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Identification of diagnostic utility and molecular mechanisms of circulating miR-551b-5p in gastric cancer

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ABSTRACT

Background: Gastric cancer (GC) is one of the most common cancers globally leading to 850,000 deaths each year. GC patients are often diagnosed at advanced stages which results in poor prognosis. This study aimed to identify a novel circulating miRNA as the diagnostic biomarker of GC and further explore its regulatory mechanisms in GC.

Materials and methods: First, the candidate serum miRNA was selected after analysis of microarray data. Then, the levels of candidate miRNA in the serum of GC patients were validated in an independent cohort. The diagnostic utility of miRNA was evaluated by using receiver operating characteristic curve (ROC) analysis. The functional and pathways enrichment analysis of targets of candidate miRNA were explored by online tool DAVID.

Results: After comprehensive analysis of Gene Expression Omnibus (GEO) dataset, miR-551b-5p was selected as candidate due to its highest differential fold-change. Another independent cohort showed that serum miR-551b-5p could differentiate GC patients from healthy controls (HCs) with area under the curve (AUC) of 0.84 (95%CI: 0.75-0.93). The functional and pathways enrichment analysis revealed that targets of miR-551b-5p mainly located in cytoplasm and significantly associated with regulation of ubiquitin-dependent protein catabolic process, cell division, and mRNA stability.

Conclusions: Circulating miR-551b-5p was a novel promising biomarker for the detection of GC and exploration of the molecular mechanisms of miR-551b-5p is useful to search for new therapeutic strategies of GC.

1. Introduction

Gastric cancer (GC), as one of the most common malignancies worldwide, is the third leading cause of cancer-related death [1], particularly, prevalent in Eastern Asia [2]. In spite of the declining incidence rate of GC, there are still over 1 million new cases and 850,000 deaths annually all over the world. A large quantity of GC patients were diagnosed at advanced stages due to the non-specific symptoms at early stage [3,4]. Although gastroscopy followed by biopsy is the criterion standard test for diagnosing GC [5], the invasiveness and high expense limit its popularization. In addition, non-invasive biomarkers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), are neither sensitive nor specific enough to facilitate detection of GC [6]. Despite the development of surgery, chemotherapy, and other therapy methods, over 50% of the GC patients may still undergo recurrence and metastasis after treatment, which results in unfavorable prognosis of patients [7,8]. Therefore, it is urgently needed to search for novel non-invasive biomarkers with high sensitivity and specificity for the detection of GC and to explore the molecular pathogenesis of GC to find new therapeutic strategies.

MicroRNAs (miRNAs), a class of endogenous noncoding RNAs with 17–25 nucleotides, play a vital role in post-transcriptional gene regulation through bind to the 3′-untranslated regions (3′-UTR) of target mRNAs leading to direct mRNA degradation or translational repression [9]. In the past decades, dysregulated miRNAs have been reported significantly associated with the development and progression of various cancers, including GC [10–12]. A large number of studies have indicated that miRNAs act as key regulators in multiple physiological processes, such as cell proliferation, apoptosis, invasion and migration [13–15]. Besides, miRNAs could be secreted and exist in biofluids stably, including peripheral blood, which makes them promising to be biomarkers for the detection of GC [16–20] In this study, we identified

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a novel promising serum miRNA as the diagnostic biomarker of GC after comprehensive analysis of a microarray assay and an independent cohort. Subsequently, we further explored its target genes and functional and pathways enrichment analysis through online tools.

2. Materials and methods

2.1. Microarray data processing

After searching in the GEO database (https://www.ncbi.nlm.nih.gov/geo/) using keywords "miRNA", "gastric cancer", "serum", "plasma" and "Homo sapiens", the most eligible GEO dataset was found (GSE59856). In order to screen differentially expressed miRNAs between GC and healthy serum samples, GEO2R (http://www.ncbi.nlm.nih.gov/geo/geo2r/) was applied [21].

2.2. Clinical individuals

GC patients and gender/age matched healthy controls were enrolled from Affiliated Hospital of Jiangsu University and The Third Affiliated Hospital of Nanjing Medical University. GC patients were confirmed through histopathological analysis of surgically resected tissues. Our study was approved by the Research and Ethical Committee of The Third Affiliated Hospital of Nanjing Medical University, and the written informed consent was obtained from each participant.

