akt pathway, which is critical for cell viability and proliferation. Additionally, miR-21 downregulates PDCD4, further enhancing tumor progression and metastasis in gastric cancer [25,26].

MiR-100, which is elevated in GC cells, restricts the expression of BMPR2 and CXCR7, genes that are essential for cancer spread and invasion. By regulating these targets, miR-100 influences the metastatic potential of GC, thereby contributing to tumor progression [27,28].

Another oncogenic miRNA, miR-27a, is significantly overexpressed in GC and promotes tumor advancement by facilitating EMT and metastasis. It also modulates the sensitivity of GC cell line to chemotherapy and influences autophagy processes [29].

MiR-19b is similarly overexpressed in GC and enhances metastasis via modulating key cellular procedures like invasion and spread. It is associated with stemness and drug resistance, making it a promising candidate for treatment strategies in the advanced stages of the disease. Likewise, miR-19a is implicated in GC metastasis and progression, contributing to the dysfunction of signaling pathways that enhance cancer cell survival, invasion, and spread [30,31].

Additionally, miR-19b-1, part of the miR-17-92 cluster, is associated with unfavorable outcomes in GC. It promotes metastasis through its regulatory roles in EMT and proliferation pathways [32]. Lastly, miR-222, which is overexpressed in gastric cancer, enhances tumor progression by targeting PTEN, resulting in increased cell growth and metastasis. It is involved in the dysregulation of signaling pathways that facilitate invasion, survival, and migration, further establishing its role as an oncogene in GC metastasis [33]. Notably, miR-10b is especially important, as it is linked to lymph node metastasis and promotes EMT by targeting HOXD10. Increased levels of miR-10b boost the migration and invasion of cancer cells, identifying it as a key player in the advancement of gastric cancer [34].

Another important miRNA is miR-221, which is increased in gastric cancer and facilitates metastasis by regulating PTEN and other tumor suppressor genes. The heightened expression of miR-221 is associated with aggressive tumor characteristics and an unfavorable prognosis, underscoring its role as an oncogenic miRNA [35]. Similarly, miR-373 contributes to the metastatic potential of GC cells by inducing their migration and invasion by targeting LATS2, a tumor suppressor involved in Hippo signaling. Through suppressing LATS2, miR-373 enhances cell motility, thereby facilitating metastasis [36].

MiR-25 is another miRNA that is found at elevated levels in gastric cancer, playing a role in tumor development and metastasis by targeting the RECK gene, which is essential for inhibiting invasion. Increased expression of miR-25 correlates with higher tumor aggressiveness [37]. Conversely, miR-206 is significantly reduced in GC tissues and cell lines, especially in instances of lymphatic metastasis. Inducing the expression of miR-206 has demonstrated the ability to suppress tumor growth, proliferation, invasion, and metastasis, indicating its potential role as a tumor suppressor [38].

Together, these miRNAs illustrate the complex interplay of regulatory mechanisms in GC and highlight their probable therapeutic targets in combating tumor progression and metastasis (Figure 2).

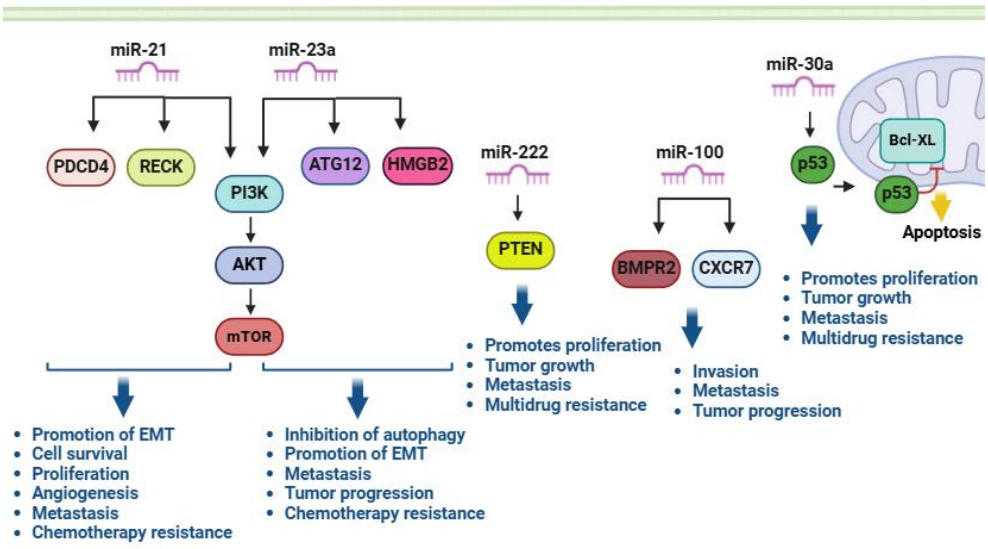


Figure 2. The complex regulatory network of miRNAs involved in gastric cancer metastasis and highlights their potential as therapeutic targets.

