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Non-coding RNA in the Regulation of Gastric Cancer Tumorigenesis: Focus on microRNAs and Exosomal microRNAs

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ABSTRACT

Gastric cancer has become the leading type of cancer on an international scale, with metastatic cancer being the leading cause of mortality associated with this illness. Consequently, methods for early detection have been established, mainly through the use of non-invasive biomarkers present in different bodily fluids. Exosomes are distinct extracellular vehicles that transport cellular signals over long distances via diverse contents. They may be readily seen in bodily fluids due to their secretion by gastric cancer cells or cells in the gastric cancer-tumor microenvironment. Given this context, multiple biological and functional features of human tumors, especially gastric cancer, are intricately connected to exosomal non-coding RNAs (ncRNAs). Exosomal microRNAs play a crucial role in several stages of gastric cancer progression, facilitating the transfer of genetic information between cancer cells and other cells. This process regulates tumor angiogenesis, growth, metastasis, immunological responses, and medication resistance. They engage with several regulatory complexes that have different enzymatic activities. These complexes then alter the chromatin landscapes, including changes to nucleosomes, DNA methylation, and alterations to histones. This research delves into the essential regulatory mechanisms of exosomes in gastric cancer. Furthermore, the existing understanding of the functions of exosomal miRNAs in this context was evaluated, aiming to confirm their potential significance in identifying biomarkers, elucidating their roles in immune evasion and drug resistance, and ultimately evaluating therapeutic strategies.

Keywords: Non-coding RNA, ncRNA, gastric cancer, tumorigenesis, exosomal microRNAs

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Introduction

The identification of exosomes, tiny vesicles measuring between 30 and 150 nm in diameter, was initially reported in 1983 within sheep reticulocytes (1, 2). Subsequent investigations have shown that exosomes are derived from several types of cells and may be detected in the cell-conditioned medium, as well as particular physiological fluids, including amniotic fluid, serum, plasma, urine, saliva, ascites, and cerebrospinal fluids (3). Initially, exosomes were believed to function only as a means for cells to eliminate trash. However, further investigations have shown their capacity to serve as a mediator in facilitating communication between cells (4-6). Exosomes have many functions in regulating the immune system, promoting the growth of new blood vessels, triggering cell death, influencing cell specialization, and facilitating cell growth. Exosomes perform these roles by binding to particular receptors located on the surfaces of target cells, which aid in the delivery of biomolecules, including proteins, lipids, messenger RNAs (mRNA), and non-coding RNAs (ncRNAs) (7, 8).

Non-coding RNAs are RNA molecules that have functional roles but do not undergo translation to become proteins (9, 10). These molecules are transcribed from about 70% of the genome and play vital roles in cellular activities, such as transcription and translation. There are around 40 distinct forms ofncRNAs, which mainly include ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and microRNAs (miRNAs) (11-13). The presence and function of miRNAs in cancer have been the primary source of evidence connecting ncRNAs to human illnesses (14). Nevertheless, our comprehension of the involvement of ncRNAs in illnesses is still evolving. An analysis of the chronology of ncRNAs is advantageous for acquiring a more profound understanding of the exploration and investigation history of ncRNAs concerning human well-being and illnesses (15-17). During the 1950s, the identification of housekeeping ncRNAs, such as tRNA (12) and rRNA (13), supported Francis Crick's "central dogma" hypothesis. This hypothesis suggests that genetic information may go from DNA to RNA to protein. Further investigations uncovered new types of ncRNAs, such as circRNAs, small nucleolar RNAs (snoRNAs) (11), and small nuclear RNAs (snRNAs) (18). The first documented mentions of lncRNAs, including Xist and H19, may be traced back to the late 1980s (19). The release of the human genome sequence in 2001 unveiled that only 1.2% of the genome's genes were responsible for encoding proteins, while the outstanding genes were categorized as "non-coding." In 1993 and 2000, the initial short temporal RNAs were discovered, lin-4 and let-7, respectively (20). Non-coding RNAs may function as universally present molecules essential for cellular processes such as proliferation and the spread of cancer cells. Furthermore, it was specified that several genes encode separate transcripts rather than proteins (21). NcRNAs are instrumental in controlling gene expression at different phases, which include transcriptional, post-transcriptional, and translational levels. This regulation, in turn, impacts the signaling networks associated with these genes (22). Moreover, their interactions may regulate the stability or frequency of different ncRNA types. In 2007, it was shown that exosomes could carry mRNA and miRNAs to other cells. Subsequently, abundant data have shown several ncRNAs, the most significant ones being miRNAs, lncRNAs, and circRNAs. These ncRNAs may be enclosed and carried by exosomes, elucidating their roles in cellular interactions (23). Notably, there are variations in how exosomal ncRNAs are expressed in gastric cancer. This implies that the macromolecules identified in exosomes could be significant in the onset and progression