2.3. Samples processing

Twenty paired CRC tissues and adjacent normal tissues (ANTs) were obtained from patients who underwent primary surgery resection. Following being pathologically confirmed, tissues were frozen in liquid nitrogen after surgery until RNA extraction. Serum samples were collected from patients diagnosed as CRC or from healthy people who had physical examinations. Serums were stored at −80 °C until RNA extraction. None of the subjects recruited in this study received chemotherapy or radiation therapy before specimens were collected.

2.4. RNA extraction

Total RNA was extracted from serum and tissues using Trizol LS reagent (Invitrogen, Carlsbad, California, USA) following manufacturer's instructions. Cel-miR-39-3p at a concentration of 1 uM (GenePharma, Shanghai, China) was added into each serum sample to serve as the external reference. SnRNA U6 was chosen to be internal reference. Then, total RNA was stored at −80 °C.

2.5. Reverse transcription and qPCR

Reverse transcription and qRT-PCR were performed using HairpinitTM microRNA RT-PCR Quantitation Kit (GenePharma, Shanghai, China) according to the manufacturer's protocol. Each reaction was performed in triplicate in 96 well plates. The reactions were initiated with denaturation at 95℃ for 3 min, followed by 40 cycles of 95℃ for 15 s and 62℃ for 34 s. The relative expression of miRNAs were calculated with $2^{-\triangle Ct}$ ^{Ct} method. $\triangle Ct = Ct_{miRNA}\text{-}Ct_{miR\text{-}39/U6}$, $\triangle CtCt = \triangle Ct_{patient}\text{-}\ Ct_{control}$.

2.6. Functional and pathways enrichment analysis of candidate targets

To further identify the potential molecular mechanisms underlying miR-551b-5pin GC, miRDB (http://mirdb.org/), TargetScan (http://www.targetscan.org/vert_71/), and LinkedOmics (http://linkedomics.org/) were used to predict the potential targets. The GO and KEGG analysis were available in the online tool DAVID Database (https://david.ncifcrf.gov/), which is a bioinformatics database composing of functional annotation of large quantities of genes.

Table 1
Significantly dysregulated miRNAs in the serums of GC patients based on GSE59856.

miRNA	logFC	P-Value	miRNA	logFC	P-Value
hsa-miR-3130-3p	1.38	1.12E-09	hsa-miR-125a-3p	−1.21	1.22E-17
hsa-miR-4792	1.23	1.04E-32	hsa-miR-4489	−1.21	3.50E-30
hsa-miR-6857-5p	1.17	2.37E-23	hsa-miR-4496	−1.22	3.85E-36
hsa-miR-6825-5p	1.15	3.37E-35	hsa-miR-920	−1.24	2.83E-35
hsa-miR-422a	1.11	8.68E-18	hsa-miR-204-3p	−1.26	8.59E-33
hsa-miR-7110-5p	1.11	4.23E-26	hsa-miR-1288-3p	−1.27	9.85E-22
hsa-miR-4514	−1.02	5.91E-24	hsa-miR-4727-3p	−1.27	2.81E-27
hsa-miR-6717-5p	−1.05	2.24E-28	hsa-miR-6501-3p	−1.33	1.70E-28
hsa-miR-6511b-5p	−1.06	1.19E-31	hsa-miR-4776-5p	−1.34	7.81E-49
hsa-miR-1471	−1.07	1.11E-26	hsa-miR-4257	−1.36	1.65E-55
hsa-miR-6726-5p	−1.08	1.59E-55	hsa-miR-6760-5p	−1.41	1.68E-37
hsa-miR-3131	−1.09	2.46E-35	hsa-miR-4635	−1.46	1.43E-26
hsa-miR-5189-5p	−1.1	1.27E-30	hsa-miR-8060	−1.47	4.85E-50
hsa-miR-3137	−1.12	1.83E-39	hsa-miR-650	−1.54	7.23E-43
hsa-miR-103a-3p	−1.16	1.36E-15	hsa-miR-1343-3p	−1.64	2.40E-49
hsa-miR-4538	−1.16	3.12E-30	hsa-miR-7641	−1.73	8.75E-31
hsa-miR-668-5p	−1.16	7.81E-33	hsa-miR-6849-5p	−1.82	3.70E-54
hsa-miR-3622b-5p	−1.19	3.11E-42	hsa-miR-551b-5p	−2.02	6.60E-52

2.7. Statistical analysis

The differential expression of miRNAs between GC group and normal group were analyzed using paired or unpaired *t*-test. ROC curve and AUC were performed to discriminate GC patients from healthy controls. The cut-off value of miR-551b-5p expression were determined by using Youden index from ROC curves. P-value < 0.05 was considered statistically significant. The statistical analysis was performed using GraphPad 7.0 (GraphPad Software, USA). All data were presented as mean ± SD.

