Mechanisms of miRNAs and their expression in gastric cancer

Abstract

Gastric cancer is the fourth most common cancer in the world and the second leading cause of cancer-related deaths worldwide. Gastric cancer was responsible for approximately 768,000 deaths. MicroRNAs (miRNAs), as short non-coding RNAs, undoubtedly play a central and decisive role in various types of cancer due to their interaction with target genes. Since the discovery of the identity and clinical functions of miRNAs in the past few decades, their potential as therapeutic targets in cancer research has been the focus of extensive study. The aim of this study is to investigate the role of microRNAs in gastric cancer, focusing on their expression, biogenesis, and potential as therapeutic biomarkers. MicroRNAs (miRNAs) are essential regulators of cell proliferation, signaling pathways, and the cell cycle. They can also serve as markers of metastasis in the stomach, liver, and lymph nodes, as well as indicators of response to chemotherapy in cancer patients. Several studies have shown that miRNAs in gastric cancer have been effective as biomarkers for cancer prognosis. Currently, various oncogenic clinical trials are underway, exploring the use of miRNAs in screening, diagnosis, and drug testing. However, many systematic molecular mechanisms, including a detailed investigation of miRNAs and their expression in gastric cancer, remain unknown. Therefore, in addition to presenting the updated results of recent preclinical studies, researchers have investigated the biogenesis of miRNAs and their expression in cancer cells. It is hoped that the analysis of molecular interaction effects and the identification of miRNA target molecules and signaling pathways will contribute to the prevention and treatment of this disease.

Key words: non-coding RNAs, miRNAs, gastric cancer, biomarkers, gene expression

1. Introduction

MicroRNAs (miRNAs) are small, non-coding RNA molecules that play a critical role in regulating gene expression, particularly in the context of cancer. In gastric cancer, miRNAs can act as either oncogenes or tumor suppressors, influencing various cellular processes such as proliferation, apoptosis, and metastasis. Dysregulation of miRNA expression in gastric cancer has been linked to disease progression, with specific miRNAs often found to be either upregulated or downregulated compared to normal gastric tissues. This abnormal expression can contribute to the cancerous phenotype by altering the expression of target genes involved in key signaling pathways (1-4).

The mechanisms by which miRNAs exert their effects in gastric cancer primarily involve the binding of miRNAs to complementary sequences in target messenger RNAs (mRNAs), leading to mRNA degradation or inhibition of translation. For example, miR-21 is frequently overexpressed in gastric cancer and targets several tumor suppressor genes, promoting cell survival and proliferation. Conversely, some miRNAs, such as miR-143 and miR-145, are often downregulated, and their loss can lead to the upregulation of oncogenes. This delicate balance of miRNA expression is crucial, as it can dictate the fate of cancer cells and influence tumor behavior (5, 6). In addition to their roles in regulating gene expression, miRNAs have emerged as potential biomarkers for gastric cancer diagnosis and prognosis. The stability of miRNAs in body fluids, such as blood and gastric juice, makes them attractive candidates for non-invasive diagnostic tests. Research is ongoing to identify specific miRNA signatures that correlate with various stages of gastric cancer, which could aid in early detection and personalized treatment strategies. Overall, understanding the mechanisms of miRNA regulation and expression in gastric cancer

holds promise for developing novel therapeutic approaches and improving patient outcomes (7-9).

Gastric cancer is an important challenge and one of the most common types of cancer worldwide. Although the death rate has decreased in recent years, the prevalence of gastric cancer is still very high in East Asian countries, especially Japan and China. So that China alone accounts for more than 40% of gastric cancer cases worldwide. Gastric cancer occurs more frequently in men than in women. Considering that gastric cancer ranks second in terms of mortality rate, it is very important to emphasize accurate diagnosis and rational treatment to control this disease (10-13). Among the risk factors and factors that increase the incidence of this type of cancer are smoking and high-salt foods, reducing the consumption of vitamins, vegetables, and fruits, viral infections such as Epstein-Barr virus, and infection by Helicobacter pylori (14-17). In recent years, several methods have been proposed to fight this cancer, including the use of natural products, traditional medicine, radiotherapy, and chemotherapy, which are among the conventional methods to control the disease. However, the investigation of systematic molecular mechanisms related to cancer and chemotherapy based on miRNA markers has opened a new therapeutic approach that has attracted the attention of many scientists (18, 19). Therefore, in this research, we tried to clinically analyze the mechanisms of the effect of miRNAs along with their expression in cancer tissues.