2.2 miRNAs as Tumor Suppressors in Gastric Cancer Metastasis

miRNAs play a significant role as tumor suppressors in GC by blocking metastasis and modulating various signaling pathways. One such miRNA is miR-34a, which suppresses invasion and metastasis by targeting genes such as NOTCH, HMGA2, and BCL2 [39]. Additionally, miR-34a increases the responsiveness of GC cells to cisplatin-based chemotherapy by regulating the PI3K/Akt pathway. Its overexpression inhibits invasion, cause apoptosis, and downregulate key oncogenic pathways, establishing it as a vital therapeutic target in GC [40].

Another important tumor suppressor is miR-145, which reduces metastasis and invasion by downregulating N-cadherin and MMP9. This miRNA inhibits EMT and extracellular matrix degradation, thereby limiting metastatic potential of GC cells [41]. Similarly, miR-101 represses GC cell proliferation and metastasis via EZH2, which is associated with chromatin remodeling and tumor progression. By regulating EZH2 and potentially other oncogenes involved in cell cycle progression, miR-101 further emphasizes its role in tumor suppression [42].

MiR-100 exhibits tumor-suppressing properties by inhibiting BMPR2 and CXCR7, which are implicated in promoting cancer invasion and metastasis. Although miR-100 can act as an oncogene in certain contexts, it is decreased in some GC scenarios which are associated with enhanced metastatic potential [27]. Let-7a, which is reduced in GC, has its reduced expression linked to poor prognosis. Its overexpression inhibits tumor growth, spread, and invasion by targeting PMK2 and other oncogenes [43].

Another notable miRNA is miR-375, whose reduced levels are observed in GC tissues and linked with advanced malignancy. This miRNA inhibits cancer progression by targeting key genes such as p53, JAK2, ERBB2, and STAT3, making it a crucial tumor suppressor [44]. Additionally, miR-206 is considerably lower in GC, particularly in cases of lymphatic metastasis or local invasion. It acts as a tumor suppressor by preventing tumor development, growth, invasion, and spread, playing a crucial role in regulating metastasis in GC [45].

MiR-214 is another miRNA that is notably reduced in GC tissues and inversely correlated with tumor size and lymph node metastasis. By targeting CSF-1, its reduced expression promotes tumor cell growth and metastasis. Restoring miR-214 expression in GC cells has been reported to weaken their migratory and invasive abilities [46]. Similarly, miR-148a, a tumor suppressor, is downregulated in GC, with its reduced expression linked to tumor progression and metastasis. It suppresses metastasis by controlling genes associated with cell invasion and migration, making it a potential therapeutic target [47].

MiR-218 negatively regulates Robo1, a receptor linked to cell spread and invasion. Through downregulating Robo1, miR-218 activates the Slit-Robo1 signaling pathway, which suppresses spread and metastasis in GC. Its reduced expression is related to enhanced metastatic potential [48]. Additionally, miR-335 inhibits spread and metastasis by Bcl-w and specificity protein 1. The reduction of miR-335 is associated with unfavorable prognosis, lymph node metastasis, and higher tumor-node-metastasis stages in GC [49].

Furthermore, miR-409-3p targets the 3′ untranslated regions of the prometastatic gene radixin (RDX). Its downregulation facilitates lymph node metastasis in GC, while overexpression suppresses metastasis [50]. MiR-574-3p, which is thought to be reduced in the early stages of gastric cancer, functions as a tumor suppressor by inhibiting cell proliferation, invasion, and metastasis. Overexpression of miR-574-3p in GC cells strongly suppresses tumor growth and metastatic behavior [51].

Lastly, miR-625 is reduced in GC tissues, and cell lines are negatively correlated with lymph node metastasis. This miRNA represses GC cell invasion and metastasis via controlling integrin-linked kinase expression, positioning it as a possible target for therapy [52]. Collectively, these miRNAs illustrate the complex regulatory networks involved in GC and their probably as treatment targets in managing the disease.

One of the notable miRNAs in this context is Let-7f, which is part of the Let-7 family. Let-7f suppresses tumor invasion and metastasis by regulating MYH9 (myosin heavy chain 9), a gene implicated in cell motility and metastatic behavior. By downregulating MYH9, Let-7f diminishes the capacity of GC cells to spread and move to distant sites, thereby acting as a metastasis suppressor [53,54].

Another important miRNA is miR-7, which suppresses metastasis by regulating the insulin-like growth factor 1 receptor (IGF1R), a crucial player in promoting EMT and metastasis. By downregulating IGF1R, miR-7 reverses the EMT process necessary for cancer cells to acquire invasive properties. Additionally, this miRNA reduces GC cell motility, further limiting the capacity for metastasis, making miR-7 a possible therapeutic target for preventing metastasis [55].

MiR-335 acts as a suppressor of metastasis by directly affecting Bcl-w and specificity protein 1 (SP1), both of which facilitate invasion and metastasis in gastric cancer. By inhibiting these targets, miR-335 diminishes the invasive capabilities of gastric cancer cells. Reduced levels of miR-335 are linked to later stages of the disease and unfavorable prognosis, underscoring its importance as a key controller of metastasis and indicating its probable as a tool for tracking disease progression [56].