3. Results

3.1. Serum miRNA microarray analysis revealed miR-551b-5p as the most promising candidate diagnostic biomarker of GC

Analysis of GSE59856 revealed thirty-six dysregulated miRNAs in serum of GC patients with|logFC| > 1 (Table 1). Among these miRNAs, serum miR-551b-5p expression showed highest differential fold-change between healthy controls and GC patients (Fig. 1A-B). Therefore, we selected miR-551b-5p as the candidate miRNA and ROC analysis indicated serum miR-551b-5p was a promising marker for the diagnosis of GC (Fig. 1C).

3.2. The diagnostic value of serum miR-551b-5p expression was validated in an independent cohort

In the validation phase, a total of 80 serum samples, including those from GC patients (n = 40) and healthy controls (n = 40), were examined to evaluate the diagnostic potential of serum miR-551b-5p. The relative expression of serum miR-551b-5p was significantly down-regulated in GC patients compared with healthy controls (Fig. 2A). Next, ROC analysis showed that serum miR-551b-5p expressions could discriminate GC patients from healthy controls with an AUC value of 0.84 (95%CI: 0.75–0.93, sensitivity: 77.5%, specificity: 80.0%, cut-off value: 0.727) (Fig. 2B).

3.3. The relative expression of miR-551b-5p in GC tissues

Subsequently, we further investigated the relative expressions of miR-551b-5p in GC tissues. As shown in Fig. 3A, the relative expressions of miR-551b-5p were remarkably decreased in GC tissues compared with normal tissues (NCs). Another GEO dataset (GSE28700) also proved the down-regulated expression of miR-551b-5p in GC tissues

