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REVIEW

Clinical application of microRNA in gastric cancer in Eastern Asian area

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Abstract

Recent research has shown that microRNA (miRNA), which is involved in almost every step of gastric carcinogenesis, has broad prospective application in diagnosis and therapy of gastric carcinoma. Eastern Asia (South Korea, Japan and China) has the highest incidence of gastric cancer in the world. There were 988 000 new cases of gastric cancer worldwide and 736 000 deaths in 2008. Approximately 60% of the cases of gastric cancer are found in East Asia (mainly China). We herein provide a brief review of the clinical applications of miRNA, which include the following aspects: (1) miRNA may serve as a potential new generation of tumor markers; (2) a complete miRNA expression profile is highly specific, can reflect the evolutionary lineage and differentiation of tumors, and be used to carry out diversity analysis; (3) detecting specific miRNA expression in peripheral blood will become a new method for diagnosis of gastric cancer; (4) miRNA can predict prognosis of gastric cancer; (5) miRNA has predictive value in determining chemotherapy and radiotherapy resistance; and (6) miRNA could be a type of innovative drug. Finally, we focus on assessing the value of miRNA from laboratory to clinical application and the challenges it faces in East Asia.

Key words: microRNA; Prognosis; Clinical application; Gastric cancer; Eastern Asia

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INTRODUCTION

Gastric cancer is a leading disease in Eastern Asia (South Korea, Japan and China) (Figure 1). The incidence and mortality of gastric cancer in East Asian areas rank respectively the second and the third among the most common cancers worldwide[1,2]. According to World Health Organization[3] statistics, there were 988 000 new cases of gastric cancer worldwide and 736 000 deaths in 2008. Approximately 60% of the cases are found in East Asia (mainly China). In China, approximately two-thirds of patients develop advanced or metastatic disease, and more than half have recurrent disease after curative surgery. The median survival time for these patients is only 6-9 mo[4-6]. Several reasons restrict the diagnosis and treatment of gastric cancer: (1) limited diagnostic measures for early detection; (2) weak prognostic value of outcome; (3) poor effect of surgery or cytotoxic cell treatment for advanced disease; and (4) lack of biomarkers for targeted therapy. The discovery of microRNA (miRNA) may change the above-mentioned difficulties, and improve the level of diagnosis and treatment of gastric cancer.

miRNAs include 20-24 nucleotides and are a class of noncoding small molecular single chain RNAs, and

have highly conservative, temporal and tissue-specific characteristics[7-9]. Through complete or incomplete base pairing with target gene mRNA, RNA-induced silencing complex degrades mRNA or blocks its translation, and regulates target gene expression at the post-transcriptional level[10]. They exist widely in eukaryotic organisms and regulate cell proliferation, differentiation and apoptosis. Although the tissues of the body appear malignant, specific miRNAs are overexpressed or underexpressed in different tumors and at different stages, which implies a correlation with occurrence and development of tumor and prognosis[11-13]. Further study of the relation of miRNA and gastric cancer could provide new applications in early tumor detection, monitoring, prognosis, gene therapy, and resolving chemotherapy resistance.

miRNA AND CANCER DIAGNOSIS

Specific tumor markers are often ideal screening tools. Existing clinical tumor markers [such as carcinoembryonic antigen (CEA), cancer antigen (CA)19-9, and CA72-4] for gastric cancer lack specificity and sensitivity[14]. miRNA may serve as a potential new generation of tumor markers for the following reasons[15-17]: (1) good tissue specificity - Rosenfeld *et al*[18] have detected unknown sources of miRNA in order to make clear its sources, and its specificity is 90%; (2) expression of miRNA in tumors differs significantly from that in normal tissues; (3) miRNA participates in tumor occurrence and development; (4) expression of miRNA has stage specificity - the same tumors at different stages have different expression profiles[19,20]; and (5) miRNA in fresh tissues, paraffin-embedded tissues, and cells and peripheral blood shows good stability[21].

Detection methods of miRNA and miRNA expression in gastric cancer: miRNA is a good tumor marker in clinical application[22,23]. At present, the detection method for miRNA has become mature. By deep sequencing, we can discover unknown miRNAs, and miRNA chips can be used for identification of the differences in miRNAs between the study and control groups. Finally, they can be verified by real-time quantitative polymerase chain reaction (qPCR)[24].

