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The Role of MicroRNAs in the Development, Diagnosis and Prognosis of Gastric Cancer

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1. Abstract

MicroRNAs (miRNAs) are a group of small non coding RNAs, which play a crucial role in Gastric Cancer (GC). miRNAs produce dual, opposite effects through target gene mRNA, namely tumor suppressor genes (TS-miRs) or oncogenes (oncomiRs). In general, carcinogenic miRNAs are overexpressed in GC and can inhibit tumor suppressor genes. On the contrary, the expression of tumor suppressor miRNAs is down regulated in GC, which leads to the development of cancer. Aberrantly expressed miRNAs, as tumor suppressor genes or oncogenes, participate in the occurrence and development of GC and regulate different phenotypes, such as proliferation, apoptosis, invasion, metastasis and drug resistance. In addition, miRNAs can also be used for the diagnosis and prognosis of GC. This article reviews the role of miRNAs in the occurrence and development of GC, and the potential application of miRNAs in diagnosis and prognosis.

1.1. Background

According to the global cancer statistics in 2020, GC accounted for 5.6% of the overall incidence rate, ranking fifth, accounting for 7.7% of the overall mortality, ranking fourth [1]. The high incidence rate and mortality of GC have brought a huge burden to the medical and health system and society. Lack of early screening and drug resistance in advanced patients are the main causes of high mortality in GC patients. Gastroscopy is still the main means of diagnosis, but because it is an invasive examination, it leads to poor compliance of physical examinees who carry out routine screening; However, conventional tumor markers have low sensitivity and specificity, and have little effect on early GC screening. Therefore, it is necessary to study and understand the mechanism of GC development and drug resistance, and identify new effective non-invasive detection and prognostic markers. miRNAs play an important role in the occurrence and development of GC. Many changes of miRNAs can be detected in the process of transformation from normal tissues to malignant tissues.

The length of miRNAs is about 22 nucleotides. It binds to the 3 '- UTR of the target gene mRNA, silences the expression of various genes by inducing translation inhibition or causing the degradation of the target gene mRNA, and plays a key role in the regulation of gene expression [2]. Aberrantly expressed miRNAs, as tumor suppressor genes or oncogenes, regulate a variety of cellular processes and promote the occurrence and development of GC, such as cell proliferation, apoptosis, angiogenesis, invasion or metastasis. In addition, the abnormally expressed miRNAs can also be used to evaluate the chemosensitivity, drug resistance, diagnosis and prognosis of GC patients [3]. The study on the characteristics of miRNAs and their regulatory genes will help us better understand the function and mechanism of GC. And because miRNAs are stable and persistent in individuals of the same species, the abnormally expressed miRNAs may be useful biomarkers for GC screening, diagnosis, prognosis, disease monitoring and treatment targets. This article mainly summarizes the mechanism of miRNAs in the occurrence and development of GC, the signal pathways involved, the mechanism of drug resistance, and the role in diagnosis and prognosis. Because there are so many GC related miRNAs and

their targets and pathways, this review only summarizes and discusses the research hotspots and new achievements in recent years.