1.1. Mechanism of miRNAs biogenesis

1.1.1. Biogenesis of MicroRNAs

As depicted in Figure 1, the biogenesis of microRNAs (miRNAs) occurs in both the nucleus and the cytoplasm. The process begins with RNA polymerase II transcribing the primary miRNA transcript, which is then polyadenylated. This initial transcript spans several kilobases and features a characteristic stem-loop structure.

1.1.2. Primary Processing

The primary miRNA (pri-miRNA) is recognized and processed by a specialized enzyme complex called Drosha, which weighs approximately 650 kDa and possesses RNase III activity. This processing results in the formation of a hairpin precursor that measures between 60 and 110 nucleotides. The precursor is then transported to the cytoplasm with the help of Exportin-5 and Ran-GTP.

1.1.3. Final Processing in the Cytoplasm

Once in the cytoplasm, another RNase III enzyme known as Dicer carries out the final processing of miRNAs. Dicer cleaves the terminal loop of the pri-miRNA, aided by the HIV-1 trans-activating response RNA-binding protein (HIV-1 TRBP). Following this, another TRBP facilitates the connection between the Argonaute protein—characterized by two conserved regions that bind RNA—and the Dicer complex, resulting in the formation of the RNA-induced silencing complex (RISC).

1.1.4. Function of RISC

Argonaute proteins are part of a highly conserved family that, along with a small single-stranded RNA, forms the core of the RISC complex. miRNAs bound to RISC interact with the corresponding 3' untranslated region (UTR) of target mRNAs. Following gene transcription, they regulate gene expression either by cleaving the target mRNA or by inhibiting its translation.

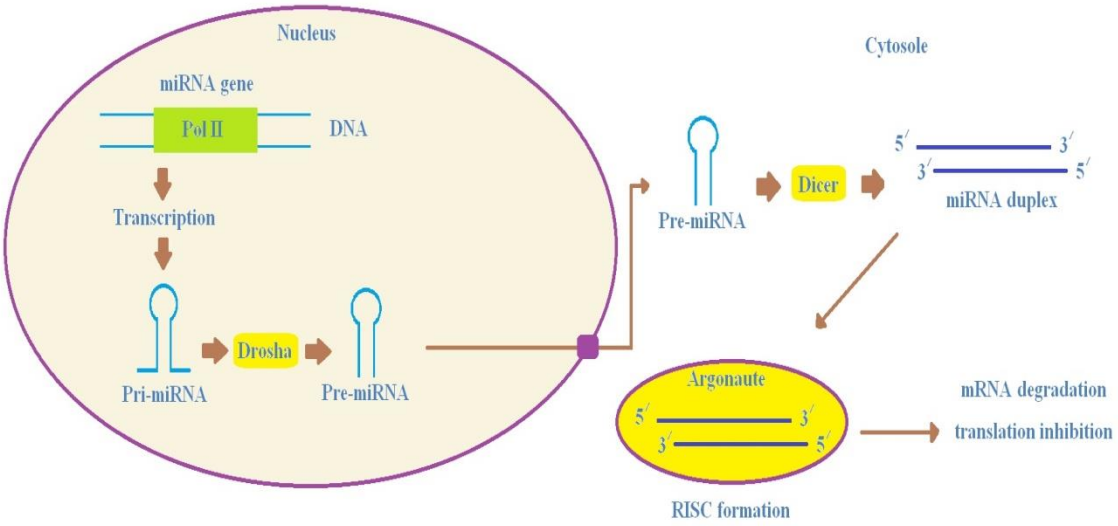

Figure 1. Mechanism of miRNAs biogenesis.

