European Review for Medical and Pharmacological Sciences 2018; 22: 5187-5193

Serum miR-629 is a novel molecular marker for diagnosis and the prognosis of pancreatic cancer

W. SHI[1], Y. LU[2], R. GONG[2], J.-J. SUN[1], G. LIU[1]

[1]Department of Hepatopancreatobiliary Surgery, The Second Hospital of Tianjin Medical University, Tianjin, China
[2]Department of Pharmacy, The Second Hospital of Tianjin Medical University, Tianjin, China

Abstract. – OBJECTIVE: Increasing evidence indicates that dysregulation of miRNAs is involved in tumor progression and development. We aimed to determine potential values of miR-629 as a serum diagnostic and prognostic biomarker in pancreatic cancer (PC).

PATIENTS AND METHODS: MiR-629 expression levels in PC tissues and serum were measured by quantitative Real-time reverse transcription-polymerase chain reaction (qRT-PCR). Receiver operating characteristic analysis (ROC) was utilized to assess the predictive power of serum miR-629 for PC. Then, the associations of serum miR-629 expression levels with clinicopathological features and prognosis were evaluated.

RESULTS: We found that the expression levels of miR-629 were significantly upregulated in both PC tissues and serum in comparison with matched normal tissues and healthy controls, respectively. Importantly, serum miR-629 could efficiently screen PC patients from healthy controls (AUC=0.765). The diagnosis capability of serum miR-629 was significantly higher than that of CA19-9, and the combination of two molecules had higher diagnosis capacity. Higher expression of serum miR-629 in PC patients was associated with advanced TNM stage (p=0.000) and distant metastasis (p=0.003). Moreover, Kaplan-Meier analysis indicated that patients with high expression of serum miR-629 had significantly shorter overall survival (p=0.0022) and disease-free survival (p=0.0003) than the low expression group. Univariate and multivariate analysis showed that serum miR-629 was a significant and independent prognostic predictor for both overall survival and disease-free survival of PC patients.

CONCLUSIONS: This study suggested serum miR-629 may be a potential biomarker for the diagnosis and prognosis of PC.

Key Words
Serum miR-629, Pancreatic cancer, Diagnosis, Prognosis.

Introduction

Pancreatic cancer (PC) is the most common malignancy and a leading cause of cancer-related mortality around the world[1]. Pancreatic carcinogenesis is known to be a multi-step process involving multiple genetic and epigenetic alterations[2]. Up to date, surgical resection offers the best chance for a possible cure. However, due to the lack of appropriate tools and specific symptoms for early diagnosis, PC is usually diagnosed at an advanced stage when surgical resection cannot be offered[3,4]. Thus, the survival rate of PC has not improved over the past decades. It is, therefore, of critical importance to screen novel biomarkers, which could be used to detect PC at an early stage and predict the prognosis of this malignancy. MicroRNAs (miRNAs) are a class of small noncoding RNAs, about 18-25 nucleotides, which exist widely in the eukaryotic organisms[5]. They directly bind to the 3'-untranslated regions (3'-UTRs) of target messenger RNAs (mRNAs), leading to mRNA degradation or translational suppression[6]. It has been identified that miRNAs play crucial roles in a vast range of biological processes, including cell proliferation, cell cycle and cellular metastasis[7,8]. Currently, growing studies indicate that up- or down-regulation of some miRNAs contributes to progression of several cancers, which reveal the potential of miRNAs as predictive biomarkers for prognosis and diagnosis of tumor patients[9-11]. Recently, circulating miRNAs have been shown to be detectable in clinical samples such as plasma or serum with high stability, suggesting that its dysregulation may be used as novel diagnostic and prognostic marker in cancer[12,13].Grow-

Corresponding Author: Wei Shi, MD; e-mail: Peisw721@163.com

ing researches reported that miRNAs might be potential noninvasive tumor biomarkers in the diagnosis and assessment of prognosis of PC, such as miR-744[14], miR-18a[15] and miR-483-3p[16]. However, to date, no serum miRNAs have been successfully used in PC patients in clinical settings.