2. The Role of Gastric Cancer Associated Mirnas in Cell Proliferation and Apoptosis

2.1. Proliferation

Dysregulated miRNAs can act on corresponding targets and cellular pathways to promote or inhibit the proliferation of GC cells [4]. Some miRNAs promote the proliferation of GC by affecting the growth of cancer cells. For example, miR-200a-3p promotes gastric cancer progression by targeting Deleted in liver cancer 1 (DLC-1) [5]. Li et al. [6] found that miR-139-5p was low expressed in GC and Tumor protein D52 (TPD52) was high expressed. The high expression of TPD52 could damage the anti-tumor effect of miR-139-5p, and miR-139-5p could inhibit the proliferation of GC cells by down regulating TPD52. Li et al. [7] found that the expression of miR-503 was down regulated in GC, and the low expression of miR-503 was related to tumor size; High mobility group AT-hook 2(HMGA2) is the target of miR-503. By targeting HMGA2, miR-503 plays a negative regulatory role in the proliferation of GC cells. In addition, Wnt/ β- Catenin signaling pathway is closely related to tumor proliferation and invasion. Overexpression of miR-503 can increase Glycogen synthase kinase-3β (GSK-3β) and β- Catenin expression level to inactivate Wnt/ β- Catenin signaling pathway can inhibit the proliferation of GC cells. Gao et al. [8] found that E2F transcription factor 1(E2F1) was overexpressed in GC and promoted the proliferation of GC cells. miR-532 inhibited the proliferation of GC cells by inhibiting E2F1; A double negative feedback loop was formed between E2F1 and miR-532, which promoted E2F1 and inhibited the expression of miR-532, and jointly regulated the proliferation of GC cells. miR-6884-5p was negatively correlated with the expression of its target S100A16 in GC. miR-6884-5p inhibited the proliferation, invasion and Epithelial-Mesenchymal Transition (EMT) of GC cells by inhibiting the expression of S100A16 [9]. Guo et al. [10] found that overexpression of miR-371-3p promoted the proliferation of GC cells, and Transducer of ERBB2.1 (TOB1) was the direct target of miR-371-3p, which played a role of tumor inhibition in GC; miR-371-3p promotes the proliferation of GC cells by targeting TOB1. Liu et al. [11] confirmed that Protein-tyrosine phosphatase MEG2 (MEG2) is a tumor suppressor gene, which is a target of miR-181a-5p. MEG2 is negatively correlated with the expression of miR-181a-5p. miR-181a-5p can act on MEG2 to inhibit the proliferation and migration of GC cells through the dephosphorylation of Epidermal growth factor receptor (EGFR) and Human epidermal growth factor receptor-2 (HER2) and indirectly inhibit the activation of Signal Transducer and Activator of Transcription 3(STAT3). Min et al. [12] confirmed that miR-30a plays an anti-tumor role in the process of carcinogenesis by regulating Integrin alpha-2(ITGA2). miR-135b promotes the growth and proliferation of GC by inhibiting the expression of Forkhead box O1(FOXO1) in endothelial cells and promoting angiogenesis [13].

The change of signal pathway also plays an important role in the development and proliferation of GC. Some miRNAs participate in the proliferation of GC cells mediated by classical signaling pathways, such as NF-kB pathway. Huang et al. [14] found that the expression of Nuclear factor kappa-B1(NFKB1) and p65 was up-regulated in GC. miR-508-3p acted on its targets NFKB1 and p65 through NF-kB signaling pathway, playing a key tumor inhibitory role in GC. The inactivation of miR-508-3p may activate NF-kB signaling pathway, thus promoting the proliferation of GC cells. Another study showed that overexpression of miR-411 could inhibit the proliferation of GC cells, while overexpression of Methyltransferase SET domain containing protein 6 (SETD6) could promote cell proliferation and colony formation; miR-411 acts on setd6 to regulate NF-kB signaling pathway and inhibit tumor proliferation [15].

Another classical signaling pathway----PI3K/AKT signaling pathway, plays an important role in promoting proliferation and inhibiting apoptosis. For example, miR-23a can promote angiogenesis in GC by negatively regulating tumor suppressor gene Phosphatase and tensin homolog (PTEN) and activating PTEN dependent PI3K/AKT signaling pathway, thus leading to cell proliferation [16]. miR-23a-3p inhibits the proliferation of GC cells by down regulating its target CCL22 and blocking PI3K/AKT signaling pathway [17]. Overexpression of miR-92B promotes tumor proliferation and inhibits cell apoptosis. Human DOC2/DAB2 interaction protein (DAB2IP) is a tumor suppressor gene and the target of miR-92b. miR-92B activates PI3K/AKT signal pathway and promotes GC cell proliferation by down regulating DAB2IP [18]. Jiang et al. [19] found that miR-1254 inhibits the PI3K/AKT signaling pathway by targeting Smad ubiquitination regulatory factor 1(Smurf1), thereby inhibiting the proliferation, migration and invasion of tumor cells.

miRNAs affect the proliferation of GC cells by acting on corresponding targets or through signal pathways. Blocking related targets or signal pathways may be an important means to inhibit the development of GC.