2. Materials and methods

To identify miRNAs in gastric cancer patients infected with Helicobacter pylori, miRNA microarrays (specifically, the microarray miRNA profile 3523 based on miRBase Sanger(20, 21)) were utilized. Total RNA was extracted from both cancerous and non-cancerous tissues, with microscopic guidance employed to avoid contamination from inflammatory and stromal cells, as confirmed by hematoxylin and eosin staining. The identification of miRNAs and subsequent network analysis were conducted using the dbDEMC database (22, 23). Finally, the expression levels of the miRNAs were analyzed using the microarray.

3. Results

3.1. Chemotherapy and miRNAs

Chemotherapy plays a crucial role in treating gastric cancer, demonstrating significant benefits for patients in both the early and advanced stages of the disease (24). However, research is still ongoing to ensure an appropriate therapeutic response for gastric cancer patients through chemotherapy approaches. Chemotherapy agents such as platinum compounds and anthracycline, epirubicin, CDDP (cis-diaminodichloroplatinum II) and 5-FU (5-fluorouracil), taxanes and irinotecan stop cellular processes and cell division. These drugs have been widely used as therapeutic agents and standard therapeutic regimens for years. However, these drugs are associated with severe and toxic side effects that limit their clinical use (25). Many studies have reported that miRNAs may influence the efficacy of chemotherapy. In 2013, Wang et al. identified a group of upregulated miRNAs that are effective in response to 5-fluorouracil (5-FU) using microarrays (26). In addition, research has shown that miR-143, miR-145, and miR-144 are involved in the treatment of 5-fluorouracil (27, 28). Table 1 shows several miRNAs that are directly and effectively involved in chemotherapy agents.

Table 1. MiRNAs involved in Chemotherapy

Chemotherapy agents	5-FU sensitivity	CPT sensitivity	CDDP sensitivity
	let-7g, miR-133b, miR-143, miR-144, miR-145, miR-181b, miR-	let-7g, miR-7, miR-31, miR-98,	let-7g, miR-1, miR-16, miR-21,

miRNAs	190, miR-197, miR-200c, miR-204, miR-210, miR-335, miR-501, miR-501-5p, miR-532, miR-615, miR-615-5p, miR-766, miR-877, miR-1224-3p, miR-1229, miR-3131, miR-3149, miR-3162-3p, miR-4763-3p	miR-126, miR-196a, miR-200, miR-338	miR-34, miR-181, miR-181b, miR-342, miR-497

3.2. Autophagy and miRNAs

Autophagy is a highly conserved catabolic and cellular self-digestion process in which proteins, organelles, and cellular components are degraded through the lysosome. Many studies consider autophagy as the opposite of apoptosis, but it should be noted that this process has a dual function in tumor cells. In fact, in the early stages, autophagy suppresses the tumor and in the advanced stages, it causes the survival of cancer tissue. In general, miRNAs are effective in the autophagy pathway through the regulation of genes and functional proteins. Many evidences show that miRNAs play a dual role in the initiation and progression of gastric cancer and can act as oncogenes or tumor suppressors (29). Research has demonstrated that various microRNAs (miRNAs) can influence cancer cells by modulating autophagy activity, leading to malignant transformations and drug resistance. Conversely, another group of miRNAs has been found to enhance cancer treatment and improve the effectiveness of chemotherapy. Pargol et al. showed in 2021 that miR-20a acts as an oncogene and miR-204-5p acts as a tumor suppressor in lung cancer (30). With a general look at the conducted research, it can be seen that the role of autophagy is determined by the upstream factors of genes and oncogenic or tumor suppressor miRNAs are dependent on different functions and autophagy modulators. For this reason, identifying molecular targets and upstream regulators in autophagy is very important. However, it remains unclear whether the role of microRNAs (miRNAs) in gastric cancer is dependent on autophagy.