MiR-629, located on human chromosome 15q23, is upregulated in several types of cancer, including gastric cancer[17], esophageal squamous cell carcinoma[18] and mature ovarian teratomas[19]. Apart from this, dysregulation of miR-629 has also been reported in several other diseases, such as systemic lupus erythematosus[20] and hepatitis C virus (HCV) infection[21]. Those results revealed miR-629 as an important regulator in development and progression of several diseases. Recently, Yan et al[22] found that miR-629 expression levels was significantly upregulated in PC cells and *in vitro* and *in vivo* indicated that knockdown of miR-629 could suppressed PC growth by targeting FOXO3. However, their work did not investigate the expression of miR-629 in clinical tissues and the clinical significance of miR-629 in PC patients. In this study, we firstly determined the levels of miR-629 in both PC tissues and serum. Then, we further explored the diagnostic and prognostic value of serum miR-629 in PC patients. Our paper indicated that serum miR-629 may be a very useful, noninvasive, biomarker for PC patients.

Patients and Methods

Patients and Specimens

We enrolled 177 PC patients who underwent curative pancreatectomy at the Second Hospital of Tianjin Medical University from 2011 to 2013. A total of 177 PC samples and matched adjacent non-tumor tissues were obtained from these patients. Attained tissue samples were cut and frozen in liquid nitrogen. All samples were diagnosed correctly based on clinical and pathological evidence. Those patients who received chemotherapy or radiotherapy were excluded from this study. Experienced pathologists provided detailed pathologic diagnosis according to UICC TNM classification standards (2002). The clinicopathologic features of all the patients were summarized in Table I. All use of human specimens was approved and supervised by the Ethics Committee of The Second Hospital of Tianjin Medical University. Written informed consent was obtained from all of the patients.

Samples Collection

Whole blood (5 ml) from all 177 patients with PC mentioned above and 64 healthy volunteers was collected in regular tubes and immediately processed to prevent contamination by cellular nucleic acids. Serum was separated within 1 h of blood collection by centrifugation at 10000 rpm for 10 min, to completely remove cell debris. The supernatant serum was then carefully collected, and the samples were stored at -80°C until further analyses.

RNA Isolation and Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR)

Total RNA was extracted using mirVana Paris Kit (Ambion, Austin, TX, USA) according to manufacturer's instructions. Complementary DNAs were synthesized using the TaqMan miRNA RT Kit based on the specific stem-loop RT primer design. QRT-PCR was performed using SYBR-Green PCR kit (TransGen Biotech, Haidian, Beijing, China) following the instructions. The reaction conditions were shown as follows: 94°C for 4 min followed by 40 cycles for 94°C for 1 min, 56°C for 1 min and 72°C for 1 min. MiRNA expression levels were normalized against the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) control. The relative expression fold change of miRNAs was calculated by the $2^{-\Delta\Delta Ct}$ method. Primer sequences were as follows: miR-629, 5'-CGTGGGTTTACGTTGGG-3' and 5'-CTCGCTTCGGCAGCACA-3'; GAPDH, 5'-ACCCAGAAGACTGTGGATGG-3' and 5'-CAGTGAGCTTCCCGTTCAG-3'.

Statistical Analysis

SPSS 18.0 software (SPSS Inc., Chicago, IL, USA) was used for data analysis and GraphPad Prism 5.0 (Version X; La Jolla, CA, USA) was used for picture editing. Difference between two groups was determined by using Student's *t*-test. Comparison between groups was done using Analysis of Variance (ANOVA) test followed by LSD (Least Significant Difference) post-hoc test. The association between the serum miR-629 and clinicopathologic features was tested using the chi-square test. Receiver operating characteristic (ROC) curves and area under the ROC curve (AUC) were used to assess the diagnostic value of serum miR-629. Kaplan-Meier method and log-rank test were performed for patients' survival analyses. Univariate and multivariate Cox proportional hazards analyses were used to analyze the independent prognostic factors for survival in PC patients. Results were considered to indicate a statistically significant difference at values of $p<0.05$.

