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A meta-analysis of the effect of microRNA-34a on the progression and prognosis of gastric cancer

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Abstract. – OBJECTIVE: To explore the value of microRNA-34a (miR-34a) as a diagnostic biomarker of gastric cancer development and prognosis.

MATERIALS AND METHODS: PubMed, Web of Science, Embase, CNKI, Wanfang Database and Gene Expression Omnibus (GEO) were searched according to the key words for the literature about the expression of microRNA-34a in the serum or tissues of gastric cancer patients. The data of gene expression were extracted and the data were analyzed by Stata 14.0 software to explore the significance of the difference of microRNA-34a expression in the development and prognosis of gastric cancer patients.

RESULTS: The expression of microRNA-34a was significantly lower in gastric cancer tissues and significantly lower in metastatic gastric cancer tissues. The 5-year survival rate of gastric cancer patients was also significantly lower.

CONCLUSIONS: The low expression of microRNA-34a can promote the progression of gastric cancer and reduce the prognosis of patients. MicroRNA-34a can be used as an important biomarker of gastric cancer progression and prognosis.

Key Words
microRNA-34a, Gastric cancer progression, Prognosis, Meta-analysis.

Introduction

Despite of a decrease in the incidence rate of gastric cancer in the past decades, epidemiological statistics show that it remains one of the critical factors contributing to the tumor-related death, particularly in developing countries[1]. So far, gastroscopy and pathological examination, deemed as the standard methods for early clinical diagnosis, hinder their application in diagnosis of gastric cancer due to its invasive features[2]. In addition, non-significant early symptoms of gastric cancer attribute to the fact that disease in almost 1/3 of the patients has evolved into the advanced stage, which is also one of the major factors affecting the postoperative survival rate of gastric cancer patients[3]. Therefore, further investigations on the indicators for early diagnosis of gastric cancer have a great significance for improvement in the prognosis and survival rate of patients. At present, various researches reported some biological indicators of early diagnosis and prognosis of gastric cancer, e.g. CEA, CA19-9, CA72-4. Moreover, microRNA (miRNA) has also been considered as one of the indicator to predict the onset and progression of gastric cancer in recent years[4]. Scholars[5-7] indicated that anomaly in expression of miRNA-34a also plays an important role in the onset and progression of gastric cancer. miRNA, a kind of long non-coding RNAs, can regulate the post-transcriptional expression of targeted genes, inhibits the translation activity of genes, or promotes the degradation of genes[8], endowing itself an important role in a variety of biological processes in gastric cancer, including onset and progression. As one of the miRNAs reported extensively, miRNA-34a is abnormally expressed in serum or cancerous tissues in gastric cancer and lung cancer, producing evident effect on the early diagnosis and prognosis of patients. However, divergence remains in the results; thus, we summarized the reports on the roles of miRNA-34a in gastric cancer tissues or serum to clarify whether it can serve as an indicator for early diagnosis, progression and prognostic survival of gastric cancer.

Materials and Methods

Literature Retrieval

Manual retrieval of literature was carried out in databases, including PubMed, Web of Science, Embase, CNKI, Wanfang Database, VIP database and Gene Expression Omnibus (GEO), with keywords, including gastric cancer, microRNA-34a,

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gastric, AND/OR cancer/neoplasms, and microRNA/miR-34a, from the time of database establishment. References of the related literature were also searched. In this procedure, two staffs were designated to screen literatures through reading the titles and the abstracts. For any divergence, discussion would be performed on the enrollment of the literature.

Inclusive and Exclusive Criteria

Inclusive and exclusive criteria were set as follows: a) studies involving the abnormal expression of miRNA-34a in plasma and tissue of gastric cancer patients were enrolled; b) studies involving the sensitivities, specificities or rates relating to the diagnosis or survival were enrolled; c) enrolled studies should be random control study, observation study or gene expression matrix; d) studies that could obtain the original data or the full article could be enrolled. Otherwise, literature not conforming to the criteria above was excluded.

Data Retrieval

According to the research type, related data could be retrieved from enrolled subjects, and the basic information included the first author, publication year, detection method of miRNA, age range and sex distribution of patients in each group, clinical staging of tumors, lymph node metastasis or distant metastasis. For random control trials (RCTs), differences in miRNA-34a expression between the control group and the observation group were retrieved; for observation study, ratio of miRNA-34a with abnormal expression should be obtained; for gene expression matrix, the results should be standardized, followed by retrieval of the relative expression of miRNA-34a.