2.2. Apoptosis

Abnormal apoptosis is an important reason for the occurrence, development and low treatment efficiency of cancer. Apoptosis related genes or miRNAs are new mechanisms for studying cancer development.

miR-1265 increases apoptosis by reducing the expression of Calcium binding protein 39(CAB39) and regulating AMPK-mTOR signaling pathway [20]. Low expression of miR-106b enhances GC cell apoptosis by inhibiting JAK1/STAT3 signaling pathway [21]. Zhou et al. [22] found that the low expression of miR-135b can induce apoptosis by inactivating MAPK signal pathway and increasing the expression of Mammalian sterile 20-like kinase 1(MST1).

Zhang et al [23] reported that overexpression of B-cell lymphoma-2-like protein 11(BCL2L11) can inhibit tumor growth and is an important factor in mediating apoptosis. miR-24 inhibits GC cell apoptosis by regulating BCL2L11 expression. According to the above literature, miRNAs regulate GC cell apoptosis by targeting apoptosis related genes or influencing signal pathways.

3. The Role of Gastric Cancer Associated Mirnas in Cell Invasion and Metastasis

The main cause of high mortality caused by cancer is the invasion and metastasis of cancer cells to adjacent tissues or blood vessels. Studying the mechanism of tumor invasion and metastasis is an important way to improve the survival rate of patients. In recent years, many studies have found that miRNAs play a key role in the metastasis of GC cells. For example, miR-885-5p inhibits the transfer of GC through negative regulation of Malic enzyme 1(ME1) [24]. Both low miR-146a and Wiskott-Aldrich syndrome protein family member 2(WASF2) can promote GC migration and invasion, miR-146a targets WASF2 to regulate GC migration and invasion [25]. Arsenic sulfide induced increased expression of miR-4665-3p could inhibit the metastasis and EMT of GC cells [26]. miR-28-5p inhibits the migration and invasion of GC cells by inhibiting the expression of Transcription factor nuclear factor-related factor 2(Nrf2) [27]. miR-520b and GATA6 can inhibit the invasion and metastasis of GC cells, cAMP responsive element binding protein 1(CREB1) is up-regulated in GC, and participates in promoting the metastasis of GC cells; GATA6 inhibits the expression of CREB1 by targeting miR-520b, thereby inhibiting the migration and invasion of GC cells [28]. miR-2392 can inhibit GC cell invasion and metastasis. Both Mastermind Like Transcriptional Coactivator 3 (MAML3) and Wolf-Hirschhorn syndrome candidate 1(WHSC1) are transcriptional regulators and participate in cancer metastasis. miR-2392 can inhibit GC cell metastasis and EMT by down regulating MAML3 and WHSC1 [29]. Juxtaposed with another zinc finger gene 1(JAZF1) expression is increased in GC and associated with lymph node metastasis. miR-1275 negatively regulates JAZF1, thereby promoting vimentin and inhibiting E-cadherin expression to promote GC cell metastasis [30]. miR-181a enhances the migration and invasion of GC cells by negatively regulating the expression of tumor suppressor gene Cell cycle associated protein 1(Caprin-1) [31].