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of gastric cancer (10, 12, 13, 24, 25). Due to their differential expression in pathological conditions, exosomal ncRNAs are proposed as potential diagnostic and therapeutic strategies for gastric cancer (1, 26, 27).

Previous studies have focused solely on reporting results without critically assessing them. Furthermore, there is a lack of review articles on the effects of exosome-containing microRNAs. Therefore, our investigation explores the impact of exosomal non-coding RNAs, including miRNAs, lncRNAs, and circRNAs, on the physiopathology, clinical diagnosis, and treatment of gastric cancer. The present review article explores exosomal microRNAs in gastric cancer, assessing their potential as biomarkers and mechanisms of action. Additionally, the manuscript emphasizes the significance of exosomal microRNAs in gastric cancer, which are crucial for intercellular communication and tumor progression.

Histological phenotypes of gastric cancer

Gastric cancer exhibits significant heterogeneity from a morphological perspective, as shown by the wide range of histological categories (28, 29). Lauren created the most often-used classification for gastric cancer, which divides it into two basic categories, intestinal and diffuse types (30). These types also differ from each other in terms of clinical and epidemiological characteristics. Intestinal-type tumors often grow outward, frequently develop ulcers, and are linked to intestinal metaplasia in the stomach. Diffuse-type tumors represent undifferentiated infiltrating injuries that contribute to the swelling of the stomach, which manifests as linitis plastica. Patients with diffuse-type tumors typically experience a less favorable prognosis in comparison to those with intestinal-type tumors (31). Intestinal-type malignancies are often found in the proximal region, while diffuse-type tumors are more prevalent in younger individuals. Notably, diffuse-type tumors have a virtually equal proportion of males and females, in contrast to the higher number of males in intestinal-type tumors (32).

Molecular characteristics associated with gastric cancer

Gastric cancer, like other cancer types, is characterized by genetic and epigenetic alterations that contribute to its development, progression, and response to treatment (33). In prior studies on gastric cancers at the genome level, certain molecular characteristics such as chromosomal instability (CIN), microsatellite instability (MSI), CpG island methylator phenotype (CIMP), and stable or diploid tumors have previously been identified and extensively acknowledged (34). The introduction of high-throughput methods for studying the genome, transcriptome and proteome have shown significant genetic and epigenetic diversities across different tumors in stomach cancers (28, 29). These findings have also emphasized the intricate molecular nature of this illness.

Several molecular categorization methods emerged as a result of profiling stomach tumors. Gene expression profiling has been used to identify subgroups that might potentially forecast patients' survival and determine their responsiveness to therapy approaches. The data obtained from cell lines have been analyzed using unsupervised hierarchical clustering, which identified two main subtypes of gastric cancer. These subtypes, named G-INT and G-DIF, have distinct genomic signatures. The G-INT subtype is related to intestinal tumors and is characterized by an enrichment of biological functions related to carbohydrate and protein metabolism and cell adhesion. In contrast, the G-DIF subtype is connected to diffuse tumors and is characterized by a higher concentration of functions related to cellular growth and fatty acid metabolism (35). While reporting a connection between Lauren's histotypes; the total agreement was only 64%. As a

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result, the G-INT and G-DIF molecular subtypes were regarded as separate. Contrary to Lauren's categorization, it was shown that the gene expression patterns of G-INT and G-DIF were predictive of poor survival in different groups of patients. Additionally, it was observed varying sensitivities among G-INT cell lines to the chemotherapeutic agent's 5-fluorouracil and oxaliplatin and differing responses of G-DIF cell lines to cisplatin. Moreover, patients diagnosed with G-INT tumors experienced advantages from adjuvant therapy utilizing 5-fluorouracil (35).