Statistical Analysis

Meta-analysis was carried out with Stata 14.0. According to the instruction of software, merged analysis and subgroup analysis were performed for retrieved data. $p<0.05$ in two-tail test suggested that the difference had statistical significance. With I^2 as the indicator for heterogeneity between the enrolled works, studies with $I^2>50\%$ had heterogeneity that required the merged or subgroup analysis by random effect model, otherwise the fixed effect model. Robustness of models was tested through sensitivity analysis.

Results

Basic Information of Enrolled Literature

In this study, there were 3 works with dichotomous data[5-7], 1 with continuous data[9], and 7 with gene expression matrix[10-16] (Tables I and II). During the screening of literature and data, conferences, reviews, letters or case reports were removed on the basis of enrolled criteria (Figure 1). Then, through reading literature and data retrieval, researches with no original data (n=6) or gene probes of miRNA-34a (n=5) were removed.

Results of Meta-Analysis

In subjects of 3 researches with dichotomous data, miRNA-34a was divided into two types, i.e. the low- and high-expression, and these works reported the tumor staging, metastatic quantity and sex ratio, respectively (Figure 2 and Table III). Results showed that sex-related difference in miRNA-34a had no statistical significance ($p>0.05$; Table III). In gastric cancer tissues with metastasis or in stage III or IV, miRNA-34a was downregulated significantly ($p<0.01$; Table III), and the SMDs were 0.769 (95% CI: 0.677, 0.873) and 0.814 (95% CI: 0.697, 0.951); in gastric cancer tissues without metastasis, the expression of miRNA-34a was elevated obviously (SMD: 1.204;

Table I. Information of included studies.

Authors	Year	Male/Female	Age	Specimen	Methods	Type
Hu et al[7]	2015	23/53	> 65 (38); ≤ 65 (38)	Tissue	qRT-PCR, SYBR Green	Dichotomous data
Yang et al[6]	2016	35/15	> 55 (29); ≤ 55 (11)	Tissue	qRT-PCR, SYBR Green	Dichotomous data
Zhang et al[5]	2015	75/62	58.3±12.4	Tissue	qRT-PCR, TaqMan	Dichotomous data
Liu et al[9]	2011	237/54	60.2±10.2	Serum	qRT-PCR	Continuous data

Table II. Gene expression matrix information of microRNA.

Authors	Year	Counts	GEO ID	Platforms
Sierzega et al[16]	2017	40	GSE93415	Exiqon miRCURY LNA microRNA array
Huang et al[14]	2016	6	GSE78091	miRCURY LNA microRNA Array
Zhang et al[16]	2014	30	GSE63121	Affymetrix Multispecies miRNA-1 Array
Lee et al[12]	2014	68	GSE26595	Illumina Human v2 MicroRNA expression beadchip
Chang et al[15]	2014	32	GSE54397	Agilent-031181 Unrestricted_Human_miRNA_V16.0_Microarray
Wang et al[10]	2011	8	GSE26645	Agilent-021827 Human miRNA Microarray
Chen et al[11]	2011	44	GSE28700	Agilent-016436 Human miRNA Microarray

95% CI: 1.012, 1.431; $p<0.05$; Table III). In these three studies, 5-year follow-ups showed that miRNA-34a in high expression can prolong 5-year survival of gastric cancer patients remarkably ($p<0.0001$; Figure 3).

In a study with continuous data[9], miRNA expressions in serum were determined twice, i.e. the observation examination and validation assay, and the results indicated that the expression of miRNA-34a in serum in tumor patients was significantly higher than that in the healthy people. Moreover, high expression of miRNA-34a was also sustained in patients with promising prognosis. In 7 enrolled gene expression matrixes, miRNA-34a was divided into three subgroups, i.e. miRNA-34a-5p, miRNA-34a-3p and miRNA-34a (Figure 4), and results showed that in the control group, expression of miRNA was decreased significantly ($p < 0.05$; Table III) with an RR of -0.24 (95% CI: -0.50, 0.03). Then, publication bias was determined to test the publication bias and the robustness of results of enrolled data collection (Begg test: z = 0.36, $p = 0.721$; Egger test: t = -0.69, $p = 0.508$). Thus, no publication bias was identified among 7 data collections. Funnel plot also showed that enrolled studies were also concentrated on the top (Figure 5A), and robustness analysis also indicated no evidently abnormal studies affecting the results of analysis (Figure 5B).