miRNAs can also act on signaling pathways to affect the metastasis of GC cells. For example, Xing et al. [32] found that miR-4521 itself can inhibit the metastasis of GC cells, miR-4521 inactivates AKT/GSK3β/SNAIL pathway by targeting Insulin-like growth factor 2(IGF2) and Forkhead box M1(FOXM1), thereby inhibiting EMT and metastasis. miR-1236-3p inhibits cell metastasis of GC by targeting Metastasis-associated protein 2(MTA2) to inhibit PI3K / AKT pathway and EMT [33]. Ma et al. [34] found that Kinesin superfamily protein 26A (KIF26A) inhibited EMT and migration invasion by increasing the stability of MTS and down regulating MAPK pathway, while miR-19a and miR-96 regulated the metastasis of GC cells by down regulating the expression of KIF26A. Yang et al. [35] found that miR-4646-5p promoted the expression of Abhydrolase Domain Containing 16A(ABHD16A) , which caused the accumulation of Lysozyme-PS by participating in lipid metabolism, thus triggering RhoA/LIMK/Cofilin signal transduction and promoting GC cell metastasis. miR-10b participates in the proliferation and metastasis of GC cells by targeting the tumor suppressor gene CUB and Sushimultiple Domains1 (CSMD1), and promotes the EMT process through the NF-kB pathway [36]. Li et al. [37] confirmed that miR-188-5p increases AKT and GSK3β phosphorylation by reducing PTEN, thereby activating Wnt /β-catenin signal pathway enhances the metastasis of GC cells and leads to poor prognosis. miR-29c-3p regulates the expression of KIAA1199 gene and activates FGFR4 / Wnt/ β- Catenin and EGFR signal pathway regulate the migration of GC cells [38]. miR-939 inhibits Raf/MEK/ERK pathway by targeting SLC34A2, thus inhibiting GC cell migration and reducing the incidence of lung metastasis in vivo [39].

Angiogenesis is the key to the progression of invasion and metastasis. For example, miR-155 promotes tumor angiogenesis by down regulating c-myb and up regulating Vascular endothelial growth factor(VEGF) [40]. miR-23a promotes tumor angiogenesis by inhibiting the expression of Phosphatase and PTEN [16].

Interaction with other noncoding RNAs can also affect invasion behavior. Circ TMC5 regulates migration and invasion of GC cells by targeting miR-3613p/RABL6 [41]. miR-150-5p and circ LMTK2 play a positive role in the proliferation and metastasis of GC by regulating the expression of c-Myc [42]. GCMA is a transfer related lncRNA in GC, which promotes the transfer of GC cells by acting on miR-124 and miR-34a [43]. lncRNA UCA1 regulates the expression of Phosphatase in regenerating liver-3(PRL-3) through miR-495 and promotes the progress of GC [44]. lncRNA RGMB-AS1 up-regulates Histone deacetylases 4(HDAC4) through miR-574 and promotes its invasive behavior [45]. The above studies show that miRNAs play a role in the invasion and metastasis of GC by targeting different genes or signal pathways. Treatment against corresponding targets and pathways may inhibit the metastasis of GC, but before that, more in-depth research and a large number of experiments are still needed to confirm. There is still a long way to go from laboratory to clinical application.

4. Gastric Cancer Associated miRNAs and Drug Sensitivity and Drug Resistance

Chemotherapy is the standard treatment for GC, and multidrug resistance is the cause of treatment failure and poor prognosis. There are many factors influencing drug response, among which miRNAs play an important role in drug sensitivity and drug resistance [3].

miRNAs can affect drug sensitivity through specific gene targets or signal pathways. miR-522 can reduce the sensitivity of Cisplatin