After conducting an initial investigation, researchers used gene expression profiling to identify several forms of gastric cancer, including those characterized by increased cell division, metabolic activity, and mesenchymal features (36). Most proliferative subtype tumors are of the intestinal type and exhibit elevated levels of genomic instability. These tumors often display amplification of the ERBB2, KRAS, CCNE1, and MYC genes, as well as DNA hypomethylation (37). Additionally, they are characterized by a high frequency of mutations in the tumor suppressor gene TP53 (38, 39). Tumors of the mesenchymal subtype are mostly of the diffuse kind and consist of cells that possess characteristics of cancer stem cells. These tumors are especially responsive to inhibitors that target the PI3K-AKT-mTOR kinase pathway (40, 41). Tumors of the metabolic subtype include both diffuse and intestinal histological types. They exhibit elevated expression of genes related to metabolic pathways and display spasmolytic polypeptide-expressing metaplasia (SPEM) characteristics. In laboratory tests, the tumor cells of the metabolic subtype showed sensitivity to 5-fluorouracil (42, 43). This aligns with the results from two separate groups of metabolic subtype gastric cancer patients, which showed that therapy with 5-fluorouracil improved their cancer-specific and disease-free survival.

Taxonomies of non-coding RNA

Eukaryotic genome transcription is a ubiquitous process. In conjunction with protein-coding genes, ncRNAs are vital in overseeing various complex cellular and molecular processes (44, 45). The advancement in RNA sequencing technology and bioinformatics techniques have significantly enhanced the study of ncRNA. These methodologies have revealed ncRNAs' critical roles in various biological processes (46). The role of ncRNAs in gene regulatory networks is crucial, as they interact with various biomolecules, such as coding RNAs, other non-coding RNAs, DNA, and proteins (47).

Eukaryotic transcription produces many species of ncRNA, which may be derived from different DNA regions and have the potential to be translated into ncRNAs (48). The ncRNA may be classified into two classes according to their regulatory activities (48). Housekeeping ncRNAs are extensively present in cells and primarily regulate fundamental cellular functions (49).

Housekeeping non-coding RNAs

Housekeeping ncRNAs, comprising rRNAs, tRNAs, snRNAs, snoRNAs, and telomerase RNAs, have seen much research in recent decades since they are among the first discovered ncRNA types (50). These ncRNAs are usually brief, spanning 50 to 500 nucleotides (nt). They are consistently generated in all kinds of cells and are crucial for cell survival. Apart from their essential involvement in RNA splicing, RNA modifications, and protein creation (rRNAs, tRNAs, and snRNAs), housekeeping ncRNAs may also cleave to perform regulatory activities. Two new types of small regulatory non-coding RNAs, known as tRNA-derived RNA fragments (tRFs) and translation-interfering tRNAs (tiRNAs), are generated from tRNA or pre-

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tRNA (51). Research has shown that miRNAs may hinder translation by attracting intricately arranged clusters of proteins and RNAs during stress (52). Furthermore, researchers have discovered other types of short RNAs derived from snoRNAs by using deep sequencing in conjunction with bioinformatics analysis. These include sno-derived RNAs, sno-miRNAs, and sno-piRNAs (53).

Regulatory non-coding RNAs

Regulatory ncRNAs may be ordered into two groups depending on their average size: short non-coding RNAs with transcripts less than 200 nt and long non-coding RNAs with transcripts more than 200 nt (54, 55). Short-interfering RNAs (siRNAs), piwi-interacting RNAs (piRNAs), and microRNAs are the main categories of short ncRNAs (56, 57). However, some non-coding RNAs with varying lengths might belong to two separate groups simultaneously: enhancer RNAs (eRNAs), circRNAs, and promoter-associated transcripts (PATs) (58-60).

MicroRNAs

The miRNAs formed from transcribed hairpin loop structures are the most common class of short ncRNAs (61, 62). They streamline the process of post-transcriptional gene silencing and regulate gene expression in both the cytoplasm and nucleus via several mechanisms (63, 64). Due to their significant involvement in the complex interactions among different RNA species, miRNAs have been widely recognized as a prominent research subject. miRBase version 22 has been updated to include 48 more species, bringing the total number of mature miRNAs to 48,860 and hairpin precursors to 38,589 (65). These miRNAs and precursors are from 271 different taxa, which include viruses, plants, mammals, and unicellular algae (66).