Similarly, miR-506 is known to be a strong inhibitor of invasion and metastasis in gastric cancer. It downregulates genes associated with epithelial-mesenchymal transition (EMT) and blocks the PI3K/Akt pathway, which plays a role in enhancing cell survival, migration, and invasion. Through these mechanisms, miR-506 diminishes the metastatic capabilities of gastric cancer cells reinforcing its function as a tumor suppressor [57].

Another significant miRNA, miR-874, suppresses of invasion and metastasis in GC. It targets crucial signaling molecules involved in promoting EMT and metastasis, thereby reducing the invasive capacity of GC cells. Additionally, miR-874 downregulates the expression of VEGF and suppresses angiogenesis, a vital process for metastatic spread. This dual role in inhibiting both invasion and angiogenesis underscore the importance of miR-874 in controlling metastasis in GC [58].

Lastly, miR-30b-3p inhibits invasion, metastasis, and angiogenesis by targeting the PI3K/Akt signaling pathway. Serving as a tumor suppressor, miR-30b-3p reduces the levels of crucial molecules that facilitate these processes, thereby restricting the metastatic capabilities of GC cells [59].

In conclusion, various miRNAs function as suppressors of metastasis in GC by targeting essential genes and signaling pathways related to invasion, epithelial-mesenchymal transition (EMT), and metastasis. These miRNAs--such as Let-7f, miR-7, miR-335, miR-145, miR-506, miR-874, and miR-30b-3p--represent promising therapeutic targets for inhibiting or mitigating metastatic spread in gastric cancer, with their decreased expression often linked to more advanced disease and an unfavorable prognosis. Table 1 highlights the dual roles of miRNAs as both oncogenes and tumor suppressors, providing valuable insights for potential therapies.

Table 1. miRNAs involved in gastric cancer invasion and metastasis: promoters and inhibitors.

Role	miRNA	Target(s)	Effect(s) on GC	Ref
Promotes invasion/metastasis	miR-10b	HOXD10	Enhances EMT, migration, and invasion	[34]
	miR-221	PTEN	Regulates tumor suppressor genes, associated with aggressive tumors	[35]
	miR-373	LATS2	Increases cell motility and invasion	[36]
	miR-21	PDCD4, PTEN	Enhances invasion, metastasis	[25]
	miR-34a	Apoptosis genes	Modulates cell migration and invasion	[60]
	miR-25	RECK	Suppresses invasion inhibitor	[37]
Inhibits invasion/metastasis	miR-335	Bcl-w, SP1	Reduces invasion and metastasis	[61]
	Let-7f	MYH9	Inhibits cell motility and metastatic behavior	[54]
	miR-7	IGF1R	Reverses EMT, reduces motility	[55]
	miR-145	PI3K/Akt, VEGF	Inhibits EMT and invasion, downregulates tumor growth pathways	[41]
	miR-506	EMT-related genes, PI3K/Akt pathway	Reduces cell survival, migration, and invasion	[57]
	miR-874	EMT-related genes, VEGF	Inhibits EMT, and angiogenesis; reduces invasion	[58]
	miR-30b-3p	PI3K/Akt signaling pathway	Inhibits invasion, metastasis, and angiogenesis	[59]

3. miRNAs in Gastric Cancer Diagnosis and Therapeutic

miRNAs have gained substantial attention as possible factors for GC diagnosis and prognosis. Their presence and dysregulation in blood and serum, make them promising non-invasive tools for the early detection and monitoring of GC progression. Below, we illustrate the roles of specific miRNAs in GC diagnosis, focusing on their possible as tools for early detection and prognostic indicators [62].

3.1 miRNAs as Biomarkers for Initial Detection

miRNAs hold great potential as biomarkers for the early identification of gastric cancer, as numerous miRNAs exhibit differing expression levels in the serum of gastric cancer patients compared to those of healthy individuals. The detection of such miRNAs in body fluids offers a non-invasive approach to diagnosing GC at an earlier stage, which is crucial for improving patient outcomes [63].

For instance, the enhancement of miR-223 has been identified in the serum of GC patients, highlighting its capability as a tool for initial detection. This miRNA plays a role in several processes, such as inflammation, cell growth, and migration, all of which contribute to tumor development. Its increased expression in the serum of GC patients suggests its viability as an early cancer detection marker [64]. In addition to miR-223, miR-378 has also been found to have elevated serum levels in patients with GC. This miRNA significant role in cell viability and angiogenesis, and its overexpression correlates with cancer progression, making it a useful biomarker for identifying GC at an early stage [65]. Similarly, miR-421 has shown elevated levels in the serum of GC patients, marking it as a potential non-invasive tool for initial detection. MiR-421 is involved in regulating multiple pathways related to tumor growth and immune evasion, further establishing its value as a candidate for early diagnosis [66].