3.3. Network of miRNAs

As can be seen in Figure 2, a large network of upstream and downstream miRNAs affect genes effectively in cancer. Overall, the activities of microRNAs (miRNAs) in cancer are associated with genomic alterations, including deletions, amplifications, and translocations, as well as epigenetic mechanisms like methylation and histone modifications. Additionally, they can be influenced by mutations in genes or non-target mRNAs, and they play a role in either promoting or inhibiting apoptosis, metastasis, and cell growth. In the case of gastric cancer, miRNAs can be involved in increasing or decreasing the disease through kinase inhibitors and autophagy changes by affecting target molecules such as P57 or Mcl-1. Research on these miRNAs is still ongoing. Tables 2 and 3 show upstream and downstream miRNAs and genes involved in gastric cancer, along with their mechanisms of action.

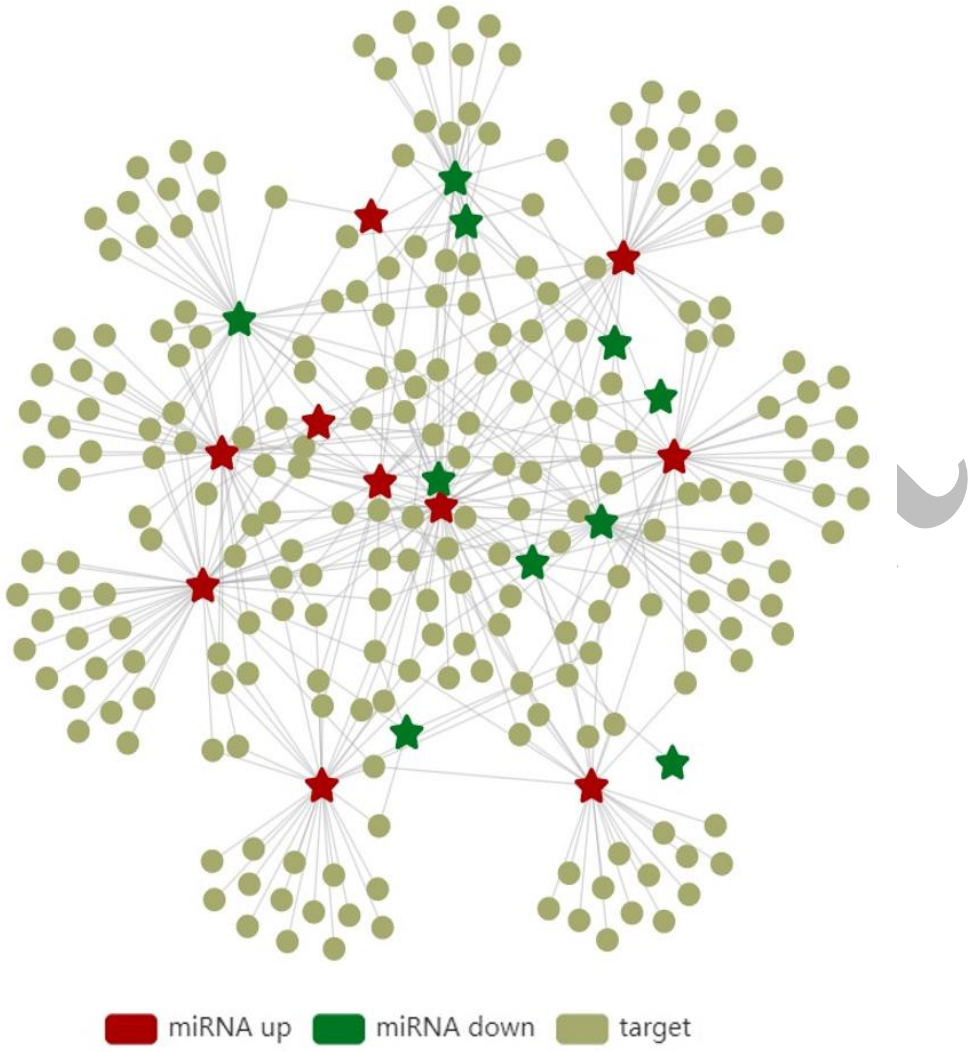

Figure 2. Network structure of upstream and downstream miRNAs along with their target genes.