Table I. Relationship between expression of serum miR-629 and clinicopathologic factors in 177 patients with PC.

Characteristics	Cases	Serum miR-629 expression		*p*-value
		Low	High	
Age				NS
< 55	91	41	50	
≥ 55	86	49	37	
Gender				NS
Male	71	33	38	
Female	106	57	49	
Location				NS
Head, urinate	119	63	56	
Body, tail	58	27	31	
CEA				NS
<4.3 μg/ml	99	52	37	
≥4.3 μg/ml	78	38	40	
CA19-9				NS
<37 U/mL	100	56	44	
≥37 U/mL	77	34	43	
Tumor diameter				NS
<2.5 cm	107	59	48	
≥2.5 cm	70	31	39	
Tumor depth				NS
T1/T2	106	60	46	
T3/T4	71	30	41	
Differentiation				NS
Well	69	40	29	
Moderate	56	28	28	
poor	52	22	30	
TNM staging				0.000
I-II	111	69	42	
III-IV	66	21	45	
Distant metastasis				0.003
Positive	62	22	40	
Negative	115	68	47	

Results

Up-Regulation of miR-629 in PC Tissues and Serum Samples

To observe the expression of miR-629 in PC, we examined the miR-629 expression levels in 177 paired PC tissues and corresponding normal tissues by using qRT-PCR. As shown in Figure 1, we found that miR-629 expression levels were significantly upregulated in PC tissues compared with the paired adjacent normal tissues ($p<0.01$). In addition, we also detected serum miR-629 levels in 177 PC patients and 64 healthy controls. It was found that serum miRNA-629 was significantly upregulated in PC patients compared to healthy controls ($p<0.01$). Overall, our results revealed that overexpression of miR-629 may play an important role the pathogenesis of PC.

Diagnostic Performance of Serum miR-629 for PC

In order to determine the diagnostic value of serum miR-629, ROC curve analyses were performed. As shown in Figure 2, we showed that serum miR-629 levels are promising to be a biomarker for the diagnosis of NSCLC. The area under the ROC curve (AUC) was 0.765 [95% confidence interval (CI)=0.679-0.851]. Furthermore, we evaluated the diagnostic significance of the conventional marker CA19-9. It was observed that the AUC was 0.612 (95% C=0.509-0.716) for serum CA19-9 and was significantly lower than that for serum miR-629, suggesting that serum miR-629 level showed a more diagnostic accuracy. In addition, further ROC analysis showed that the combination of serum miR-629 and CA19-9 had an increased AUC value