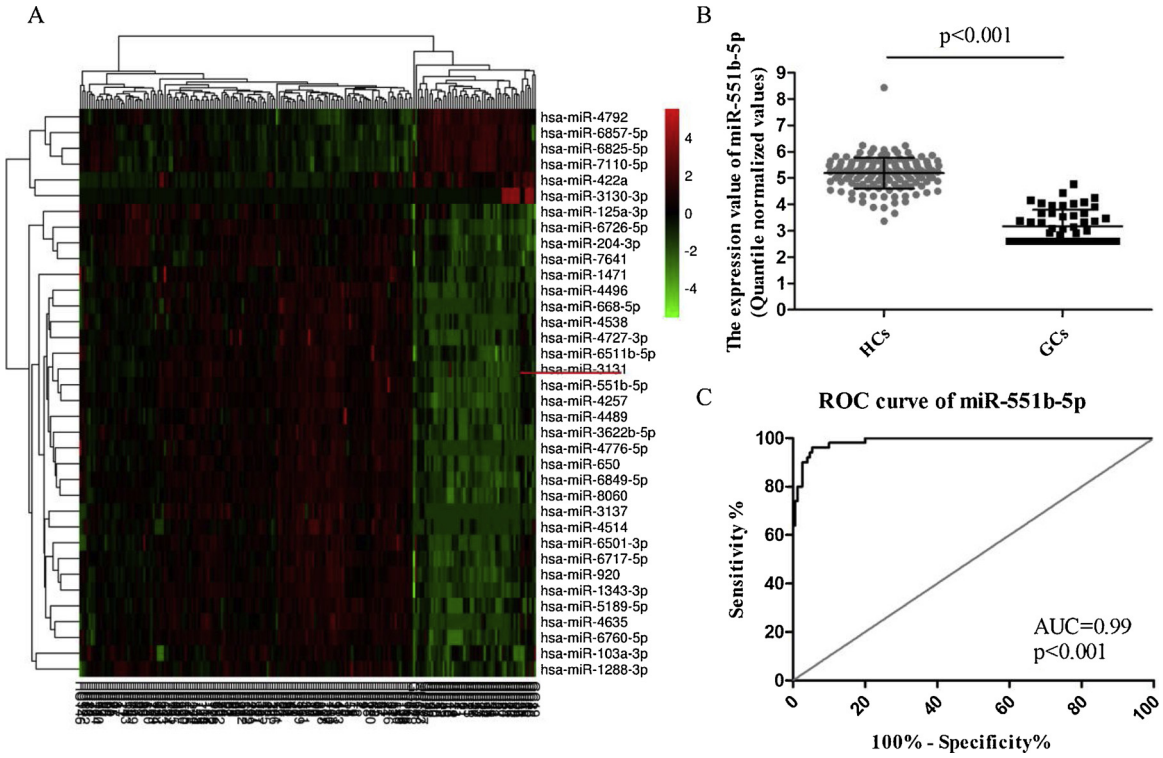

Fig. 1. Selection of candidate circulating miR-551b-5p based on GSE29856. (A) Partial miRNAs that were significantly dysregulated in the serum of GC patents. (B) The expression of serum miR-551b-5p in GC patients and HCs. (C) The AUC of serum miR-551b-5p analyzed by ROC curves.

(Fig. 3B).

3.4. The potential targets of miR-551b-5p in GC

After integrated analysis of miRDB and TargetScan, 996 mRNAs were predicted to be potential targets of miR-551b-5p. In order to improve the accuracy, TCGA database was used to select candidate targets that were significantly negative-associated with miR-551b-5p expression through online tool LinkedOmics (Table 2). Thereafter, 172 genes were selected to be candidate targets of miR-551b-5p (Fig. 4).

3.5. Functional and pathways enrichment analysis of candidate targets of miR-551b-5p in GC

The GO term enrichment analysis revealed that in the BP category, targets were significantly enriched in ubiquitin-dependent protein catabolic process, cell division, and regulation of mRNA stability. CC analysis showed that most targets were located in cytoplasm. Furthermore, according to the results of MF analysis, targets were mainly associated with protein binding and poly(A) RNA binding. If there were more than ten terms enriched in these categories, the top ten terms based on p-value were chosen. In addition, KEGG pathway analysis showed that most of the targets participated in RNA transport and Ubiquitin mediated proteolysis (Table 3).

4. Discussion

In this study, we conducted a comprehensive analysis of differentially expressed miRNAs based on GEO database, and discovered serum miR-551b-5p was most dysregulated in GC patients. Next, we identified and validated that circulating miR-551b-5p was a novel promising biomarker for diagnosis of GC to differentiate GC patients from healthy controls. Then, we further explored its target genes through integrated analysis of miRDB, TargetScan, and TCGA database. Functional

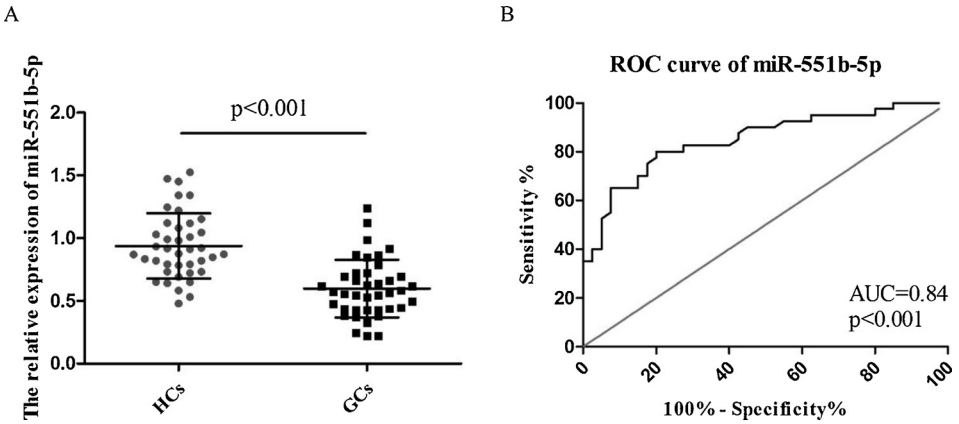

Fig. 2. Validation of serum miR-551b-5p as diagnostic biomarker of GC. (A) The relative expression levels of miR-551b-5p in the serum of GC patients. (B) The AUC of serum miR-551b-5p to differentiate GC patients from HCs.