Table 2. Upstream miRNAs and their target genes.

Upregulated miRNAs	Functions	Targets
miR-15b, miR-16	Cell survival	BCL2
miR-21	Cell proliferation, invasion	PTEN PDCD4
miR-23a	Cell proliferation	IRF1, IL6R
miR-27a		PROHIBITIN
miR-150		EGR2
miR-43c	Epigenetic regulation	VEZT
miR-106a	Cell cycle regulation	RB1
miR-106b-25 cluster	Cell cycle arrest, apoptosis	E2F1 p57, p21, p27
miR-107	Invasion, metastasis	DICER1
miR-130b	Apoptosis, epigenetic regulation	BIM, RUNX3
miR-223	Invasion, metastasis	EPB41L3

Table 3. Downstream miRNAs and their target genes.

Downregulated miRNAs	Functions	Targets
let-7a	Cell proliferation	RAB40C
miR-212		MeCP2
miR-451		MIF
miR-124a		CDK6
miR-126		CRK
miR-143		AKT
miR-145		IRS-1
miR-148b		CCKBR
miR-9	Cell proliferation Cell proliferation, cell cycle regulation	NFkB CDX2
miR-34b	Cell proliferation, transcription, epigenetic regulation	NOTCH1, c-Myc BCL2, SIRT1
miR-129-2	Cell proliferation, differentiation, epigenetic regulation	SOX4
miR-146a	Invasion, migration	EGFR, IRAK1
miR-181c	Transcriptional activation	NOTCH4, K-ras
miR-200 family	Cell proliferation, invasion, migration	ZEB2, E-cadherin
miR-218	Invasion, metastasis Transcriptional activation	ROBO1 receptor NFκB
miR-375	Cell survival Cell proliferation	PDK1, 14-3-3zeta JAK2

3.4. Microarray analysis and miRNAs

Microarray is an important and useful tool to investigate miRNA expression in cancer. The comparison of miRNAs of cancerous and non-tumor tissues has provided researchers with useful information about the differentiation, progression, and prognosis of gastric cancer. More than 80 percent of these samples have been detected and classified by miRNAs with high accuracy and repeatability. Thus, predicting and validating downstream targets is crucial in research. Table 3 shows a list of information obtained from Microarray regarding miRNAs.

Table 4. Microarray analysis of miRNAs.

	Up-regulated miRNAs	let-7a, miR-9, miR-10a, miR-10b, miR-17, miR-17-5p, miR-18a, miR-18b, miR-19a, miR-19b, miR-20a, miR-20b, miR-21, miR-23a, miR-23b, miR-25, miR-26b, miR-27, miR-29b-1, miR-30b, miR-31, miR-34a, miR-34b, miR-34c, miR-92, miR-98, miR-99a, miR-100, miR-103, miR-106a, miR-106b, miR-107, miR-125b, miR-126, miR-128a, miR-130b, miR-138, miR-142-3p, miR-146a, miR-147, miR-150, miR-151-5p, miR-155, miR-181a, miR-181a-2, miR-181b, miR-181c, miR-185, miR-191, miR-192, miR-194, miR-196a, miR-196b, miR-199a, miR-199a-3p, miR-200b, miR-210, miR-214, miR-215, miR-221, miR-222, miR-223, miR-296-5p, miR-301a, miR-302f, miR-337-3p, miR-340, miR-370, miR-421,