In diagnosis of gastric cancer, a single miRNA is often characterized by poor specificity or sensitivity, but a complete miRNA expression profile is highly specific, can reflect the evolutionary lineage and differentiation of tumors, and be used to carry out diversity analysis[25,26]. Through horizontal comparison of gastric carcinoma with adjacent normal tissues, we have found specific expression of miRNAs in cancer tissues. Further longitudinal comparison at different tumor stages has enabled us to identify the different miRNAs at each stage and to complete final tumor diagnosis and staging[27,28].

We acquired gastric cancer miRNA expression profiles from numerous Chinese and international study groups from 2008 to 2012[29-36] (Table 1). These results differed considerably and lacked stability and consistency

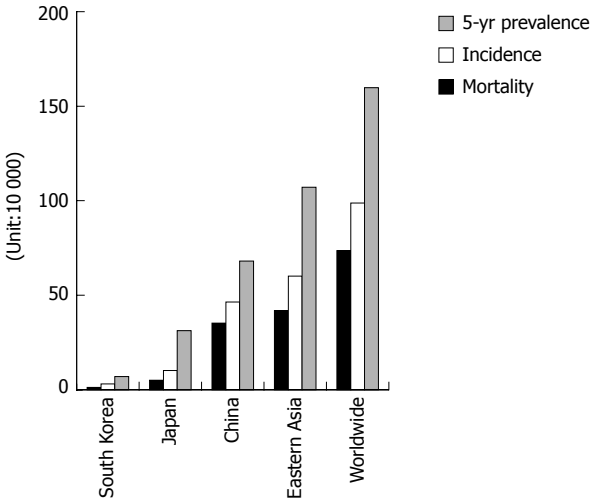

Figure 1 Gastric cancer incidence, mortality and prevalence in South Korea, Japan, China, Eastern Asia, and worldwide in 2008.

for the following reasons: (1) differences in miRNA chips and software; (2) individual differences between races and patients; (3) differences in collected specimen standards; (4) differences in sample size; and (5) miRNA expression profile differences for different cancer types and stages. According to the above expression profiling, we confirmed several reliable miRNAs in the multiple experiments which had 1.5 fold differential expressions between gastric cancer and normal gastric tissues. We are looking forward to having a large sample multi-center study or even international cooperation to compare complete miRNA expression profiling based on different pathological types and stages of gastric cancer. In particular, countries like China, Japan and South Korea should cooperate using the same platform in complete standard miRNA expression profiling of gastric cancer in East Asian populations.

Change in miRNA expression is an early event during the development of gastric tumor[37,38]. Tracking the changes in miRNA expression profiling in the relevant gastric tissues might enable early tumor diagnosis. Traditional methods for the detection of gastric cancer are endoscopy and biopsy. A minimally invasive examination method would be helpful for screening and early detection of cancer in high-risk populations[39]. Detection of tumor in the peripheral blood of patients with specific miRNA expression level has been a research hotspot in recent years, which will perhaps become a new method for diagnosis of gastric cancer[40-42].

Researchers have shown that 90% of plasma miRNA is based on protein-miRNA complex formation. As tumor markers in peripheral blood, miRNAs have the following advantages: (1) miRNAs exist in great volume in peripheral blood[43,44]; (2) miRNAs can resist enzymatic digestion[45-47]; (3) miRNAs have strong resistance to the external environment; and (4) miRNAs show abnormal expression in tumor patients' serum[48].