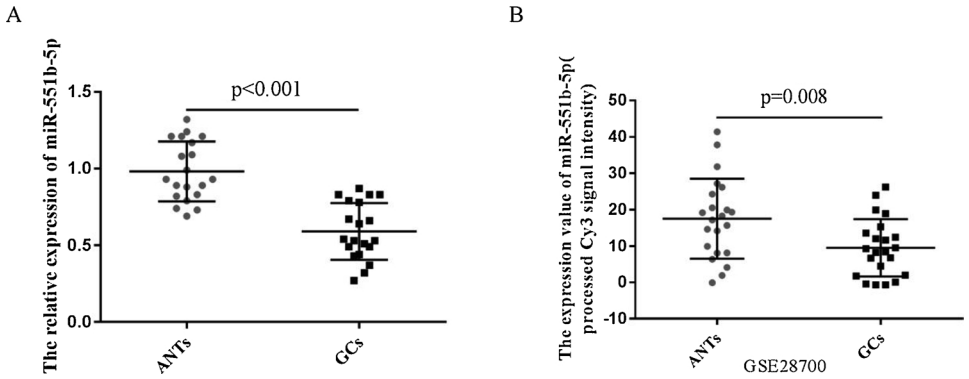

Fig. 3. The expression levels of miR-551b-5p in GC tissues. (A) The relative expression levels of miR-551b-5p were significantly down-regulated in GC tissues. (B) GSE28700 revealed that miR-551b-5p were significantly down-regulated in GC tissues.

Table 2
Part candidate targets that significantly negative-associated with miR-551b-5p expression in GC ($p < 0.001$).

Targets	Statistic	P-Value	Targets	Statistic	P-Value
GNG10	−0.27851	5.11E-08	RBBP6	−0.18561	0.000331
EIF5A2	−0.25847	4.64E-07	SOX11	−0.18235	0.000423
ANKRD10	−0.23925	3.25E-06	JRKL	−0.18161	0.000447
DYNC1I2	−0.23859	3.47E-06	NUCKS1	−0.17888	0.000546
TCEA1	−0.23823	3.59E-06	PABPC1	−0.1783	0.000569
PLA2G12 A	−0.23551	4.66E-06	YOD1	−0.17808	0.000579
UBE2D1	−0.23512	4.84E-06	GPR180	−0.17768	0.000596
MTDH	−0.21332	3.52E-05	FMR1	−0.17743	0.000607
SUMO1	−0.21332	3.52E-05	SLC25A32	−0.17611	0.000667
NT5DC3	−0.21128	4.19E-05	ARL13B	−0.17477	0.000734
PPIG	−0.20328	8.21E-05	GRPEL2	−0.17452	0.000748
RAB33B	−0.20322	8.25E-05	CCDC84	−0.17315	0.000824
PRPF39	−0.20253	8.73E-05	PICALM	−0.17286	0.000841
SEC62	−0.20055	0.000103	IMPAD1	−0.17259	0.000857
STK3	−0.19302	0.000187	C5orf22	−0.17147	0.000928
RUFY3	−0.19269	0.000192	PRKRIR	−0.17144	0.000929
GBAS	−0.18963	0.000244	NUPL2	−0.17139	0.000932
EIF1AX	−0.18862	0.000264	FBXO33	−0.17125	0.000942
CBX3	−0.18604	0.000321	CSAD	−0.17052	0.000991

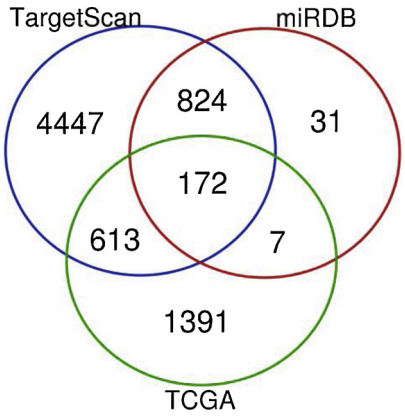

Fig. 4. Identification of candidate targets of miR-551b-5p through integrated analysis of miRDB, TargetScan, and TCGA database.

enrichment analysis revealed that miR-551b-5p may work in GC through regulation of ubiquitin-dependent protein catabolic process and mRNA stability. KEGG pathway analysis showed that most of the targets participated in RNA transport and Ubiquitin mediated proteolysis.