Long non-coding RNA (lncRNA)

LncRNAs refer to transcripts that are longer than 200 nt and cannot code proteins. LncRNA may be classified into five classes based on its proximity to protein-coding genes (10, 67). Transcription on both strands in intergenic regions produces lincRNAs or long intergenic noncoding RNAs. Protein-coding genes undergo complete transcription of their introns, producing lengthy intronic ncRNAs (9, 68, 69). Exons of protein-coding genes are incorporated into sense-long non-coding RNAs, which are generated from the same strand of DNA (70-72). LncRNAs may be classified into two classes based on their regulatory effects on DNA sequences: trans-lncRNAs (trans-acting lncRNAs) that influence genes located far away, and cis-lncRNAs (cis-acting lncRNAs) that regulate the expression of genes close (73). Additional processing of certain lncRNAs may produce small non-coding RNAs such as miRNAs, piRNAs, and snoRNAs (11,74-76).

Circular RNA

Circular RNAs are a specific category of endogenous non-coding RNAs with covalently closed loop structures (27, 77, 78). In recent years, circRNA has gained more attention due to advanced deep sequencing and bioinformatics studies despite being known for many years (79-82). Although most circRNAs found in plants and animals are typically several hundred nucleotides in length, their sizes may range from 100 nucleotides to more than 10,000 nucleotides (83-86). Circular RNAs function similarly to other non-coding regulatory RNAs, participating in various biological activities, including transcription and alternative RNA splicing. They act as miRNA sponges and compete with endogenous RNAs (ceRNAs) (87-89).

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Relationship between microRNA and gastric cancer

Recent research on miRNAs has shed light on their role in the formation and progression of gastric cancer (GC). This analysis has been focused on the functional relationships between specific miRNAs, their potential target genes, and the signaling pathways involved in the main pathological processes of GC. The presence of *Helicobacter pylori* infection is well acknowledged as an essential contributor to the significant morbidity associated with gastric cancer. Yang et al. analyzed the quantity of miRNA in individuals with GC infected with *H. pylori*. It was revealed that *H. pylori* infection correlates with distinct cancer-related pathways modulated by the communication networks connecting miRNA and mRNA (90). Notably, miR-155 forms T helper 17 (Th17) and Th1 cells, which are crucial for immunological responses against *H. pylori* infection (91). It was shown that the presence of pylori cytotoxin-associated gene A (Cag A) hinders the action of miR-26b, leading to an upregulation of its possible target gene, karyopherin alpha 2 (KPNA2), which is known to facilitate the spread of cancer (92). MiR-143-3p was identified as the miRNA, exhibiting the most significant elevation in gastric cancer tissues that tested positive for Helicobacter pylori, hindering the development of tumors.

It has also been shown that miR-155, miR-16, and miR-146a demonstrate heightened expression in gastric epithelial cells infected with *H. pylori. Helicobacter pylori* infection was correlated with increased concentrations of miR-155 in the mucosal tissues of patients diagnosed with *Helicobacter pylori* infection (93). These studies illustrate the simultaneous influence of miRNAs on *H. pylori*-related tumorigenesis, which is linked to the inflammation caused by *H. pylori* infections. Several investigations have particularly

Table 1. Up-regulated miRNAs and their putative targets and signaling pathways relevant to gastric cancer tumorigenesis.

miRNA	Target genes	Signaling pathway
21	15-PGDH	PGE2/PI3K/Akt/Wnt/β-catenin
21	PTEN	PTEN/PI3K/mTOR
27a	SFRP1	Wnt/β-catenin
103	KLF4	-
106a	FAS	-
107	NF1	-
107	PTEN	PI3K
146a	SMAD4	
151-5p	P53	Notch1
192/215	APC	Wnt/β-catenin
194	SUFU	Wnt/β-catenin
200c	$P27^{Kip1}$	-
558	HPSE	-
590-5p	RECK	Akt/ERK; STAT3
208a-3p	PDCD4	
423-3p	Bim	
454	CHD5	-
520c	IRF2	-
3174	ARHGAP10	-

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examined the influence of miRNAs on the progression of GC by targeting cellular signaling networks and genes. In Table 1, the miRNAs and their important targets are detailed, highlighting their critical involvement in the development and programmed cell death associated with gastric cancer. The PI3K/Akt/mTOR signaling pathway regulates gene expression across multiple human cancers (94-96). This pathway is also involved in regulating the progression of the cell cycle, apoptosis, translation of genetic data into proteins, cellular metabolism, and angiogenesis (97-100).