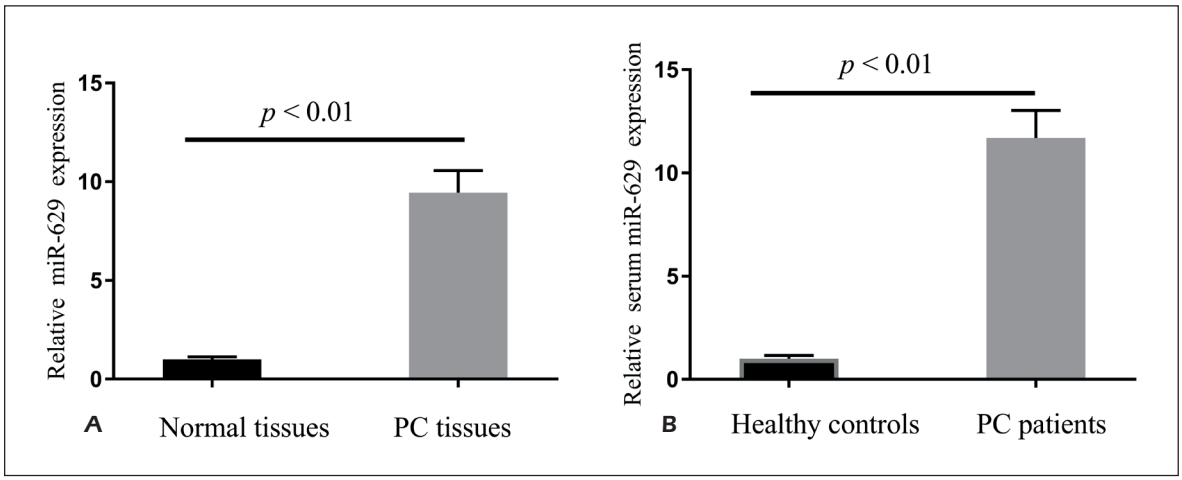

Figure 1. Expression level of miR-629 in human PC tissues and patients' serum detected by qRT-PCR assay. **A**, The expression level of miR-629 was significantly higher in PC tissues than in adjacent noncancerous tissues (p<0.01). **B**, Serum level of miR-629 in patients with PC was also significantly higher than that in healthy controls (p<0.01).

to 0.812 (95% CI=0.733 to 0.8927), which was significantly higher than that for serum miR-629 or CA19-9 alone. Taken together, we suggested that serum miR-629 might function as a useful biomarker for PC diagnosis.

Correlations between Serum miR-629 and Clinical Features of PC

To assess the correlation of serum miR-629 expression with clinicopathologic features, according to the mean value of relative serum miR-629 expression (6.78) in PC patients, the 177 PC patients were classified into two groups (High and Low). Then, x^2-test was performed to evaluate clinicopathological factors between the two groups. As shown in Table I, it was observed that high serum miR-629 expression was closely associated with TNM staging (p=0.000) and distant metastasis (p=0.003). However, there were no significant associations between serum miR-629 expression and other clinical features including age, gender, location, CEA, CA19-9, tumor diameter, tumor depth and differentiation (p>0.05).

High-Expression Level of Serum miR-629 Predicts Poor Prognosis in PC Patients

Then, we evaluated whether serum miR-629 expression had prognostic potential for overall survival (OS) and disease-free survival (DFS) of PC patients. The Kaplan-Meier method and log-rank test were performed and the results indicated that patients with high serum miR-629 expression had a shorter OS and DFS time than those with low serum miR-629 expression (Figure 3A and 3B). In addition, univariate analysis indicated that OS and DFS were significantly correlated with TNM staging, distant metastasis and serum miR-629 expression levels (Table II and III). Furthermore, multivariate analysis confirmed serum miR-629 expression as an independent prognostic indicator for both OS (p=0.006, Table II) and DFS (p=0.001, Table III) of PC patients.

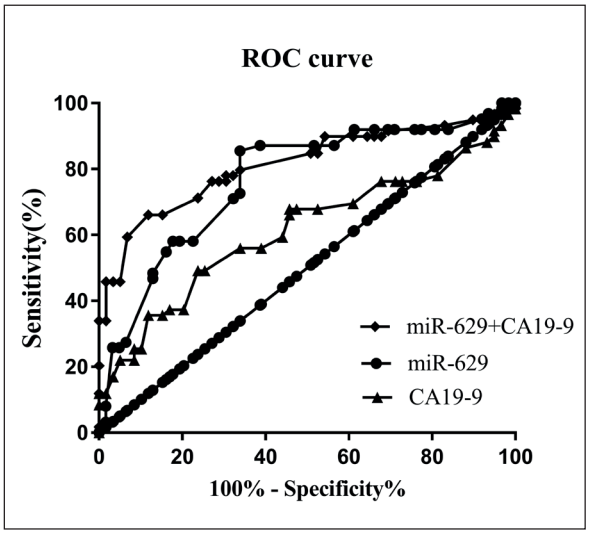

Figure 2. ROC analysis for the diagnosis of pancreatic cancer using serum miR-629, CA19-9 alone or the combination.