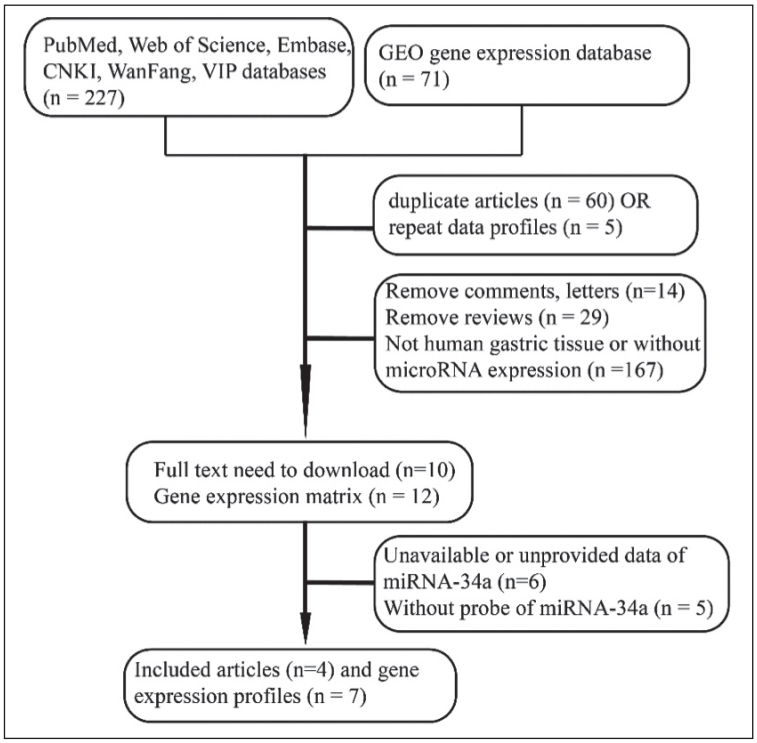

Figure 1. Flow Diagram of literature search and selection.

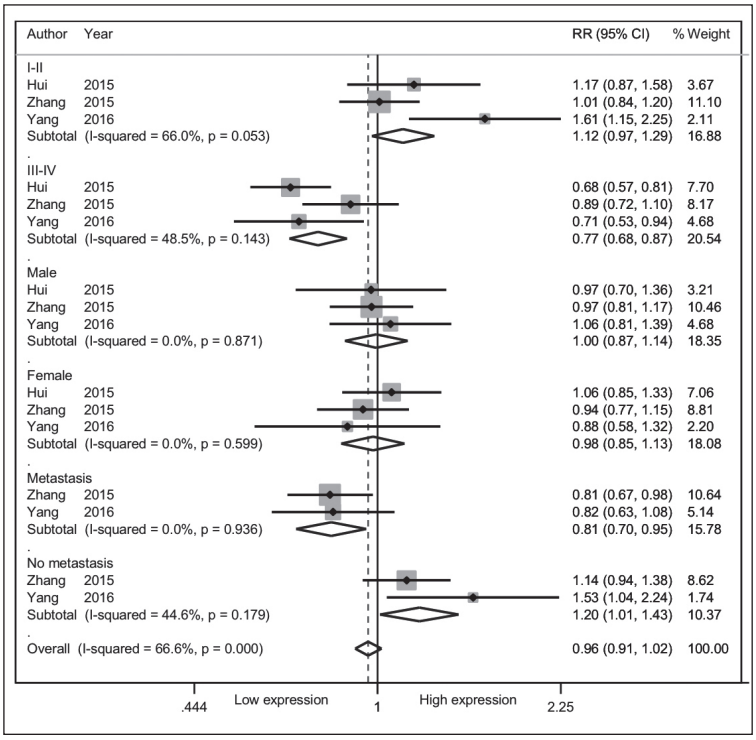

Figure 2. Forest plot of subgroup analysis with included studies.