An instance of this is the observation that elevated levels of miR-21 in GC specifically target the 15-hydroxyprostaglandin dehydrogenase (15-PGDH) gene and the phosphatase and tensin homolog (PTEN) gene, hence stimulating the growth of GC (Tables 2, 3) (101). Through activating the prostaglandin E2 (PGE2)/PI3K/Akt/Wnt/β-catenin axis, miR-21 stimulates the development of GC cells, resulting in cell proliferation (101-104). Furthermore, miR-495 selectively interacts with Akt and mTOR, and its up-regulation hinders proliferation and triggers apoptosis in GC cells. This mechanism operates through the suppression of the PI3K/Akt/mTOR signaling cascade, leading to modifications in the expression levels of Bax, caspase-3/-9, and cyclin D1 (105). Additionally, research has shown that MiR-495 induces the death of GC cells by initiating a form of autophagy that does not rely on the Beclin 1 protein but is triggered via the Akt/mTOR axis (106).

MiR-25 has a suppressive impact on diffuse-type gastric cancer in humans. Inhibition of miR-25 results in elevated levels of collagen type I alpha 2 chain (COL1A2) and decreased expression of the E-cadherin gene (107). Furthermore, it has been shown that miR-25 inhibits the expression of the p53 gene and enhances the activation of c-Src, indicating its involvement in intestinal-type gastric cancer (107). Overexpression of miR-30a in SGC-7901 cells resulted in a rise in E-cadherin levels and a reduction in N-cadherin levels. This activity of miR-30a helped to reduce multidrug resistance (MDR) and regulate epithelial-mesenchymal transition (EMT) in GC cells (108). The tumor microenvironment (TME) refers to the intricate surroundings inside the tumor, consisting of fibroblasts, blood vessels, immunological and inflammatory cells, adipose cells, and the extracellular matrix (46). Every element inside the TME has a distinct role and serves a specific purpose concerning the growth and advancement of the tumor. This section will discuss the close relationship between miRNAs and the regulation of the tumor microenvironment (TME) in GC.

CAFs play a crucial role in forming the reactive stroma, creating a favorable environment for tumor growth in cancer (109-111). Researchers have advanced our existing comprehension of the oncogenic roles of cancer-associated fibroblasts (CAFs), discovering that the disruption of miRNAs in stromal cells has a substantial impact on this crucial TME, potentially facilitating the conversion of CAFs to enhance cancer advancement (112-114). For example, the expression of miR-149 has a detrimental effect on CAFs, facilitating communication with tumor cells via the PGE2/interleukin-6 (IL-6) signaling pathway (115, 116). CAF cells have been shown to have increased expression of miR-106b, which enhances cell motility and invasion by specifically targeting the PTEN gene (117). Studies have shown that low miR-200b and miR-200c levels are associated with a generally worse outcome in individuals with GC (50). Recent research found that the downregulation of miR-200b was linked to the transformation of CAF in GC (118-120). More precisely, researchers identified the methylation of the miR-200b promoter in gastric cancer (GC) patients who had high levels of alpha-smooth muscle actin (α-SMA), a particular marker for CAF (108). Additional

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Table 2. Down-regulated miRNAs and their putative targets and signaling pathways relevant to GC tumorigenesis.

miRNA	Target genes	Signaling pathway
15a	Bmi-1	-
15a-3p 16-1-3p	Twist1	-
16-5p	Smad3	-
26b	KPNA2	KPNA2/c-Jun
29b	KDM2A	RUNX3/miR-29b/KDM2A
29c-3p	KIAA1199	FGFR4/Wnt/β-catenin; EGFR
31	HDAC2	-
101	MCL1/ZEB1	-
127	MAPK4	-
132-3p	MUC13	Akt/ ERK
135a	KIFC1	-
143-3p	AKT2	-
154	DIXDC1	Wnt
194	KDM5B	-
199a/b-3p	PAK4	PAK4/MEK/ERK
202-3p	Gli1	-
203a	E2F3	-
203	Slug	-
204	CKS1B/CXCL1/GPRC5A	-
337-3p	MMP-14	-
338-3p	SOX5	Wnt/β-catenin
375	YAP1/TEAD4/CTGF	Hippo
495	Akt; mTOR	PI3K/Akt/mTOR
511	TRIM24	PI3K/Akt; Wnt/β-catenin
520f-3p	SOX9	Wnt/β-catenin
524-5p	MMP-2/MMP-9	-
584-3p	MMP-14	-
647	SRF	SRF/MYH9
873	STRA6	Wnt/β-catenin
1284	EIF4A1	-
3978	LGMN	-