or Paclitaxel, increase drug resistance, and improve the drug effect by blocking the secretion of miR-522 [46]. Overexpression of circCUL2 promotes the sensitivity of GC cells to Cisplatin through miR-142-3p/Rho associated coiled coil forming protein kinase 2(ROCK2) [47]. circ AKT3 up-regulates the expression of PIK3R1, activates PI3K/AKT pathway, and finally enhances the resistance of GC cells to Cisplatin by targeting miR-198 [48]. Sun et al. [49] found that circMCTP2 was down regulated in Cisplatin resistant GC cells, and circMCTP2 up-regulated Myotubularin related protein 3(MTMR3) through miR-99a-5p, increasing the sensitivity of GC cells to Cisplatin. lncRNA PCAT-1 is up-regulated in Cisplatin resistant GC cells, Zinc finger E-box binding protein 1(ZEB1) helps GC develop resistance to Cisplatin, lncRNA PCAT-1 reduces ZEB1 expression through miR-218, thereby improving the sensitivity of GC cells to Cisplatin [50]. Curcumol increases the sensitivity of GC cells to Cisplatin by inhibiting NF-kB/SNAIL axis through miR-7 [51]. lncRNA ADAMTS9-AS2 activates Nucleotide binding domain like receptor protein 3(NLRP3) through miR-223-3p and enhances the sensitivity of GC cells to Cisplatin [52]. Zhang et al. [53] found that the expression of miR-874-3p was low in Cisplatin resistant GC cells, LINC00922 targeted GDPD5 through miR-874-3p to enhance Cisplatin sensitivity, making GC cells sensitive to chemotherapy. miR-301b-3p promotes the resistance of GC cells to Cisplatin and Vincristine by inhibiting Thioredoxin-interacting protein(TXNIP) [54]. miR-4486 can enhance the sensitivity of GC cells to Cisplatin by inhibiting JAK3/STAT3 signal pathway [55]. Zheng et al. [56] confirmed that E2F1 enhanced the resistance of GC cells to Paclitaxel and Cisplatin by reducing the expression of miR-34c. Jing et al. [57] showed that miR-769-5p could make GC cells resistant to Cisplatin by down regulating Caspase-9 (CASP9) and promoting ubiquitin degradation of p53, and knock-down miR-769-5p could reverse the resistance; And miR-769-5p can be transferred from drug-resistant GC cells to adjacent sensitive GC cells through exosomes, thus spreading Cisplatin resistance. Deng et al. [58] found that Sirtuin 1(SIRT1) caused GC multidrug resistance by regulating the expression of a series of drug resistance related proteins, such as P-glycoprotein(P-gp) and Multidrug resistance-associated protein 1(MRP1); miR-34a-5p was low expressed in GC cells with multidrug resistance and participated in the occurrence of multidrug resistance in GC; By promoting the expression of SIRT1, MRP1 and P-gp, low expression of miR-34a-5p induced GC cells to develop resistance to 5-FU and gradually developed into multi drug resistant GC cells.

Treatment with these miRNAs may be a new method to reverse drug resistance. The above research results are of great significance for clinical improvement of chemotherapeutic drug resistance and sensitivity, especially for patients with advanced GC.

5. Clinical Application of miRNAs

5.1. miRNAs as Biomarkers for the Diagnosis of Gastric Cancer

Most GC patients are easy to be ignored because they have no obvious symptoms in the early stage. As a result, more than 80% of patients are in the late stage at the time of diagnosis, resulting in poor survival rate. Therefore, early detection is an important method to improve the survival rate of patients [3]. Although endoscopy and gastroscopy are the most common and effective methods, their sensitivity is only about 69%, and due to their aggressive characteristics, the compliance of patients is poor, so they are still rarely used in physical examination and early screening [59]. At present, the common tumor markers used to screen early GC include Carcinoembryonic Antigen (CEA), Carbohydrate Antigen (CA) -CA19-9, CA72-4, CA125, Pepsinogen (PG) and Alpha fetoprotein (AFP). Although the concentration of these antigens may increase in GC patients, the overall sensitivity is still insufficient for GC screening. So far, none of the biomarkers based on body fluid has enough sensitivity or specificity to implement early GC screening. Therefore, it is very important to develop biomarkers with higher sensitivity and specificity for screening and diagnosis of early GC [60].