Aberrant expression of miRNAs in gastric cancer		miR-520c-3p, miR-575, miR-601, miR-616, miR-658, miR-1259
	Down-regulated miRNAs	let-7a, let-7f, miR-7, miR-9, miR-22, miR-29c, miR-30a-5p, miR-31, miR-34a, miR-34b, miR-34c, miR-101, miR-126, miR-128b, miR-129, miR-129-2, miR-129-3p, miR-130b, miR-133b, miR-135a, miR-137, miR-141, miR-145, miR-146a, miR-148, miR-148b, miR-149, miR-152, miR-155, miR-181b, miR-181c, miR-182, miR-193b, miR-195, miR-195-5p, miR-197, miR-200, miR-204, miR-206, miR-210, miR-212, miR-218, miR-219-2-3p, miR-302b, miR-331-3p, miR-375, miR-378, miR-408-3p, miR-429, miR-433, miR-486, miR-495, miR-551a, miR-574-3p, miR-610, miR-622, miR-638, miR-663, miR-874
Circulating miRNAs as biomarkers	**Up-regulated miRNAs**	miR-1, miR-17, miR-17-5p, miR-20a, miR-21, miR-27a, miR-31, miR-34, miR-103, miR-106a, miR-106b, miR-107, miR-194, miR-200c, miR-210, miR-221, miR-223, miR-370, miR-376a, miR-378, miR-421, miR-423-5p, miR-451, miR-486, miR-744
	Down-regulated miRNAs	miR-218, miR-375
miRNAs associated with prognosis in gastric cancer patients		let-7a , let-7i, miR-10b, miR-20a, miR-20b, miR-21, miR-22, miR-25, miR-27a, miR-30a-5p, miR-34a, miR-93, miR-103, miR-106a, miR-106b, miR-107, miR-125a-5p, miR-126, miR-130, miR-142-5p, miR-144, miR-146a, miR-150, miR-155, miR-181c, miR-195, miR-196a, miR-199a-3p, miR-200c, miR-206, miR-221, miR-222, miR-223, miR-335, miR-338, miR-372, miR-375, miR-451

3.5. Examination of the expression of miRNAs

Out of the 30 samples examined, in 14 samples, the expression level of miRNAs in cancer cells was higher than in non-cancerous cells, in other miRNAs, the expression level in cancer cells was lower. Figure 3 illustrates the expression levels of seven of these microRNAs. In the other 7 cases, the expression level was too low or too high, so that miR-21 and miR-27a showed the expression levels of 46756 and 2042, respectively.