functional investigations have shown that CAF might enhance the invasion of tumors by modifying the expression of miR-200b in gastric cancer (GC) cells via epigenetic mechanisms (108). MiR-141 is a kind of gene that helps prevent the growth of tumors. It belongs to a group of genes called the miR-200 family. In the case of GC cells, MiR-141 was shown to be less active, and this was linked to increased cell growth in the MGC-803, HGC-27, SGC-7901, and BGC-823 cell lines (121). It targets the STAT4 gene, which plays a role in converting normal fibroblasts into CAF in AGS cells (121)

In addition, the responsiveness of GC cells to chemotherapeutic medicines can be increased by the

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Table 3. Exosomal miRNAs as prognostic molecular markers.

Cancer	Exosomal miRNAs	Type of biomarker
Esophageal cancer(ESCC)	30a	Growth
Gastric cancer	21	Invasion
Gastric cancer	221	Invasion
Colorectal cancer	19a	Invasion
Colorectal cancer	21, 192 and 221	-
Colorectal cancer	23b-3p	Inhibitor
Liver cancer	122	Inhibitor
Liver cancer	223	Inhibitor
Pancreatic cancer	19b	Diagnosis
Pancreatic cancer	23b-3p	Growth and Invasion
Pancreatic cancer	122-5p and 193b-3p	Growth
Pancreatic cancer	141	Invasion
Pancreatic cancer	141 and 375	Invasion
Pancreatic cancer	145	Inhibitor
Pancreatic cancer	196a-5p	Invasion
Pancreatic cancer	200c-3p	Inhibitor
Pancreatic cancer	1246	Invasion
Pancreatic cancer	1290 and 375	Survival

increased expression of miR-7, miR-23b-3p, miR-30a, miR-33b-5p, miR-34a, miR-101, miR-204, miR-375, miR-647, and miR-939 (122-125). For instance, miR-101 was found to be reduced in GC tissues and in GC cells that are resistant to chemotherapy. This reduction in miR-101 is associated with a reverse relationship to the annexin A2 (ANXA2) gene expression. Inducing the expression of miR-101 could improve the reaction of GC cells to DDP and vincristine (VCR) (126). Furthermore, the GC chemoresistant cell line, SGC-7901/VCR, exhibited resistance to VCR 5-FU, and DDP. Importantly, the mechanistic studies revealed that a specific type of RNA called metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) played a role in developing resistance to chemotherapy in SGC-7901/VCR cells. MALAT1 interacted with a protein called autophagy-related 12 (ATG12) (127). Remarkably, miR-23b-3p was discovered to act as a "connector" between MALAT1 and ATG12. It can inhibit the production of ATG12 and is also directly targeted by MALAT1. The experiments on living organisms showed that the increased expression of MALAT1 led to drug resistance. However, this resistance could be overcome by introducing the expression of miR-23b-3p (127). Figure 1 depicts the mechanistic role of these miRNAs and their potential target genes in gastric cancer chemoresistance (26, 128-130).

The significance of exosomal miRNAs in the onset and progression of gastric cancer

Gastric cancer, a highly malignant tumor with a bleak prognosis, is becoming more prevalent and resulting in increased death rates in China. In 2015, there were 679,100 newly diagnosed cases of GC, accounting for 15.8% of all newly diagnosed cancer cases (131). Consequently, there were 498,000 recorded deaths. CAF, an essential element of the tumor microenvironment (TME), is believed to be responsible for synthesizing several tumor components, growth factors, and chemokines (132). Elevated levels of exosomal