In the past two years, Japanese and Chinese research-

Table 1 microRNA expression in gastric cancer in 2008-2012

Group	Method	Sample	Upregulated	Downregulated
Katada *et al*[29]	TaqManmiRNA assays + qRT-PCR	42 undifferentiated gastric cancer and controls	miR-34b miR-34c miR-128a	miR-128b, miR-129, miR-148
Guo *et al*[30]	Microarray	3 gastric cancers and adjacent normal tissues	miR-20b, miR-20a, miR-17, miR-106a, miR-18a, miR-21, miR-106b, miR-18b, miR-421, miR-340, miR-19a, miR-658	miR-768-3p, miR-378, miR-31, miR-139-5p, miR-195, miR-497, miR-133b, miR-638, miR-378
Yao *et al*[31]	Microarray + qRT-PCR	10 gastric cancers and adjacent normal tissue	miR-223, miR-106b, miR-147, miR-34a, miR-130b, miR-106a, miR-18a, miR-17, miR-98, miR-616,miR-181a-2, miR-185, miR-1259, miR-601, miR-196a, miR-221, miR-302f, miR-340, miR-337-3p, miR-520c-3p, miR-575 and miR-138	
Luo *et al*[32]	Microarray + qRT-PCR	24 gastric cancers	MiR-26b, miR-30a-5p, miR-212, miR-320, miR-379, miR-518b, miR-409-3b	MiR-9, miR-19b, miR-155, miR-188, miR-197, miR-338, miR-370, miR-383, miR-433, miR-490, miR-503, miR-545, miR-551a, miR-567, miR-575, miR-611, miR-630, miR-649, miR-652
Ueda *et al*[33]	Microarray + qRT-PCR	353 (184 gastric cancers 169 controls)	miR-181d, miR-181a-1, miR-181a-2, miR-181c, miR-181b-1, miR-181b-2, miR-21, miR-25, miR-92-1, miR-92-2, miR-93, miR-17-5p, miR-106a, miR-20b, miR-135a-1, miR-135a-2, miR-425-5p, miR-106b, miR-20a, miR-19b-1, miR-19b-2	miR-148a, miR-148b, miR-375, miR-29b-1, miR-29b-2, miR-29c, miR-152, miR-218-2 miR-451, miR-30d
Tsukamoto *et al*[34]	Microarray (470) + qRT-PCR	22 gastric cancers	miR-18a, miR-106a, miR-17, miR-146a, miR-93, miR-19a, miR-20a, miR-20b, miR-25, miR-15b, miR-425, miR-92a, miR-194, miR-10a, miR-222, miR-7, miR-106b, miR-320a, miR-21, miR-34a, miR-19b, miR-103, miR-215, miR-192, miR-429, miR-27a, miR-223, miR-23a, miR-107, miR-200b, miR-24, miR-15a, miR-16	miR-375, miR-29c, miR-148a, miR-30a-5p, miR-30e-5p, miR-638
Li *et al*[35]	TaqManmiRNA assays + qRT-PCR	30 gastric cancer and controls	miR-223, miR-21, miR-23b, miR-222, miR-25, miR-23a, miR-221, miR-107, miR-103, miR-99a, miR-100, miR-125b, miR-92, miR-146a, miR-214 and miR-191,	let-7a, miR-126, miR-210, miR-181b, miR-197, miR-30aa-5p
Carvalho *et al*[36]	Microarray + qRT-PCR	76 gastric cancers	miR-582-5p, miR-151-5p, miR-296-5p, miR-30b, miR-513-5p, miR-335, miR-576-5p, miR-219-2-3p, miR-331-5p, miR-889, miR-152, miR-992, miR-93, miR-519c, miR-599, miR-520a-5p, miR-631, miR-550, miR-136, miR-22, miR-515-5p, miR-127-3p, miR-374a, miR-181a, miR-192, miR-532-3p, miR-30d, miR-640, miR-425, miR-92b, miR-501-5p, miR-514, miR-576-3p, miR-519e, miR-149, miR-219-1-3p, miR-424, miR-220, miR-96, miR-218-2, miR-649, miR-215, miR-182, miR-122, miR-524-3p, miR-187, miR-526b, miR-770-5p, miR-545, miR-200b, miR-9, miR-141, miR-579, miR-493, miR-137, miR-216a, miR-503, miR-126, miR-23b, miR-99b, miR-101, miR-323-3p, miR-25, miR-92a-1, miR-429	miR-451, miR-502-3p, miR-101 miR-33a, miR-516a-3p/miR-516b

qRT-PCR: Quantitative reverse transcriptase polymerase chain reaction.