The diagnostic role of circulating miRNAs has been widely investigated in the past decades. Li et al. reported that miRNA-199a-3p in plasma could be a potential diagnostic biomarker for GC detection [22].

Table 3
Functional and pathways enrichment analysis of candidate targets of miR-551b-5p in GC.

Category	Term	Count	%	P-Value
GOTERM_BP	Regulation of mRNA stability	8	4.8	3.80E-05
GOTERM_BP	Ubiquitin-dependent protein catabolic process	9	5.4	2.30E-04
GOTERM_BP	Protein ubiquitination involved in ubiquitin-dependent protein catabolic process	7	4.2	2.50E-03
GOTERM_BP	Global genome nucleotide-excision repair	4	2.4	2.90E-03
GOTERM_BP	mRNA splicing, via spliceosome	8	4.8	3.80E-03
GOTERM_BP	Viral process	9	5.4	5.50E-03
GOTERM_BP	Transcription elongation from RNA polymerase II promoter	5	3	7.40E-03
GOTERM_BP	G2/M transition of mitotic cell cycle	6	3.6	7.70E-03
GOTERM_BP	Positive regulation of translation	4	2.4	1.20E-02
GOTERM_BP	Cell division	9	5.4	1.30E-02
GOTERM_CC	Nucleoplasm	50	29.8	2.30E-07
GOTERM_CC	Cytosol	52	31	7.40E-06
GOTERM_CC	Cytoplasm	68	40.5	7.20E-05
GOTERM_CC	Nucleus	63	37.5	3.90E-03
GOTERM_CC	Membrane	31	18.5	5.80E-03
GOTERM_CC	Perinuclear region of cytoplasm	13	7.7	6.90E-03
GOTERM_CC	U2-type prespliceosome	3	1.8	9.00E-03
GOTERM_CC	Cytoplasmic ribonucleoprotein granule	3	1.8	1.90E-02
GOTERM_CC	Nuclear pore	4	2.4	2.30E-02
GOTERM_CC	Ribonucleoprotein complex	2	1.2	2.50E-02
GOTERM_CC	Catalytic step 2 spliceosome	4	2.4	4.40E-02
GOTERM_MF	Protein binding	114	67.9	3.40E-09
GOTERM_MF	Poly(A) RNA binding	31	18.5	5.20E-08
GOTERM_MF	RNA binding	16	9.5	1.10E-04
GOTERM_MF	mRNA 3'-UTR binding	5	3	9.30E-04
GOTERM_MF	Ubiquitin-protein transferase activity	9	5.4	9.20E-03
GOTERM_MF	mRNA binding	5	3	2.50E-02
GOTERM_MF	Ubiquitin conjugating enzyme activity	3	1.8	2.70E-02
GOTERM_MF	Microtubule motor activity	4	2.4	3.40E-02
GOTERM_MF	Thiol-dependent ubiquitin-specific protease activity	4	2.4	3.40E-02
GOTERM_MF	Translation elongation factor activity	3	1.8	3.70E-02
KEGG_PATHWAY	RNA transport	7	4.2	4.20E-03
KEGG_PATHWAY	Ubiquitin mediated proteolysis	5	3	3.40E-02

Shin et al. discovered that levels of plasma miR-627, miR-629 and miR-652 were significantly higher in GC patients than healthy controls and this three-miRNA signature as a promising classifier for gastric cancer [17]. Besides, Peng et al. demonstrated that the level of serum miR-191 was significantly higher in the GC group than in the control group when using serum miR-16 as an endogenous control which indicated the

potential use of serum miR-191 as a stable biomarker for GC diagnosis [23]. Here, we found circulating miR-551b-5p was a novel promising biomarker for GC detection with high sensitivity and specificity enhancing the feasibility of miRNAs in peripheral blood as non-invasive diagnostic markers for this disease.