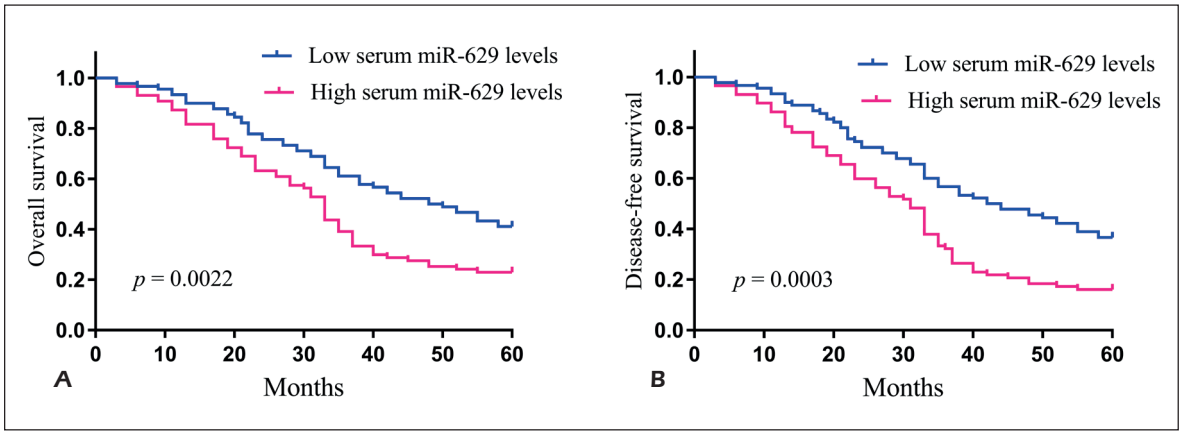

Figure 3. Kaplan-Meier survival curves based on serum miR-629 relative expression. **A**, Upregulation of serum miR-629 decreased overall survival in patients with PC. **B**, The high expression of serum miR-629 reduced disease-free survival in patients with PC.

Table II. Univariate and multivariate analyses for overall survival by Cox regression model.

Parameters	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Age	1.556	0.672-2.233	0.562	–	–	–
Gender	1.834	0.479-2.782	0.261	–	–	–
Location	2.143	0.763-3.261	0.163	–	–	–
CEA	1.663	0.784-2.351	0.157	–	–	–
CA19-9	2.677	0.752-3.662	0.081	–	–	–
Tumor diameter	1.892	0.471-2.884	0.132	–	–	–
Tumor depth	2.663	0.783-3.223	0.073	–	–	–
Differentiation	2.163	0.678-3.632	0.118	–	–	–
TNM staging	4.556	1.532-8.732	0.001	3.687	1.263-6.531	0.001
Distant metastasis	3.894	1.482-5.263	0.005	3.137	1.211-4.263	0.008
Serum miR-629 expression	3.273	1.641-7.239	0.001	2.763	1.237-5.745	0.006

Table III. Univariate and multivariate analyses for disease-free survival by Cox regression model.

Parameters	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Age	1.344	0.562-2.188	0.352	–	–	–
Gender	1.378	0.632-2.554	0.167	–	–	–
Location	1.562	0.569-3.778	0.123	–	–	–
CEA	1.335	0.114-2.782	0.122	–	–	–
CA19-9	2.235	0.562-3.442	0.099	–	–	–
Tumor diameter	1.321	0.663-2.785	0.167	–	–	–
Tumor depth	2.532	0.623-3.288	0.081	–	–	–
Differentiation	2.234	0.893-3.117	0.123	–	–	–
TNM staging	4.232	1.462-7.451	0.001	3.452	1.277-6.783	0.001
Distant metastasis	3.672	1.663-4.452	0.008	2.893	1.334-3.893	0.011
Serum miR-629 expression	3.783	1.552-8.532	0.001	3.144	1.337-7.237	0.001

Discussion

Pancreatic cancer (PC) characterized by extremely aggressive invasion, early migration, and dismal prognosis is regarded as a grievous problem to human health in China[23]. Despite many treatment advances that have improved the outcomes of some PC patients, the median survival time after diagnosis is less than six months[24]. Clinical practice shows that early detection of PC can reduce the mortality to a low level. Currently, several tumor-related molecules, such as carbohydrate antigen 19-9 (CA19-9), have been used as convenient diagnostic assays for early detection PC[25,26]. However, they have insufficient sensitivity and specificity at early stage. Currently, several miRNAs were found to have associations with different cancer types. For instance, circulating miR-222 was reported to serve as a novel and noninvasive biomarker for the early detection and prognostic prediction in gastric cancer[27]. Serum miR-195 levels in osteosarcoma patients were found to have a clinically satisfactory degree of sensitivity and specificity with an AUC of 0.892[28]. However, the value of serum miRNAs in diagnosis of PC has yet to be determined.