Conversely, several miRNAs are reduced in GC and act as tumor suppressors. Their reduced expression is often a hallmark of early tumorigenesis. One such miRNA is miR-375, which is detected at lower levels in both the tissue and serum of GC patients. This miRNA regulates critical oncogenic pathways, including the p53, JAK2, ERBB2, and STAT3 signaling pathways. Its downregulation is strongly linked to the advancement of GC, indicating that monitoring miR-375 levels could assist in the initial detection of malignancies [67]. Another important tumor-suppressing miRNA is let-7a,

which is significantly reduced in the plasma and tissue samples of GC patients. Let-7a targets multiple oncogenes, and its decreased expression is associated with enhanced tumor growth, migration, and invasion. Therefore, let-7a is a valuable biomarker for the early detection of GC [68].

In summary, the detection of specific miRNAs in body fluids offers a promising avenue for the initial diagnosis of GC. Their altered expression patterns not only provide insight into the tumor's biological behavior but also hold the potential for improving patient management and outcomes through timely intervention. Accordingly, Table 2 highlights the dual role of certain miRNAs that may act as either oncogenes or tumor suppressors based on the context of their expression and target genes. The table also provides insights into specific miRNA targets, which can be crucial for developing targeted therapies in GC.

Table 2. miRNAs involved in gastric cancer metastasis, categorized as oncogenes or tumor suppressors, along with their target genes/pathways and functional roles in the metastatic process.

Role	miRNA	Target Genes/Pathways	Function in Gastric Cancer	Ref
Oncogene	miR-23a	ATG12, HMGB2, PI3K/Akt pathway	Promotes metastasis by inhibiting autophagy, enhancing EMT, and linking to chemotherapy resistance	[22]
	miR-30a	P53-mediated mitochondrial apoptosis pathway	Promotes proliferation, and metastasis, and contributes to multidrug resistance	[24]
	miR-21	*PTEN*, *RECK*, PI3K/Akt pathway, *PDCD4*	Facilitates metastasis, angiogenesis, EMT, and tumor progression	[25]
	miR-27a	EMT-related genes	Promotes EMT, metastasis, and modulates chemotherapy sensitivity and autophagy	[69]
	miR-19b	Stemness and drug resistance-related pathways	Enhances metastasis, invasion, and migration	[30]
	miR-19a	Invasion and migration-related pathways	Promotes cell survival, invasion, and metastasis	[30]
	miR-19b-1	EMT and proliferation pathways	Linked to poor prognosis and promotes metastasis	[30]
	miR-222	PTEN	Enhances proliferation, invasion, and metastasis	[33]
Tumor Suppressor	miR-34a	*NOTCH*, *HMGA2*, *BCL2*, PI3K/Akt/survivin pathway	Suppresses invasion and metastasis, enhances chemotherapy sensitivity, induces apoptosis	[40]
	miR-145	*N-cadherin*, *MMP9*	Inhibits EMT, extracellular matrix degradation, and metastasis.	[41]
	miR-101	EZH2	Suppresses proliferation and metastasis	[42]
	Let-7a	PMK2	Inhibits tumor growth, migration, and invasion	[68]
	miR-375	*p53*, *JAK2*, *ERBB2*, *STAT3*	Inhibits tumor progression, invasion, and metastasis	[44]
	miR-206	Invasion and lymphatic metastasis-related genes	Reduces proliferation, invasion, and metastasis	[45]
	miR-214	CSF-1	Inhibits metastasis and tumor size; restoring expression reduces migratory and invasive	[46]
	miR-148a	Invasion and migration-related genes	Suppresses metastasis, linked to tumor progression	[47]
	miR-218	Robo1	Inhibits invasion and metastasis	[48]
	miR-335	*Bcl-w*, *Sp1*	Inhibits invasion and metastasis	[49]
	miR-409-3p	*RDX*	Inhibits lymph node metastasis	[50]
	miR-574-3p	Proliferation, invasion, and metastasis-related genes	Inhibits cell proliferation and metastasis	[51]
	miR-625	ILK	Inhibits invasion and metastasis	[52]
Oncogene/Tumor Suppressor	miR-100	*BMPR2*, *CXCR7*	Promotes invasion and metastasis as an oncogene	[27]

3.2 miRNAs as Prognostic Markers

In addition to their role in early detection, certain miRNAs have been linked to patient outcomes in GC. The expression levels of these miRNAs provide important clues about the potential progression of the malignancy and survival outcomes, making them useful tools for stratifying patients and personalizing treatment approaches [70].

As mentioned previously, high expression levels of miR-21 correlate with poor prognosis, as this miRNA enhances tumor growth, spread, and metastasis. It targets several tumor suppressor genes, including PTEN and RECK, and it is linked to lower viability rates and more advanced disease stages [71]. Similarly, increases in miR-196a are connected to poor survival outcomes in GC patients. This miRNA promotes the growth and movement of cancer cells by inhibiting tumor suppressor genes. Elevated levels of this miRNA correlate with more advanced tumor stages and lower differentiation, reinforcing its significance as a robust prognostic indicator [72].