ers have investigated miRNA in the peripheral blood of patients with gastric cancer[49-55] (Table 2) and have obtained some positive results. For example, by comparing serum of 61 gastric cancer patients with that of 61 healthy persons, Liu *et al*[49] found that the expression of miR-378 in the gastric cancer group was significantly higher than that in the healthy group. The area under the receiver-operating characteristic curve was 0.861 (95%CI: 0.766-0.928), and sensitivity/specificity was 87.5%/70.7%, respectively. Similarly, after investigating the peripheral serum in 69 gastric cancer patients and 30 healthy volunteers by qRT-PCR, Tsujiura *et al*[55] found that the plasma concentrations of miRNAs (miR-106a and miR-106b) were significantly higher in the patients than in the controls, whereas let-7a concentration was lower in the patients, in which the area under the curve (AUC) for miR-106a and let-7a was 0.879, and sensitivity/specificity was 85.5%/80.0%, respectively. These miRNAs could become ideal tumor markers for gastric cancer. In addition, Liu *et al*[49] observed that the plasma miRNAs (miR-1, miR-20a, miR-27a, miR-34, and miR-423-5P) in the gastric cancer patients had significantly higher expression than in the control group (164 gastric cancer patients *vs* 127 healthy individuals). The AUC was 0.879 (95%CI: 0.822-0.936). It is interesting that, in the same sample, they also compared the AUC values of CEA and CA19-9 which were only 0.503 and 0.600, respectively. The results show that miRNA has some advantages as a tumor marker. We have found that miRNAs have good sensitivity and specificity for gastric cancer and are promising tumor markers. However, at present, some factors still limit their clinical diagnostic applications[56]: (1) relative difficulty of detection (in quality and quantity); (2) lack of a unified testing platform and standardization; (3) plasma miRNA source and release mechanism are not clear; and (4) differences in expression of tissue and peripheral blood miRNA still exist[57]. Thus, searching and identifying specific miRNAs for the diagnosis of gastric cancer is the first task that

Table 2 Expression of miRNA and area under curve, sensitivity and specificity in serum samples of patients with gastric cancer

Group	Sample	MicroRNA	AUC	Method	Sensitivity/specificity (%)
Liu *et al*[49]	61 GC/61 C	miR-378↑	0.861	qRT-PCR	87.5/70.7
Liu *et al*[50]	164 GC/127 C	(miR-1, miR-20a, miR-27a, miR-34,	0.879	Microarray + qRT-PCR	79.3/86.5
		miR-423-5P)↑	0.831		
Konish *et al*[51]	56 GC/30 C	miR-451↑	0.96	Microarray + qRT-PCR	96.0/100
		miR-486↑	0.92		86.0/97.0
Song *et al*[52]	82 GC/82 C	miR-221, miR-744 and miR-376c↑	NA	qRT-PCR	82.4/58.8
Zhou *et al*[53]	90 GC/27 C	miR-106a↑	0.684	Microarray + qRT-PCR	48.2/90.2
		miR-17↑	0.743		51.9/92.7
Wang *et al*[54]	174 GC/39 C	miR-21↑	0.81	Microarray + qRT-PCR	56.7/94.9
Tsujiura *et al*[55]	69 GC/30 C	miR-106b↑	0.72	Microarray + qRT-PCR	NA
		miR-106a↑, let-7a↓	0.879		85.5/80.0

qRT-PCR: Quantitative reverse transcriptase polymerase chain reaction; GC: Gastric cancer, C: Control; AUC: Area under curve; NA: Not available; ↑: Upregulated; ↓: Downregulated.

Table 3 Gastric cancer with potential predictive role of miRNAs

	Potential predictive role of miRNA	
	MiRNAs of high expression	MiRNAs of low expression
Short survival time	miRNA-20b, miRNA-150[29], miRNA-142-5p[61], miRNA-375, miRNA-214[62]	miRNA-451, let7g[1], miRNA-433[1][33], miRNA-125-5p[3][63]
Lymph node metastasis	miRNA-27a[29], miRNA-650[64]	miRNA-126[65], miRNA-146a[66], miRNA-148[67], miRNA-218[68], miRNA-335[69], miRNA-429[70]
Relapse	miRNA-375[61], miRNA-451[2], miRNA-199-3p[2], miRNA-195[2][71]	miRNA-142-5p[61]
Advanced gastric cancer	miRNA-221[4][72]	miRNA-126[65], miRNA-148a[67], miRNA-218[68]
Invasion, metastasis	miRNA-223[35], miRNA-148a[73], miRNA-107[74]	miRNA-610[75], miRNA-200b[5][76], miRNA-7[77]

[1]The two miRNAs also indicate short survival and lymph node metastasis, and deeper invasion; [2]The three miRNAs also indicate short survival and recurrence, especially miRNA-451; [3]The miRNA also indicates short survival and hepatic metastases, deeper invasion, and tumor enlargement; [4]The miRNA also indicates lymph node metastasis and deeper invasion, and advanced gastric cancer; [5]The miRNA also indicates lymph node metastasis and deeper invasion, and the tumor is enlarged.