Discussion

Emerging evidence in research on miRNAs has altered the understanding on the regulation of gene expression: miRNA can regulate the transcriptional expression of targeted genes, affecting the functions of tumor suppressor gene and oncogene[17-22]. We collected and analyzed the gastric cancer-related expression of miRNA-34a, and the results showed that the dysregulation in miRNA-34a expression can affect the metastasis and survival rate of gastric cancer significantly. In a meta-analysis[16], miRNA-34a is of great significance for predicting the prognosis and survival of gastrointestinal tumors after treatment. Imani et al[22] also revealed that miRNA-34a, as a non-invasive method, has a potential value in diagnosis of breast cancer. In this study, we obtained the data of 4 clinical observation studies and 7 gene expression matrixes. Through multi-center and -type analyses, we concluded: a) a low expression of miRNA-34a in gastric cancer tissues suggests a poor development of tumors; b) dynamic change of miRNA-34a serves as a reference indicator for progression and metas-

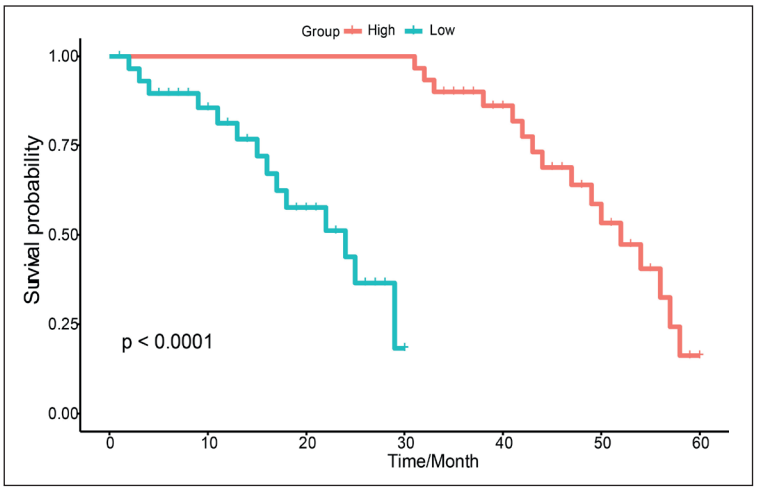

Figure 3. Survival curves of included studies in 5 years.

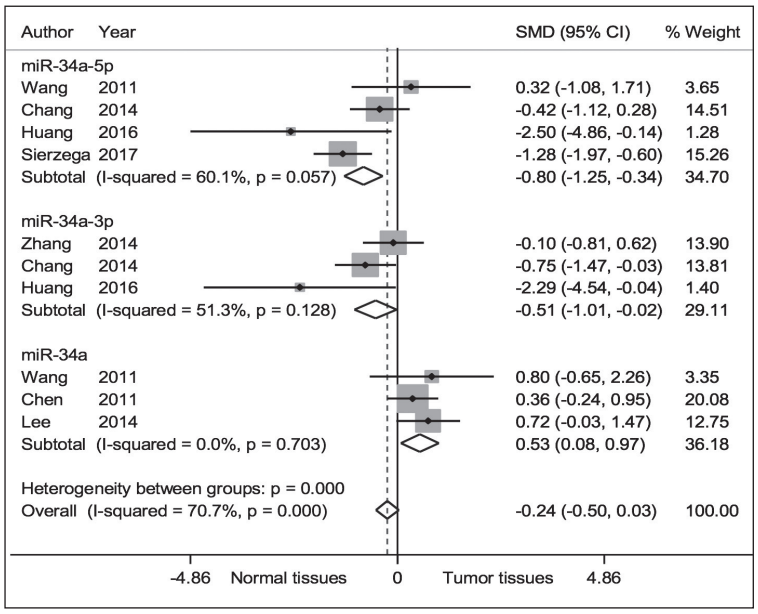

Figure 4. Forest plot of micorRNA-34a probe with included microarrays.