Another significant miRNA, miR-146a, is reduced in GC and is associated with worse clinical outcomes, increased

tumor size, more advanced tumor-node-metastasis (TNM) classification, and reduced overall survival rates. Acting as a tumor suppressor, miR-146a regulates inflammatory responses and genetic instability, with its downregulation linked to more aggressive tumor behavior [73]. Similarly, miR-204 is markedly downregulated in GC, and lower expression levels are linked with larger tumor size, advanced stage, and poor survival outcomes. This miRNA inhibits key oncogenic pathways involved in cell viability and spread, making it a valuable prognostic marker for GC patients [74].

MiR-375 is also significant for prognosis, as diminished levels of this miRNA are linked to later stages of GC and poorer outcomes for patients. It targets oncogenes such as p53, JAK2, ERBB2, and STAT3, contributing to tumor suppression, and its downregulation indicates poor prognosis [75]. The downregulation of let-7a is another critical factor, as it is linked not only to early detection but also to poor prognosis in gastric cancer patients. Let-7a targets oncogenes such as KRAS and HMGA2, with reduced expression characterized by heightened tumor aggression and decreased viability rates [76].

Additionally, miR-218 is observed to be reduced in GC, and its reduced levels correlate with poor prognosis, including an increased risk of metastasis. This miRNA targets Robo1, a receptor related to cell migration and invasion, and its reduced expression is linked to enhanced metastatic potential and worse clinical outcomes [77]. Lastly, miR-145 functions as a tumor suppressor and is found to be diminished in gastric cancer, where its reduced levels are associated with poorer prognostic outcomes. By inhibiting metastasis through the downregulation of N-cadherin and MMP9, both of which are involved in EMT and tumor invasion, reduced levels of miR-145s are indicative of larger tumors, more advanced disease stages, and lower survival rates [78].

These findings highlight the significant potential of miRNAs as diagnostic and prognostic biomarkers in GC. Their ability to be detected in non-invasive samples like serum makes them attractive candidates for early detection and personalized treatment strategies in GC management.

3.3 miRNAs as Therapeutic Targets

MiRNAs have become promising therapeutic targets in gastric cancer due to their role in regulating critical signaling pathways associated with tumor growth, metastasis, and resistance to treatment. By adjusting the expression of certain miRNAs, it is feasible to increase the sensitivity of gastric cancer cells to chemotherapy and targeted therapies, paving the way for improved patient outcomes [79].

3.3.1 miRNAs Enhancing Chemosensitivity and Radiosensitivity

Numerous miRNAs have been identified that can boost the chemosensitivity of gastric cancer GC cells to conventional chemotherapy, making them appealing targets for therapeutic strategies. Among these, miR-34a is one of the most extensively researched miRNAs in GC. It increases sensitivity to cisplatin-based treatments by downregulating the PI3K/Akt/survivin pathway, which is vital for cell survival and apoptosis resistance. In the SGC7901 gastric cancer cell line, overexpressing miR-34a results in reduced cell invasion and promotes apoptosis, thereby enhancing the cytotoxic effects of cisplatin. Furthermore, miR-34a targets genes such as NOTCH, HMGA2, and BCL2, which play roles in cancer stem cell maintenance and viability, thereby further enhancing its ability to improve chemosensitivity [80].

Another important miRNA, miR-144, has been shown to increase sensitivity to 5-fluorouracil (5-FU), a commonly used chemotherapeutic agent in GC. By targeting ZFX (zinc finger protein X-linked), miR-144 suppresses the growth of GC cells and induces apoptosis, thereby increasing the effectiveness of 5-FU treatment. Similarly, miR-30a, while functioning as an oncomiR, plays a significant role in reducing chemoresistance in gastric cancer. It lowers multidrug resistance (MDR) through controlling the p53-mediated mitochondrial apoptosis pathway. By acting on key genes involved in apoptosis, miR-30a sensitizes gastric cancer cells to chemotherapeutic agents, positioning it as a potential target for overcoming MDR in GC treatment [81].

MiR-23a, although overexpressed in gastric cancer and associated with promoting chemoresistance, can have its effects reversed by targeting it to modulate autophagy-related genes such as ATG12 and HMGB2. Inhibiting these genes allows miR-23a to enhance the sensitivity of GC cells to chemotherapy, particularly in the context of autophagy inhibition [82]. Additionally, miR-100 has been shown to regulate critical genes like BMPR2 and CXCR7, promoting invasion and metastasis. By targeting these genes, miR-100 boosts the responsiveness of gastric cancer cells to chemotherapy drugs, limiting their metastatic potential and enhancing apoptosis [83].