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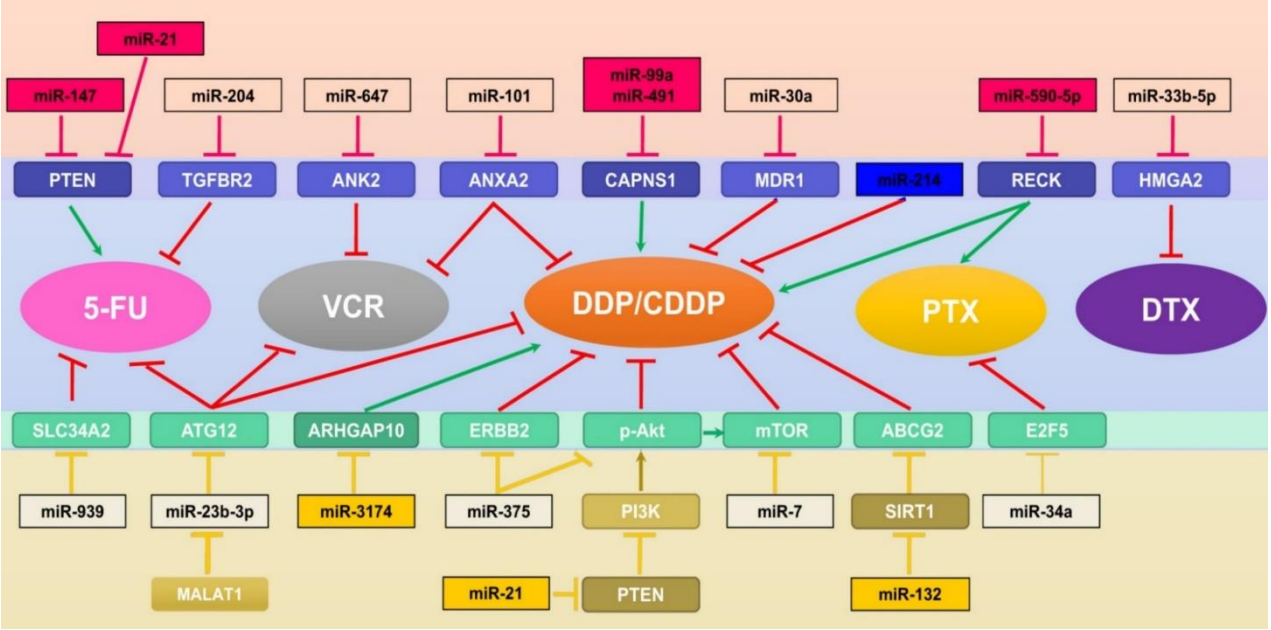


Fig. 1. MiRNAs modulate the chemoresistance of chemoresistanceer cells. PTEN; Phosphatase and tensin homolog: TGFBR; Transforming growth factor beta receptor 1: ANK; Ankyrin 1: ANXA; Annexin A1: CAPNS; Calpain Small Subunit 1: MDR; Multidrug- resistance: RECK; Reversion inducing cysteine rich protein with kazal motifs; HMGA; High mobility group A; 5-FU; 5-Fluorouracil: VCR; Vestibulocollic reflex: CDDP; cis- diamminedichloroplatinum: SIRT; Selective internal radiation therapy.

MMP11 were seen in gastric CAFs. MMPs, also known as zinc-dependent endopeptidases, play a crucial role in regulating the degradation of the extracellular matrix. The overexpression of several members of the MMP family, such as MMP2, MMP9, and MMP11, has been shown to have a role in cancer progression (133). Overexpression of MMP11 in humans' stromal cells indicates a poor survival rate. Additionally, the expression of MMP11 was increased by exosomal miR-139, which was shown to be expressed at lower levels in CAFs. This increase in MMP11 expression resulted in a greater proliferation, invasion, and metastasis of gastric cancer cells (134). While there are additional dioxygenases that play a role in this process, the arachidonate lipoxygenases (ALOX) family is regarded to be the main contributor to the formation of lipid peroxidation, which eventually leads to ferroptosis (135). miR-522 acts as a crucial element in promoting tumor growth by playing a vital role in controlling the decrease of ALOX15 and lipid-ROS, suppressing cell death (136). Although it has been shown that USP7, hnRNPA1, and miR-522 are increased in gastric cancers, normal tissues also have elevated levels of these transcripts (137). Cancer-associated fibroblasts (CAFs) mitigate the accumulation of lipid reactive oxygen species (ROS) and diminish the occurrence of ferroptosis in neoplastic cells through the inhibition of ALOX15. This process is facilitated by the secretion of exosomal miR-522. The miR-15b family of crucial gene regulators is involved in apoptosis, cellular proliferation, and cell cycle regulation. Furthermore, they have been shown to exhibit malfunctions in many illnesses. Moreover, there is strong evidence indicating that miR-15b specifically acts on important BCL-2 family proteins, including pro-apoptotic (Bax) and anti-apoptotic (Bcl-2) members (138). Additionally, it controls the activation of caspases 3, 7, 8, or 9 and influences the formation of tumors by either promoting or inhibiting