must be undertaken. Establishment of a suitable standard testing system for clinical application, including quality control, and diagnostic threshold determination are still issues that require some work. There is a high incidence of gastric cancer in East Asian countries. High-risk populations could be screened by miRNAs, which should be able to increase the detection rate of early gastric cancer and improve the effects of treatment.

miRNA AND PROGNOSIS PREDICTION

Predicting patient survival time, disease progression, prognostic outcome or response to treatment is challenging. Because of the stability and specificity of expression in tissues and circulation, miRNA may be regarded as a forecasting tool for disease outcomes. A lot of the literature suggests that miRNAs have a close relationship with survival time of gastric cancer patients, disease stage, tumor recurrence, and lymph node metastasis. Li *et al*[58] have shown that a seven-miRNA signature (miR-10b, miR-21, miR-223, miR-338, let-7a, miR-30a-5p, and miR-126) is an independent predictor of overall survival [hazard ratio (HR) = 3.046; P = 0.015] and relapse-free survival (HR = 3.337; P = 0.012). It can predict the prognosis of the patient in relation to tumor stage, cytological subtypes, and Lauren classification[59,60]. In gastric cancer, many Chinese and other research teams have discovered a number of miRNAs that play a role as a predictor. For example, high expression of miRNA-20b, miRNA-150, miRNA-142-5p[61], miRNA-375 and miRNA-214[62] and low expression of miRNA-451, let7g, miRNA-433 and miRNA-125-5p[63] are associated with short survival time. High levels of miRNA-27a and miRNA-650[64] and low levels of miRNA-126[65], miRNA-146a[66], miRNA-148[67], miRNA-218[68], miRNA-335[69] and miRNA-429[70] indicate lymph node metastasis. Patients with overexpression of miRNA-375, miRNA-451, miRNA-199-3p and miRNA-195[71] and decreased expression of miRNA-142-5p are more likely to relapse. High levels of miRNA-221[72] and decreased levels of miRNA-126, miRNA-148a and miRNA-218 indicate advanced gastric cancer. High expression of miRNA-223, miRNA-148a[73] and miRNA-107[74] and reduced expression of miRNA-610[75], miRNA-200b[76] and miRNA-7[77] were associated with invasion and metastasis (Table 3). Therefore, many potential predictors have proved useful for judging the prognosis of gastric cancer patients and are the basis for targeted therapy. However, researching miRNAs as prognostic factors involves small sample sets, high volume of work in validation, and research of independent cohorts,

Table 4 Expression of miRNA and prediction of the effect of chemotherapy and radiotherapy

	Upregulated	Downregulated
Chemosensitivity	(let-7g, miR-342, miR-16, miR-181, miR-1, miR-34)[1][81]	
Chemoresistance	(miR-518f, miR-520a, miR-520d, miR-519e, miR-363, miR-517)[1][81]	(miR-196a, miR-200family, miR-338, miR-126, miR-31, miR-98, let-7g, miR-7)[2][82] miR-15b, miR-16[83]
Radiosensitivity	miR-451[85]	
Radioresistance	miR-221/222[97]	

[1]Drugs were cisplatin and 5-fluorouracil; [2]Drug was hydroxy camptothecin.

all of which are required before assays for miRNAs can be used clinically.

miRNAs AND CHEMOTHERAPY AND RADIOTHERAPY

Resistance to chemotherapy and radiotherapy is a major obstacle to improving the survival of the patients with gastric cancer[78-80]. We can predict the occurrence of resistance to chemotherapy and radiotherapy[81-83] (Table 4) through detecting the miRNA expression profile of the patients. Through investigating drug resistance to cisplatin and 5-fluorouracil in 90 patients with gastric cancer and comparing patients' miRNA expression before and after chemotherapy, Kim *et al*[81] found that high expression of let-7g, miR-342, miR-16, miR-181, miR-1 and miR-34 indicated sensitivity to chemotherapy, and high expression of miR-518f, miR-520a, miR-520d, miR-519e, miR-363 and miR-517 indicated resistance to chemotherapy. By predicting miRNAs, we used a new method for choosing chemotherapy regimen and monitoring its effects, and even reversing the chemotherapy resistance through transfecting specific pre-miRNA. miRNA-15b and miRNA-16 are downregulated severely in the multidrug resistant gastric carcinoma cell line SGC7901/VCR. By improving miRNA-15b and miRNA-16 expression levels, sensitivity to vincristine was enhanced. Chen *et al*[84] transfected miRNA-200c into SGC7901/DDP gastric cancer cells, which increased sensitivity to DDP, 5-fluorouracil, paclitaxel and doxorubicin. The same situation occurred in radiotherapy on gastric cancer by transfection into AS-miRNA-221/222, which down-regulated the miRNA-221/222 expression in gastric cancer cell line SGC7901. Zhang *et al* found that the survival rate of cancer cell was significantly lower than that in the control group. Radiosensitivity was promoted through 0-6 Gy irradiation. In addition, Bandres *et al*[85] transfected cancer cells with pre-miRNA-451, which improved expression of miRNA-451 in AGS gastric cancer cells. Under 0-4 Gy irradiation, the effect of treatment was significantly better than that in the control group.