Furthermore, miR-19b also contributes to enhancing chemosensitivity by regulating essential cellular processes such as stemness, metastasis, and resistance to treatment in GC. Targeting miR-19b may effectively reduce chemoresistance and enhance the effectiveness of chemotherapy [84]. These miRNAs represent potential therapeutic targets for enhancing the responsiveness of GC cells to chemotherapy, presenting a promising strategy to combat resistance and enhance the effectiveness of current therapies.

miRNA have emerged as pivotal regulators of radiosensitivity in various cancers, including gastric cancer. These small, non-coding RNAs modulate key cellular responses to ionizing radiation, such as DNA damage repair, cell cycle progression, and apoptosis [85]. Research highlights that specific miRNAs, including miR-21, miR-210, and miR-451, directly influence the expression of proteins essential for DNA repair mechanisms, such as H2AX, ATM, and BRCA1. This regulation can significantly affect the radiosensitivity of gastric carcinoma cells. For instance, inhibition of miR-21 and miR-210 has shown promise in enhancing radiosensitivity by impairing the ability of cancer cells to

repair radiation-induced DNA damage, making them more vulnerable to radiotherapy [86-88].

Furthermore, extracellular vesicles (EVs), particularly exosomes, have been identified as carriers of miRNAs that mediate intercellular communication and modulate the tumor microenvironment. EVs can transfer miRNAs like miR-222, which targets PTEN and influences survival pathways such as PI3K/AKT, indirectly affecting cellular response to radiation. Radiation-induced changes in exosome content and miRNA profiles highlight their role in shaping bystander effects and the overall radiosensitivity of tumor cell [89,90].

The dual functionality of miRNAs in cancer therapy extends beyond their role as radiosensitizers. Their expression profiles can serve as valuable biomarkers for predicting treatment responses in gastric cancer patients. This makes miRNAs attractive therapeutic targets for enhancing the efficacy of radiotherapy while also providing diagnostic insights [79,91]. Collectively, these findings underscore the significant potential of miRNAs in advancing precision medicine approaches for gastric cancer treatment.

3.3.2 miRNAs in Targeted Therapy

In addition to enhancing chemosensitivity, miRNAs are essential in modulating important signaling pathways that are frequently disrupted in GC. As a result, they hold significant potential for use in targeted therapies aimed at inhibiting specific oncogenic pathways. One notable miRNA, miR-302b, has been identified as a critical inhibitor of both the RAS/RAF/ERK/MAPK and Wnt/β-catenin pathways, which are vital for promoting tumor growth and metastasis. Reintroducing miR-302b expression in GC cells can significantly decrease proliferation, metastasis, and spread, positioning it as a possible candidate for personalized treatments targeting multiple oncogenic pathways [92].

Similarly, miR-100 targets BMPR2 and CXCR7, through targeting these pathways, miR-100 diminishes the metastatic capabilities of gastric cancer cells. Furthermore, miR-100 has been found to regulate the PI3K/Akt signaling pathway, which is essential for the viability and cell growth of cancer cells. Targeting miR-100 presents a potential strategy for disrupting the PI3K/Akt pathway in personalized treatments for GC [28].

MiR-34a is another important miRNA that, aside from enhancing chemosensitivity, regulates several oncogenic pathways, including the PI3K/Akt and Notch pathways. By inhibiting these pathways, miR-34a reduces tumor growth and stem cell renewal, positioning it as a candidate for targeted therapies designed to eradicate GC stem cells (GCSCs) and minimize the risk of tumor relapse [39].

Additionally, miR-23a has multifaceted capability in GC by inducing EMT, invasion, and metastasis, while regulating autophagy-related genes. Targeting miR-23a in conjunction with other therapies could provide a promising approach to inhibit the PI3K/Akt and EMT pathways, both of which are crucial for metastatic progression and therapeutic resistance [93].

MiR-145 suppresses key signaling pathways consist PI3K/Akt and VEGF. By targeting these pathways, miR-145 effectively represses spread, metastasis, and angiogenesis in GC. Its potential for use in targeted therapies aims to suppress tumor growth and metastatic spread by disrupting pro-angiogenic and pro-survival signaling [94].

In summary, miR-302b, miR-100, miR-34a, miR-23a, miR-145, and miR-21 regulate key oncogenic pathways in gastric cancer, including PI3K/Akt, Wnt/β-catenin, and Notch. Targeting these miRNAs offers a promising approach for personalized therapies aimed at inhibiting tumor growth, metastasis, and therapeutic resistance in gastric cancer.

4. miRNAs and Tumor Angiogenesis in Gastric Cancer

Angiogenesis, the development of new blood vessels, is crucial for tumor development, invasion, and metastasis. In gastric cancer, various miRNAs have been recognized as important modulators of this process by influencing angiogenic factors, signaling pathways, and tumor suppressor genes. For example, miR-21 notably enhances angiogenesis by inhibiting the tumor suppressor gene RECK, which plays a role in both metastasis and angiogenesis. Through the downregulation of RECK, miR-21 promotes the creation of new blood vessels, thereby aiding in tumor advancement [95].

Another important miRNA, miR-132, enhances angiogenesis by targeting p120RasGAP, an inhibitor of Ras signaling. This action promotes endothelial cell activation and pathological angiogenesis, which are crucial for the growth and dissemination of gastric tumors [96]. Conversely, some miRNAs act as tumor suppressors by inhibiting angiogenesis. miR-26a/b targets VEGFA (vascular endothelial growth factor A), a major pro-angiogenic factor in the tumor microenvironment. By suppressing VEGFA, these miRNAs reduce angiogenesis and the growth of GC tumors in vivo [97].