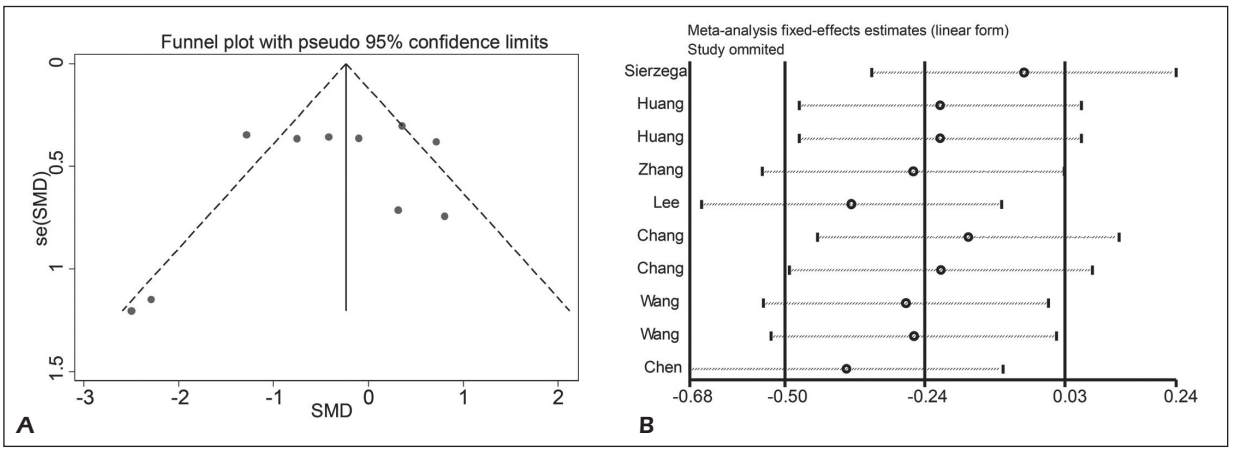

Figure 5. Funnel plot of publish bias and sensitivity analysis.

Table III. Pooled and subgroup analysis results of meta-analysis.

Subgroup	Merged effect size and 95% CI			Heterogeneity test		Significance test	
	RR/SMD	95% CI		p	I^2	z	p
I-II	1.12	0.975	1.286	0.053	66.00%	1.6	0.11
III-IV	0.769	0.677	0.873	0.143	48.50%	4.05	0
Male	0.995	0.866	1.143	0.871	0.00%	0.07	0.944
Female	0.98	0.852	1.127	0.599	0.00%	0.29	0.774
Metastasis	0.814	0.697	0.951	0.936	0.00%	2.6	0.009
No metastasis	1.204	1.012	1.431	0.179	44.60%	2.1	0.036
Overall	0.96	0.905	1.018	0	66.60%	1.37	0.169
miR-34a-5p	-0.798	-1.251	-0.344	0.057	60.10%	3.45	0.001
miR-34a-3p	-0.514	-1.009	-0.019	0.128	51.30%	2.04	0.042
miR-34a	0.527	0.083	0.97	0.703	0.00%	2.32	0.02
Overall	-0.236	-0.503	0.031	0	70.70%	1.73	0.083

tasis of gastric cancer; c) expression of miRNA-34a can affect the prognostic survival rate of gastric cancer patients indirectly. In addition, it can also be used as a biological indicator for auxiliary diagnosis of gastric cancer. Researches[21] have shown that miRNA-34a can directly regulate PI3K/AKT/survivin pathway to improve the sensitivity of p-AKT to chemotherapeutics. Additionally, miRNA-34a can also inhibit the EMT process and weaken the proliferation, invasion and migration abilities of gastric cancer cells through targeting PDGFR and Tgif2[22-24]. Therefore, miRNA-34a can alter the pathological progression of gastric cancer through regulating the expression of PDGFR and Tgif2, which explains why miRNA-34a can serve as a key indicator for analysis of the progression, prognosis and survival of gastric cancer. However, this study also has some limitations. First, confidence of the results is weakened by the small sample size and the quantity of literatures. Therefore, it is necessary to increase the quantity of enrolled literature and expand the sample size. Besides, although heterogeneity is eliminated to a certain degree by subgroup analysis for data collected from different origins, data of race, age, and gene expressions remain the origin of heterogeneity.

Conclusions

We showed the significance of miRNA-34a expression in progression and prognosis of tumors in gastric cancer patients.Further studies are conducive to enhancing the value of the results of this study.

Conflict of Interests:

The Authors declare that they have no conflict of interests.