miRNAs AND TREATMENT

miRNAs are regulatory factors for gene expression and act as a control center in the process of tumor development[86,87]. miRNAs can modulate protein expression and affect multiple information pathways[88]. miRNAs will be more effective than coding genes as a biological treatment of tumor target molecules. The basic strategy of current treatment based on miRNAs is to adopt gene knockout to inhibit or downregulate the expression level of oncogene miRNAs. On the contrary, for anti-oncogenes, we used the method of gene knock-in to introduce foreign miRNAs, increase the expression level, and achieve the purpose of tumor treatment. The following strategies were used: administration of small molecule drugs for inhibiting miRNA, *e.g.*, anti-miRNA oligonucleotides (AMOs) following base pairing rules, competitively blocked the miRNA with target gene interaction[89], such as locked nucleic acid[90-91]; miRNA sponges, *e.g.*, the adsorption with miRNA could not combine with the natural target[92]; and miR-Mask[93], miRNA inhibitors and so on. miRNA expression is often increased by using viruses as a carrier to introduce a specific miRNA or miRNA mimics and finally upregulate miRNA and inhibit the tumor[94].

A number of Eastern Asian researchers followed the above principle of miRNA-mediated treatment and achieved good results *in vitro* and in animal experiments. For example, miRNA-221/222 is upregulated in gastric cancer cell line SGC7901. By transfecting AS-miR-221/222 2000 into cancer cells with liposomes, miRNA-221/222 is knocked out. This inhibits gastric cancer cell growth and invasion. Their target molecule is PTEN[95]. MiR-516-3p has been transfected into the gastric scirrhous carcinoma cell line 44AS3 with liposomes, was significantly overexpressed, and finally inhibited cancer cell growth, invasion and metastasis[96]. Similar results were obtained in a nude mouse transplantation model of human gastric cancer. Zhang *et al*[97] through AMOs, knocked down the originally high expression of miRNA-21 and caused the proliferation of gastric cancer cells to slow and apoptosis to increase visibly. In addition, Ji *et al*[98] have added a miRNA-34 analog to *p53* mutated gastric cancer cell lines to restore its function and upregulate its expression, which inhibited cell growth and maintained them at phase G1.

Many studies based on treatment of gastric cancer by miRNA have shown good results. In particular, Chinese, Japanese and South Korean researchers have attempted this. However, we still have several major obstacles to overcome. First, the multi-targeting nature of miRNAs brings the risk of unconscious off-target effects. Second, the expression of target genes may often be regulated by

multiple miRNAs, which could greatly reduce the effect of treatment based on a specific miRNA. Finally, we still lack good specificity and an efficient miRNA delivery system for treatment[99,100].

CONCLUSION

miRNAs are involved in almost all stages of gastric carcinogenesis, and may have broad applications in early diagnosis of gastric carcinoma, prognosis, detection of radiotherapy and chemotherapy efficacy, and be a new target for treatment. However, studies based on the clinical application of miRNAs for gastric cancer still lack reliable and exact data from large multi-center studies. In recent years, miRNAs have been a focus of biomedical research. New miRNAs have been discovered and research techniques constantly updated. It will be a great challenge to integrate new data and establish standard procedures. For diagnosis, we need unified standards and testing platforms. For treatment, we need better-designed small-molecule drugs based on a well detailed and more accurate medication carrier without toxic side effects. We look forward to further studies of miRNAs improving their clinical applications for the diagnosis and treatment of gastric cancer. East Asia, as an area with a high incidence of gastric cancer, should undertake more studies for the application of miRNAs in gastric cancer.

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