Similarly, miR-205-5p serves as a tumor suppressor by downregulating VEGFA and fibroblast growth factor 1 (FGF1), both essential for angiogenesis. Through this mechanism, miR-205-5p inhibits the angiogenic signaling required for tumor progression [98]. Additionally, miR-29c regulates the VEGFA/VEGFR2/ERK pathway, which is critical for cancer stem cells (CSCs) and EMT. By inhibiting this pathway, miR-29c effectively reduces both angiogenesis and metastasis in GC [99].

Other miRNAs, such as miR-145, miR-506, and miR-874, have also been shown to inhibit angiogenesis and metastasis through key signaling pathways, such as the PI3K/Akt and VEGF pathways [100,101]. Furthermore, miR-574-3p and miR-210 are associated with hypoxia-induced angiogenesis in gastric cancer. Their

overexpression results in elevated levels of VEGF and hypoxia-inducible factor 1-alpha (HIF-1α), promoting cell proliferation, migration, invasion, and angiogenesis [102,103].

Additionally, miR-612 has been shown to suppress invasion, migration, angiogenesis, and EMT in gastric cancer cells, aligning its effects with the overexpression of paired box 8 (PAX8) [104].

Consequently, miRNAs in GC can act in opposing ways, either facilitating or suppressing angiogenesis, depending on their particular targets and the pathways they influence.

MiRNAs are essential for regulating TME, which includes diverse cell types such as immune cells, fibroblasts, endothelial cells, and non-cellular elements like cytokines and the extracellular matrix (ECM). By managing the interactions between tumor cells and their surrounding environment, miRNAs can affect tumor growth, immune evasion, and resistance to therapy [105,106].

One important miRNA, miR-210, is engaged in the control of M2 macrophage polarization, a process associated with immunosuppression and tumor promotion. In GC, elevated levels of miR-210 correlate with the infiltration of M2-like TAMs, which facilitate angiogenesis and metastasis, particularly in cases of peritoneal metastasis. This indicates that miR-210 contributes to the establishment of an immunosuppressive and pro-angiogenic environment [107].

Similarly, miR-21 not only promotes angiogenesis but also modulates the immune response by affecting the polarization of TAMs toward the M2 phenotype. This shift enhances tumor cell motility, metastasis, and resistance to therapy. Furthermore, miR-21 affects the expression of PD-L1, thereby further reinforcing the immunosuppressive environment in GC [108].

MiR-30c regulates macrophage differentiation within the TME. Under hypoxic conditions, reduced expression of miR-30c in TAMs lowers mTOR and glycolysis activity, inhibiting M1 macrophage differentiation and their associated antitumor effects, facilitating an environment conducive to tumor progression [109].

In addition, miR-145 and miR-506 inhibit angiogenesis by targeting VEGF and other signaling molecules within the TME. These miRNAs act as tumor suppressors, diminishing the pro-angiogenic signaling required for tumor growth and metastasis [100,110]. MiR-23a, which is overexpressed in GC, promotes angiogenesis by inhibiting the tumor suppressor gene PTEN, which negatively controls the PI3K/Akt pathway. Consequently, miR-23a enhances EMT and angiogenesis, playing a role in the aggressive characteristics of GC [111].

Furthermore, miR-616-3p activates the AKT/mTOR signaling pathway by targeting PTEN, thus driving EMT and angiogenesis in GC. This miRNA reshapes the TME to support tumor growth and metastasis [112]. Additionally, miR-487a and miR-588 are transferred from M2 macrophages to GC cells via exosomes, promoting GC progression and increasing resistance to chemotherapy. These findings underscore the impact of cell-to-cell communication within the TME in supporting tumor survival and therapy resistance [113].

In summary, miRNAs are key regulators of angiogenesis and the tumor microenvironment in gastric cancer. By targeting multiple pathways, including VEGF, PTEN, and PI3K/Akt, miRNAs promote or inhibit angiogenesis and modulate immune cell function, stromal cell behavior, and the extracellular matrix. This makes miRNAs critical players in gastric cancer progression and potential targets for therapeutic intervention.

5. miRNAs and Immune Regulation in Gastric Cancer

The TME in gastric cancer comprises various immune cells, including macrophages, T cells, myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs). Together with non-cellular elements like cytokines, the extracellular matrix (ECM), and stromal cells, these components establish an immunosuppressive setting that facilitates tumor growth and spread. MiRNAs are vital in regulating the activities of these immune cells, influencing the function, differentiation, and polarization within the gastric cancer TME [114,115].

5.1 miRNAs Modulating Macrophage Polarization

TAMs are a major component of the GC TME, and their polarization toward the M2 phenotype is linked to immunosuppression, proliferation, angiogenesis, and metastasis. MiRNAs have been demonstrated to significantly regulate the polarization of TAMs, thereby impacting the immune response in GC [116].