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cell activity, growth, or programmed cell death. The DYNLT1/Caspase-3/Caspase-9 signaling pathway is a mechanism by which exosomes generated by BGC-823 cells may transfer miR-15b-3p to recipient cells. This transfer can enhance the development of tumors and the conversion of cells into a malignant state while also inhibiting programmed cell death in laboratory settings and living organisms (139). Human serum exo-miR-15b-3p presents a promising healing objective for GC and may also serve as a valuable biomarker for its diagnosis and prognosis. Research suggests macrophages can experience phenotypic changes in response to the evolving TME. These changes are typically categorized into conventionally activated (M1) and alternatively activated (M2-like) phenotypes. M2-like macrophages secrete a range of potent pro-angiogenic cytokines, growth factors, and enzymes that regulate angiogenesis. While chemotherapy remains the standard treatment for gastric cancer with liver metastases (GC-LM), its effectiveness is somewhat constrained (140). Exo-miR-519a-3p has the potential to be used as a therapeutic target for GC-LM. It is crucial in promoting the contact between primary GC cells and intrahepatic macrophages (6). In addition, the validated miRNAs exhibited increased expression levels in stages III and IV compared to stages I and II and were linked to lymphatic metastases in gastric cancer. The findings indicate that assessing the concentrations of specific miRNAs in serum may act as innovative biomarkers for detecting and managing gastric cancer (125).

Discussion

Over 2500 unique human miRNAs have been discovered, with abnormal functions linked to tumor growth, programmed cell death, invasion, and disease spread. These miRNAs may act as biomarkers for detecting and managing gastric cancer. Exosomal miRNAs within extracellular vesicles play a crucial role in tumorigenesis and disease progression by enabling communication networks between tumor cells and their surrounding microenvironment. They are promising candidates for liquid biopsy methodologies. However, the study of exosomal miRNA remains limited, particularly in cancer biology. This review aimed to investigate the dynamic interactions between exosomal miRNA and various cellular elements, including their relationships with tumor stroma, immune modulation, and drug resistance mechanisms. Exosomes promote communication between cancer cells and their environment, facilitating intercellular dialogue. They transport proteins, mRNAs, and miRNAs to specific cells, suppressing immune responses, enhancing tumor growth, aiding in metastatic processes, nurturing angiogenic development, and establishing resistance to chemotherapy. Exosomal miRNAs present a promising avenue for cancer treatment and management but several limitations exist, including insufficient discovery of exosomal miRNAs, unexplored mechanisms, and lack of reliable extraction methods. The sensitivity and specificity of exosomal miRNA as biomarkers still need enhancement. Exosomal miRNA functions as multi-faceted entities, interacting with a wide array of targets, making it challenging to develop a comprehensive understanding of the regulatory networks involved in exosomal miRNA.

Future directions and research opportunities

Future research should focus on clinical applications of exosomal ncRNAs as biomarkers for early detection and prognosis in gastric cancer. Investigating their presence in bodily fluids may lead to the development of non-invasive diagnostic tools. Targeting exosomal ncRNAs may be a significant area of research, focusing on strategies to inhibit or enhance their function to modulate tumor progression and

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treatment response. Comparative studies between exosomal ncRNAs in gastric cancer and other types of cancers can identify unique signatures and common pathways. Longitudinal studies could track changes in exosomal ncRNA profiles throughout disease progression and treatment, providing insights into tumor dynamics and patient outcomes. Integrating exosomal ncRNAs with other biomarkers may improve diagnostic and prognostic assessments in gastric cancer. Finally, investigating regulatory mechanisms governing exosomal ncRNA release and uptake could reveal new therapeutic targets and enhance intercellular communication in cancer.

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