Circulating miRNAs meet many criteria, such as high specificity and sensitivity, non-invasive, long half-life, screening early lesions, etc. Researchers focused on miRNAs in body fluids, especially in blood, as biomarkers for early diagnosis of GC [59]. miRNAs can be released from tumor tissues into body fluids, including serum, plasma, urine, tears and gastric juice, by secreting exosome particles [4]. Mitchell et al. [61] showed that circulating miRNAs in plasma/serum of GC patients were consistent with circulating miRNAs in tissues; Therefore, they can be used as noninvasive biomarkers for early screening and recurrence evaluation of GC. For example, the increased expression of miR-200 family members is associated with the early stage (stage IA) of GC patients [62]. Zhu et al. [63]. Confirmed that some miRNAs in circulating plasma (miR-425-5p, miR-1180-3p, miR-122-5p, miR-24-3p and miR-4632-5p) can distinguish early GC patients from atrophic gastritis patients. Shin et al. [64] found some miRNAs (miR-652, miR-629 and miR-627), which were detected in the plasma samples of patients. The sensitivity and specificity for diagnosing GC were 86.7% and 85.5%. In another study, it was found that the level of miR-21 in serum and peripheral blood monocytes of GC patients increased, and the positive predictive rate was about 90%, while the predictive rate of CA199 and CEA was about 50%; In addition, circulating miR-21 levels can distinguish between stage I and IV of GC [65]. Tsai et al. [66] found that compared with the healthy control group, GC patients detected elevated preoperative circulating miR-196a and miR-196b levels, and the expression levels of these miRNAs decreased after tumor resection. In addition, compared with CEA or CA19-9, circulating miR-196a and miR-196b can distinguish GC

patients from healthy controls, with higher sensitivity and specificity. The overexpression of miR-1246 in serum usually occurs in GC patients, ROC analysis confirmed that miR-1246 may be a good indicator to distinguish GC patients from healthy controls [67]. Compared with normal tissues, miR-551b-5p showed low expression in GC tissues; In addition, the serum miRNAs microarray analysis verified that the down-regulation of miR-551b-5p was closely related to GC and could be used as a biomarker for the diagnosis of GC [68]. Compared with gastritis and healthy control group, the level of miR-25 in serum of GC patients was increased, and the sensitivity and specificity of GC screening were 67.3%~69.4% and 80.4%~81.0% respectively [69]. In addition, miR-222 [70], miR-3185, miR-6083, miR-659-3p and miR-6792-3p were confirmed to be highly expressed in the plasma of GC patients, while the expression of miR-936 and miR-1306-3p were down regulated, They can be used as biomarkers for early GC diagnosis [71].

Besides blood, detecting the expression of miRNAs in other fluids, such as gastric juice and urine, may also be a useful diagnostic method. Compared with gastritis patients, the levels of miR-21 and miR-106a in gastric juice of GG patients decreased significantly, and the area values under ROC curve were 0.969 and 0.871 respectively; When gastric juice miR-21 was used as a marker, the positive rate of early GC was as high as 71.4% [72]. The expression of miR-6807-5p and miR-6856-5p in the urine of patients with GC was higher, and the expression level decreased after radical resection of GC [73]; Similarly, miR-376c was found to be up-regulated in tissues, plasma and urine of GC patients, even from the early stage of tumor [74], indicating the possibility of miR-376c as a biomarker for the diagnosis of GC.

5.2. miRNAs as Biomarkers for Prognosis of Gastric Cancer

Predicting the survival time, cancer progression, prognosis, treatment effect and recurrence of GC patients is an important part of GC diagnosis and treatment, but there is still a lack of indicators that can accurately predict the prognosis of GC. Therefore, screening effective prognostic indicators is of great significance for predicting the prognosis of GC patients, adjusting treatment strategies and improving the survival rate of patients. Because miRNAs are stable and specific in tissues and circulation, they can be regarded as biomarkers with clinical significance for the prognosis of GC.