One of the key miRNAs in this context is miR-21, which promotes the M2 phenotype by modulating pathways that enhance tumor progression and immune evasion. By affecting tumor cell movement, M2 macrophage polarization, and the levels of PD-L1 expression, miR-21 contributes to the immunosuppressive state of the TME. This promotion of M2 macrophage differentiation enhances the pro-tumor functions of TAMs, such as supporting angiogenesis and metastasis, while simultaneously weakening the antitumor immune response [117].

Another important miRNA, miR-30c, regulates TAMs under hypoxic conditions, which are frequently encountered in the GC TME. Reduced expression of miR-30c in these conditions decreases mTOR and glycolysis activity in TAMs, inhibiting their differentiation into M1 macrophages, which typically exert antitumor effects. This shift towards the M2 phenotype diminishes the antitumor functions of TAMs, facilitating tumor growth and immune escape [109].

Additionally, miR-487a and miR-588 are transferred from M2 macrophages to gastric cancer cells via exosomes, supporting cancer progression and increasing resistance to chemotherapy. These miRNAs highlight the importance of intercellular communication within the

TME and demonstrate how TAMs can promote tumor survival through miRNA signaling [113,118].

Moreover, miR-210 has been linked to the infiltration of M2-like TAMs in gastric cancer tissues, particularly in the context of peritoneal metastasis. High levels of miR-210 in TAMs promote a pro-tumor environment, that supports tumor progression, angiogenesis, and immune suppression. Collectively, these miRNAs contribute to the polarization of TAMs toward the M2 phenotype, fostering an immunosuppressive environment that favors gastric cancer progression and metastasis [103,107].

5.2 miRNAs and T-cell Regulation

T-cells are essential for the immune response against tumors, but in the context of gastric cancer, TME often inhibits T-cell activity. This creates an environment that allows tumors to evade immune detection effectively. Various miRNAs are significant controls of T-cell differentiation and function, contributing to the immunosuppressive characteristics of GC TME [119].

Among these, miR-34a stands out as a crucial miRNA that influences T-cell function in gastric cancer TME. Under hypoxic conditions typically found in tumors, the expression of miR-34a is diminished, negatively impacting the immune response against gastric cancer cells. The reduction of miR-34a leads to a weakened T-cell-mediated immune response, allowing the tumor to escape immune surveillance and promoting tumor progression. Specifically, miR-34a is vital for the differentiation of T cells, decreasing the population of effector T cells, such as Th1 and Th17 cells, which are crucial for antitumor activity, while simultaneously promoting the differentiation of Tregs that suppress the immune response [60,120,121].

Moreover, exosomes originating from GC cells have been found to influence T-cell differentiation. through the transfer of miRNAs. For example, miRNAs present in these exosomes can facilitate the formation of neoplastic Tregs, further suppressing the immune response within the TME. This alteration in T-cell differentiation contributes to an immunosuppressive environment that supports tumor growth and metastasis [89]. Moreover, miR-130b and miR-130-3p have been implicated in enhancing the interactions between macrophages and T cells, which further promotes immune suppression within the gastric cancer TME. These miRNAs can indirectly modulate T-cell function by influencing other immune cells, such as TAMs and MDSCs, which ultimately affect T-cell activity [122]. Furthermore, miR-107 is delivered via exosomes to MDSCs, amplifying and activating these immunosuppressive cells. The activation of MDSCs leads to further inhibition of T-cell activity, thereby contributing to the overall immunosuppressive environment in gastric cancer [123].

In summary, miR-34a, miR-21, and miR-130b are critical regulators of T-cell differentiation and activity within the gastric cancer TME. By modulating T-cell activity and promoting the proliferation of regulatory T-cells, these miRNAs contribute to creating an immunosuppressive milieu that facilitates tumor growth, metastasis, and resistance to immune therapies.

6. Conclusions and Prospects

MiRNAs are key components in the metastatic dynamics of gastric cancer, acting as both oncogenes and tumor suppressors. They influence essential processes like EMT, invasion, migration, angiogenesis, and immune evasion, all vital for the progression of gastric cancer. The alteration of miRNA expression in this context underscores their potential as biomarkers for early detection, prognostic assessment, and therapeutic targets. Oncogenic miRNAs, such as miR-23a, miR-21, and miR-100, promote tumor progression by enhancing metastasis and drug resistance, while tumor-suppressing miRNAs including miR-34a, miR-145, and let-7a, inhibit these processes, offering hope for therapeutic intervention. Harnessing miRNAs for clinical applications could revolutionize GC management by enabling more effective, personalized treatments to curb metastasis and improve overall patient survival. Future research should focus on validating miRNAs as therapeutic targets and exploiting their role in shaping the tumor microenvironment for better clinical outcomes.

Authors' Contributions

AZT and SV wrote the manuscript comprehensively in all parts, and SV supervised and edited the manuscript scientifically and technically. All the authors read the manuscript comprehensively and confirmed the final revised version. Importantly, there is no conflict of interest.

Conflict of Interest

The authors have no conflicts of interest to disclose, both financially and intellectually.

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