The GO term enrichment analysis revealed that targets of miR-551b-5p were significantly enriched in regulation of ubiquitin-dependent protein catabolic process, cell division, and mRNA stability. These biological processes have been investigated in the past decades. Le et al. reported that mRNA stability was associated with the invasive phenotype in breast cancer [24]. Pine et al. discovered that human lung tumor cell fate decisions may be regulated during the cell division process and the characterization and modulation of asymmetric cell division in lung cancer may provide insight into tumor initiation, growth, and maintenance [25]. Qi et al. demonstrated that the E3 ubiquitin ligase Siah2 contributes to castration-resistant prostate cancer by regulation of androgen receptor transcriptional activity [26]. KEGG pathway analysis showed that targets of miR-551b-5p significantly participate in RNA transport and ubiquitin-mediated proteolysis. Taniuchi et al. exhibited KIF20A-mediated RNA granule transport system could promote the invasiveness of pancreatic cancer cells [27]. Zhi et al. reported E3 ubiquitin ligase RNF126 promotes cancer cell proliferation by targeting the tumor suppressor p21 for ubiquitin-mediated degradation [28]. Our study provided a comprehensively systematic description about the molecular mechanism of miR-551b-5p in GC, which is helpful to search for new therapeutic strategies.

Indeed, there are several limitations in our study. First of all, the sample size included was relatively small, and more studies with larger sample numbers are needed to clarify the diagnostic value of serum miR-551b-5p in GC. Second, the pathologic effect of miR-551b-5p ought to be further investigated by conducting gain and loss of function assays.

In conclusion, we demonstrated that circulating miR-551b-5p was a novel promising diagnostic biomarker of GC and described a comprehensively systematic description about the molecular mechanism of miR-551b-5p in GC.

Disclosure of interests

None.