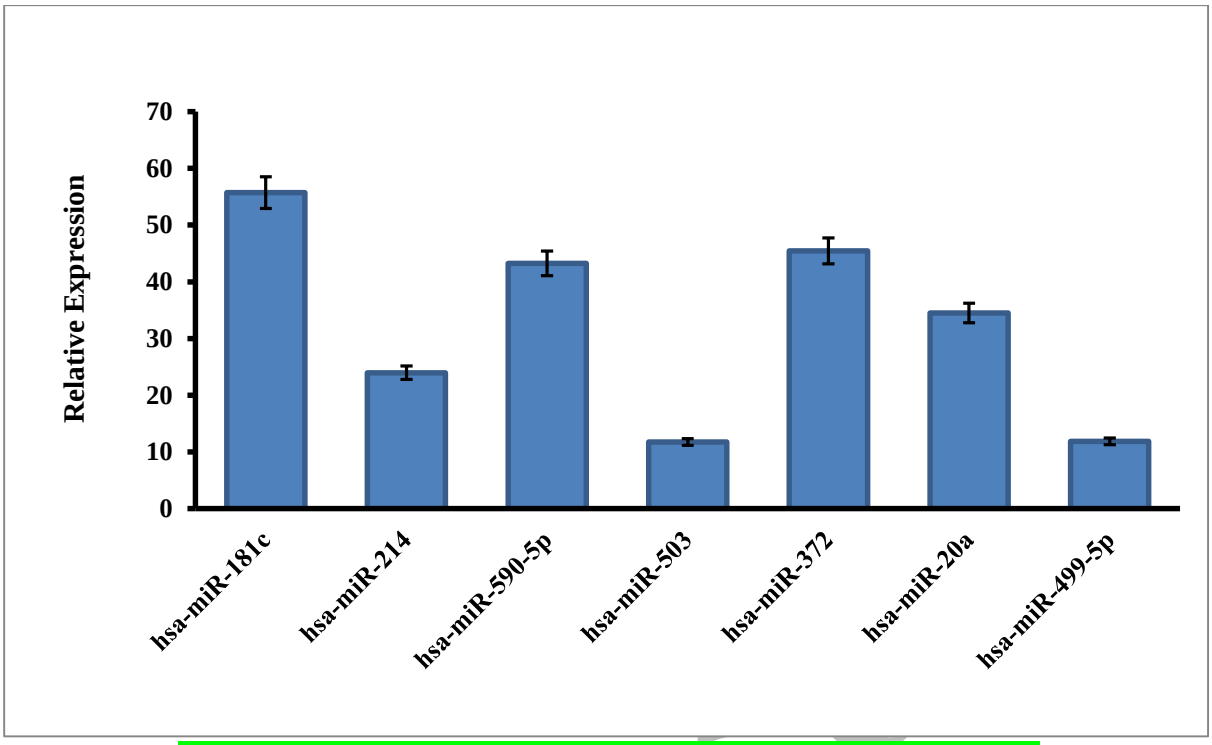

Figure 3. Investigating the expression of effective miRNAs in gastric cancer.

4. Discussion

Recent research has shown that mortality from advanced stages of gastric cancer is associated with peritoneal dissemination, hematogenous spread, and lymph node metastasis. Therefore, it is crucial to identify the mechanisms involved in the development of gastric cancer, including proliferation, growth, migration, invasion, and apoptosis (31). Research shows that there are mechanisms that cause cancer cells to express miRNAs differently from healthy tissues and cells. As we know, miRNAs are vital regulators in biological processes such as cell growth, migration, and invasion in cancer. On the other hand, Luo et al. reported in 2023 that miRNAs may circulate in extracellular fluids and blood (32). So far, more than 2,500 miRNAs have been identified in miRBase. In this research, we examined 30 miRNAs that are expressed in both cancerous and non-cancerous cells. The results showed that miR-21 and miR-27a exhibit high expression in gastric cancer cells compared to non-cancerous cells. Furthermore, this study identified microRNAs associated with chemotherapy response and explored their potential as biomarkers. As we know, one miRNA can bind to several different mRNAs at multiple points, and this ability can also be exploited to prevent the spread of cancer cells (33). It has been investigated the simultaneous effects of miR-145 and paclitaxel on the activation of autophagy and apoptosis. Their results showed that the rate of apoptosis increased by 12.32% and 19.69% (34). It has been demonstrated that the targeted inhibition of lysyl oxidase (LOX) family members, along with HIF1A-AS2 and RP11-366L20.2 as upstream regulatory lncRNAs and miR-29c as an upstream regulatory miRNA in gastric cancer, may serve as a new prognostic marker and a potential therapeutic strategy for the disease (35). There are also reports regarding the significant effects of miR-219a-1-3p in pancreatic and gastric cancer; however, these investigations require further research, and its exact role in gastric cancer has not yet been determined. In general, while the molecular biology of gastric cancer is well characterized, research on miRNAs in this context is still in its early stages.

Because most common methods for early-stage cancer screening are unable to diagnose the disease effectively, the identification of tumor miRNAs released into the bloodstream during the gradual progression of gastric cancer is considered a key approach for timely diagnosis. Considering the above, we understand that we need more extensive research in this field to

optimally use and increase the efficiency of miRNAs and reduce the adverse effects of binding antisense oligonucleotides to non-target miRNAs.

Conflict of Interests

All authors declare no conflict of interest.

Ethics approval and consent to participate

No human or animals were used in the present research.

Consent for publication

All authors read and approved the final manuscript for publication.

Availability of data and material

All the data are embedded in the manuscript.

Informed Consent

The authors declare not used any patients in this research.

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