The expression of miR-4317 [75], miR-153 [76], miR-187 [77], miR-124-3p [78], miR-383-5p [79], miR-133b [80], miR-381 [81], miR-1236-3p [82], miR-588 [83] were low, miR-21-3p [84], miR-208a [85], miR-214 [86], hsa-miR-3923[87], miR-135b[88] were high in GC tissues, The relationship between the expression of the above miRNAs and the clinicopathological status of GC patients was analyzed. The results showed that it was related to lymph node metastasis, distant metastasis and TNM stage; Kaplan-Meier analysis confirmed that the expression of the above miRNAs was associated with shorter Overall Survival (OS), and could be used as an independent prognostic indicator. Xu et al. [89] screened 9 miRNAs related to prognosis: miR-125b-5p, miR-99a-3p, miR-145-3p, miR-328-3p, miR-133a-5p and miR-1292-5p, their high expression is closely related to prolonged OS; The high expression of miR-675-3p, miR-92b-5p and miR-942-3p was associated with shorter OS and poor prognosis. Chen et al. [90] developed six prognosis models of miRNAs (miR-549, miR-100, miR-653, miR-374a, miR-668 and miR-509-3), these miRNAs can distinguish high-risk and low-risk patients, and can predict the 3-year and 5-year survival rates of GC patients. A meta-analysis involving 6148 patients showed that the OS of GC patients with high expression of miR-21, low expression of miR-20b, miR-106b, miR-196a, miR-196b, miR-214, miR-125a, miR-137, miR-141, miR-145, miR-146a, miR-206, miR-218, miR-451, miR-486-5p and miR-506 was significantly shorter [91].

The expression of miRNAs in blood samples can also be used to predict prognosis, high levels of miR-25 in serum and miR-1229-3p in plasma are independent predictors of poor prognosis of GC [69, 92]. Liu et al. [93] found that 7 miRNAs in plasma (miR-125b, let-7e, miR-222, miR-148a, miR-21, miR-26a and miR-126) can independently or in combination predict the recurrence and prognosis of GC.

Some miRNAs are abnormally expressed in patients after treatment, and these abnormal expressions may become indicators of prognosis. miR-501 is highly expressed in patients with poor prognosis [94]; Increased expression of miR-519a is associated with longer OS in GC patients [95], which can help patients determine the treatment effect and prognosis.

A large number of data showed that these miRNAs showed good sensitivity and specificity in the prognosis of GC. However, the reliability of the results needs further large-scale multicenter experiments. However, miRNAs may be a new group of noninvasive biomarkers with sufficient accuracy in GC prognosis [3]. In the future, these prognostic miRNAs may contribute to the choice of treatment.

6. Conclusions

In recent years, the relationship between miRNAs and GC has been a research hotspot. From basic experiments to clinical applications, the related research is very extensive. A large number of studies have also confirmed that there is a close relationship between miRNAs imbalance and GC. In this paper, we summarized the abnormal expression of miRNAs, their functions, characteristics and the role of the involved signal pathways in the occurrence and development of GC, as well as their potential as diagnostic and prognostic biomarkers. In addition, we also mentioned that miRNAs play a huge role in regulating drug resistance and form a complex regulatory network. Targeted therapy against corresponding miRNAs, targets or signal pathways may reverse GC resistance. Related drugs such as anti-HER-2 monoclonal antibodies, anti-EGFR monoclonal antibodies, TKIs of EGFR/HER-2, c-Met signal pathway inhibitors,

IGF-IR inhibitors may be used to molecular targeted therapy in the GC cell drug resistance to chemotherapy.

However, there are still many problems. First, the interaction between miRNAs, synergy or mutual offset, is still unclear. Secondly, the same miRNAs have conflicting results in different studies, which may be caused by small sample size case-control studies, so further large-scale experiments are needed to verify. In addition, the expression of miRNAs can be affected by many factors, such as pathology, hypoxia, infection and cytotoxic therapy, infectious diseases, genetic diseases and so on. Sample acquisition, RNA extraction methods, miRNA measurement, etc. will also affect the final experimental results. Therefore, a more rigorous sample collection and analysis scheme is required, or the unification and standardization of all stages from sample preparation to evaluation results can reduce the deviation and differences between studies and produce highly repeatable results. In addition, compared with a single miRNA, the combination of multiple miRNAs can be better used in the diagnosis, prognosis and treatment of GC. Finally, the ultimate goal of the above related studies is to the clinical treatment of GC, but there is still a lack of breakthrough progress. Using miRNAs as therapeutic molecules or therapeutic targets is expected to be further studied. In a word, a large number of experiments are needed to verify miRNAs before they are applied to all aspects of GC. There is still a long way to go from basic medical research to clinical practice, but this is a promising research direction.

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