Acknowledgement

All authors took part in writing the manuscript and approved the final submitted version.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer Stat. 68 (2018) 7–30.
[2] F. Bray, J.S. Ren, E. Masuyer, J. Ferlay, Global estimates of cancer prevalence for 27 sites in the adult population in 2008, Int. J. Cancer 132 (2013) 1133–1145.
[3] H.H. Hartgrink, E.P. Jansen, N.C. van Grieken, C.J. van de Velde, Gastric cancer, Lancet 374 (2009) 477–490.
[4] E. Faghihloo, Y. Araei, M. Mohammadi, H. Mirzaei, H.R. Mohammadi, T. Mokhtari-Azad, The effect of oxamflatin on the E-cadherin expression in gastric cancer cell line, Cancer Gene Ther. 23 (2016) 396–399.
[5] A.M. Veitch, N. Uedo, K. Yao, J.E. East, Optimizing early upper gastrointestinal cancer detection at endoscopy, Nat. Rev. Gastroenterol. Hepatol. 12 (2015) 660–667.
[6] H. Shimada, T. Noie, M. Ohashi, K. Oba, Y. Takahashi, Clinical significance of serum tumor markers for gastric cancer: a systematic review of literature by the Task Force of the Japanese, Gastric Cancer 17 (2014) 26–33.
[7] V.Y. Shin, K.M. Chu, MiRNA as potential biomarkers and therapeutic targets for gastric cancer, World J. Gastroenterol. 20 (2014) 10432–10439.
[8] A.D. Newton, J. Datta, A. Loaiza-Bonilla, G.C. Karakousis, R.E. Roses, Neoadjuvant therapy for gastric cancer: current evidence and future directions, J. Gastrointest. Oncol. 6 (2015) 534–543.
[9] D.P. Bartel, MicroRNAs: genomics, biogenesis, mechanism, and function, Cell 116 (2004) 281–297.
[10] H. Yu, J. Zhang, Q. Wen, Y. Dai, W. Zhang, F. Li, et al., MicroRNA-6852 suppresses cell proliferation and invasion via targeting forkhead box J1 in gastric cancer, Exp. Ther. Med. 16 (2018) 3249–3255.
[11] X. Liu, B. He, T. Xu, Y. Pan, X. Hu, X. Chen, et al., MiR-490-3p functions As a tumor suppressor by inhibiting oncogene VDAC1 expression in colorectal Cancer, J. Cancer 9 (2018) 1218–1230.
[12] D. Sun, X. Li, M. Ma, J. Liu, Y. Xu, L. Ye, et al., The predictive value and potential mechanisms of miRNA-328 and miRNA-378 for brain metastases in operable and advanced non-small-cell lung cancer, Jpn. J. Clin. Oncol. 45 (2015) 464–473.
[13] T. Yan, S. Zhu, J. Zhang, G. Lu, C. Lv, Y. Wei, et al., MicroRNA944 targets vascular endothelial growth factor to inhibit cell proliferation and invasion in osteosarcoma, Mol. Med. Rep. (2018).
[14] Y.W. Deng, W.J. Hao, Y.W. Li, Y.X. Li, B.C. Zhao, D. Lu, Hsa-miRNA-143-3p reverses multidrug resistance of triple-negative breast Cancer by inhibiting the expression of its target protein cytokine-induced apoptosis inhibitor 1 in vivo, J. Breast Cancer 21 (2018) 251–258.
[15] T. Akamine, Y. Morodomi, Y. Harada, K. Teraishi, T. Tagawa, T. Okamoto, et al., miR-3148 is a novel Onco-microRNA that potentiates tumor growth in vivo, Anticancer Res. 38 (2018) 5693–5701.
[16] S. Gilad, E. Meiri, Y. Yogev, S. Benjamin, D. Lebanony, N. Yerushalmi, et al., Serum microRNAs are promising novel biomarkers, PLoS One 3 (2008) e3148.
[17] V.Y. Shin, E.K. Ng, V.W. Chan, A. Kwong, K.M. Chu, A three-miRNA signature as promising non-invasive diagnostic marker for gastric cancer, Mol. Cancer 14 (2015) 202.
[18] L. Jamali, R. Tofigh, S. Tutunchi, G. Panahi, F. Borhani, S. Akhavan, et al., Circulating microRNAs as diagnostic and therapeutic biomarkers in gastric and esophageal cancers, J. Cell. Physiol. 233 (2018) 8538–8550.
[19] H. Mirzaei, S. Khataminfar, S. Mohammadparast, S.S. Sales, M. Maftouh, M. Mohammadi, et al., Circulating microRNAs as potential diagnostic biomarkers and therapeutic targets in gastric Cancer: current status and future perspectives, Curr. Med. Chem. 23 (2016) 4135–4150.
[20] M. Simonian, M. Mosallayi, H. Mirzaei, Circulating miR-21 as novel biomarker in gastric cancer: diagnostic and prognostic biomarker, J. Cancer Res. Ther. 14 (2018) 475.
[21] T. Barrett, S.E. Wilhite, P. Ledoux, C. Evangelista, I.F. Kim, M. Tomashevsky, et al., NCBI GEO: archive for functional genomics data sets–update, Nucleic Acids Res. 41 (2013) D991–5.
[22] C. Li, J.F. Li, Q. Cai, Q.Q. Qiu, M. Yan, B.Y. Liu, et al., miRNA-199a-3p in plasma as a potential diagnostic biomarker for gastric cancer, Ann. Surg. Oncol. 20 (Suppl 3) (2013) S397–405.
[23] W.Z. Peng, R. Ma, F. Wang, J. Yu, Z.B. Liu, Role of miR-191/425 cluster in tumorigenesis and diagnosis of gastric cancer, Int. J. Mol. Sci. 15 (2014) 4031–4048.
[24] J. Le Quesne, UTRly malignant: mRNA stability and the invasive phenotype in breast cancer, J. Pathol. 230 (2013) 129–131.
[25] S.R. Pine, B.M. Ryan, L. Varticovski, A.I. Robles, C.C. Harris, Microenvironmental modulation of asymmetric cell division in human lung cancer cells, Proc. Natl. Acad. Sci. U S A 107 (2010) 2195–2200.
[26] J. Qi, M. Tripathi, R. Mishra, N. Sahgal, L. Fazli, S. Ettinger, et al., The E3 ubiquitin ligase Siah2 contributes to castration-resistant prostate cancer by regulation of androgen receptor transcriptional activity, Cancer Cell 23 (2013) 332–346.
[27] K. Taniuchi, M. Furihata, T. Saibara, KIF20A-mediated RNA granule transport system promotes the invasiveness of pancreatic cancer cells, Neoplasia 16 (2014) 1082–1093.
[28] X. Zhi, D. Zhao, Z. Wang, Z. Zhou, C. Wang, W. Chen, et al., E3 ubiquitin ligase RNF126 promotes cancer cell proliferation by targeting the tumor suppressor p21 for ubiquitin-mediated degradation, Cancer Res. 73 (2013) 385–394.