References

1) Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.
2) Kim JI, Kim YH, Lee KH, Kim SY, Lee YJ, Park YS, Kim N, Lee DH, Kim HH, Park DJ, Lee HS. Type-specific diagnosis and evaluation of longitudinal tumor extent of Borrmann Type IV gastric cancer: CT versus gastroscopy. Korean J Radiol 2013; 14: 597-606.
3) Müsri FY, Mutlu H, Karaağaç M, Eryilmaz MK, Gündüz Ş, Artaç M. Primary tumor resection and survival in patients with stage IV gastric cancer. J Gastric Cancer 2016; 16: 78-84.
4) Song MY, Pan KF, Su HJ, Zhang L, Ma JL, Li JY, Yuasa Y, Kang D, Kim YS, You WC. Identification of serum MicroRNAs as novel non-invasive biomarkers for early detection of gastric cancer. PLoS One 2012; 7: e33608.
5) Zhang H, Li S, Yang J, Liu S, Gong X, Yu X. The prognostic value of miR-34a expression in completely resected gastric cancer: tumor recurrence and overall survival. Int J Clin Experiment Med 2015; 8: 2635-2641.
6) Yang B, Huang J, Liu H, Guo W, Li G. miR-335 directly, while miR-34a indirectly modulate survivin expression and regulate growth, apoptosis, and invasion of gastric cancer cells. Tumor Biol 2016; 37: 1771-1779.
7) Hu Y, Pu Q, Cui B, Lin J. MicroRNA-34a inhibits tumor invasion and metastasis in gastric cancer by targeting Tgif2. Int J Clin Exp Pathol 2015; 8: 8921-8928.
8) Lee S, Vasudevan S. Post-transcriptional stimulation of gene expression by microRNAs. Adv Experiment Med Biol 2013; 768: 97-101.
9) Liu R, Zhang C, Hu Z, Li G, Wang C, Yang C, Huang D, Chen X, Zhang H, Zhuang R, Deng T, Liu H, Yin J, Wang S, Zen K, Ba Y, Zhang CY. A five-microRNA signature identified from genome-wide serum microRNA expression profiling serves as a fingerprint for gastric cancer diagnosis. Eur J Cancer 2011; 47: 784-791.
10) Choi B, Yu J, Han TS, Kim YK, Hur K, Kang BC, Kim WH, Kim DY, Lee HJ, Kim VN, Yang HK. Gastric carcinogenesis in the miR-222/221 transgenic mouse model. Cancer Res Treat 2017; 49: 150-160.
11) Song J, Bai Z, Zhang Z. MicroRNAs are implicated in the initiation and progression of gastric cancer. Chin Med J (Engl) 2014; 127:554-559.
12) Shrestha S, Hsu SD, Huang WY, Huang HY, Chen W, Weng SL, Huang HD. A systematic review of microRNA expression profiling studies in human gastric cancer. Cancer Med 2014; 3: 878.
13) Mei ZB, Duan CY, Li CB, Cui L, Ogino S. Prognostic role of tumor PIK3CA mutation in colorectal cancer: a systematic review and meta-analysis. Ann Oncol 2016; 27: 1836-1848.
14) Chang H, Kim N, Park JH, Nam RH, Choi YJ, Lee HS, Yoon H, Shin CM, Park YS, Kim JM, Lee DH. Different microRNA expression levels in gastric cancer depending on Helicobacter pylori infection. Gut Liver 2015; 9: 188-196.
15) Pan HW, Li SC, Tsai KW. MicroRNA dysregulation in gastric cancer. Curr Pharm Des 2013; 19: 1273-1284.
16) Zhang R, Wang W, Li F, Zhang H, Liu J. MicroRNA-106b~25 expressions in tumor tissues and plasma of patients with gastric cancers. Med Oncol 2014; 31: 243.
17) Nicoloso MS, Spizzo R, Shimizu M, Rossi S, Calin GA. MicroRNAs--the micro steering wheel of tumour metastases. Nat Rev Cancer 2009; 9: 293-302.
18) Cho WC. MicroRNAs: potential biomarkers for cancer diagnosis, prognosis and targets for therapy. Int J Biochem Cell Biol 2010; 42: 1273-1281.
19) Mactier KE, Glaire MA, Basavaraju U, El-Omar EM, Hold GL. MicroRNAs in gastrointestinal malignancy: a tool in cancer prevention? Eur J Cancer Prev 2014; 23: 540-549.
20) Xu M, Li D, Yang C, Ji JS. MicroRNA-34a inhibition

of the TLR signaling pathway via CXCL10 suppresses breast cancer cell invasion and migration. Cell Physiol Biochem 2018; 46: 1286-1304.
21) Cao W, Yang W, Fan R, Li H, Jiang J, Geng M, Jin Y, Wu Y. miR-34a regulates cisplatin-induce gastric cancer cell death by modulating PI3K/AKT/survivin pathway. Tumour Biol 2014; 35: 1287-1295.
22) Imani S, Zhang X, Hosseinifard H, Fu S, Fu J. The diagnostic role of microRNA-34a in breast cancer: a systematic review and meta-analysis. Oncotarget 2017; 8: 23177-23187.
23) Shin VY, Chu KM. MiRNA as potential biomarkers and therapeutic targets for gastric cancer. World J Gastroenterol 2014; 20: 10432-10439.
24) Jiang HB, Yang TJ, Lu P, Ma YJ. Gene expression profiling of gastric cancer. Eur Rev Med Pharmacol Sci 2014; 18: 2109-2115.