Up-regulation of miR-629 has been observed in various cancers and its tumor-promotive roles are also reported. For instance, Shao et al[29] reported that miR-629 was highly expressed in ovarian cancer and its knockdown suppressed ovarian cancer cells proliferation, migration, and invasion by targeting TSPYL5. Jingushi et al[30] found that miR-629 expression was significantly upregulated in human renal cell carcinoma and functioned as a tumor promoter by inhibiting migration and invasion of renal cell carcinoma cells via targeting TRIM33. Wang et al[31] indicated miR-629 as a potential biomarker in triple-negative breast cancer which was significantly associated with advanced TNM stage and poor overall survival. In addition, their *in vitro* and *in vivo* revealed that suppression of miR-629 could inhibit cell proliferation and invasion of triple-negative breast cancer. In line with above findings, up-regulation of miR-629 was also observed in pancreatic cancer. Yan et al[22] performed *in vitro* and *in vivo* experiments to explore the role of miR-629 in PC and their results showed that overexpression of miR-629 promoted metastasis of pancreatic cancer cells by targeting FOXO3. Taken together with previous studies, it was confirmed that miR-629 functioned mainly as a metastasis promoter in various tumors, including PC. However, to the best of our knowledge, no study has yet been conducted to detect the levels of miR-629 in the serum of PC patients and to explore its clinical significance in PC.

In this study, we showed for the first time that miR-629 expression was increased in PC tissues. In addition, serum miR-629 levels were also observed to be up-regulated in PC patients. Then, we analyzed the ROC curve to assess diagnostic value of serum miR-629. The results showed that the expression of serum miR-629 could be used to discriminate PC from healthy controls. More importantly, we also found that miR-629 has a higher sensitivity and specificity than CA19-9 in discriminating PC patients from healthy controls. Further analysis indicated that the combination of serum miR-629 and CA19-9 processed a better diagnostic accuracy. Subsequently, we further explore the association between miR-629 expression and clinicopathologic features and the results showed that the serum miR-629 expression was positively associated with TNM staging and distant metastasis. Moreover, through Kaplan-Meier survival analysis and Cox analysis, it was found that increased serum miR-629 expression was associated with a shorter OS and DFS time in patients with PC. However, like many other research, the limitation of our study was that the sample size was small. Besides, the precise molecular mechanisms behind the altered expression of miR-629 in PC and its function are not very clear. Therefore, future research need to solve these problems.

Conclusions

We showed that serum miR-629 was significantly up-regulated in patients with PC and its detection might serve as a clinical predictor in the diagnosis or prediction of clinical outcomes for the patients with PC. Prospective investigations with larger sample size should be performed to confirm these data in future.

Acknowledgments:

This work was financed by Science and Technology Fund of Tianjin Municipal Commission of Health and Family Planning (Grant No: 2014KZ109).

Conflict of Interests:

The Authors declare that they have no conflict of interests.

References

1) Saif MW. Pancreatic cancer: highlights from the 42nd annual meeting of the American Society of Clinical Oncology, 2006. JOP 2006; 7: 337-348.
2) Michl P, Gress TM. Current concepts and novel targets in advanced pancreatic cancer. Gut 2013; 62: 317-326.
3) Singh P, Srinivasan R, Wig JD. Major molecular markers in pancreatic ductal adenocarcinoma and their roles in screening, diagnosis, prognosis, and treatment. Pancreas 2011; 40: 644-652.
4) Hawes RH, Xiong Q, Waxman I, Chang KJ, Evans DB, Abbruzzese JL. A multispecialty approach to the diagnosis and management of pancreatic cancer. Am J Gastroenterol 2000; 95: 17-31.
5) Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004; 116: 281-297.
6) Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell 2009; 136: 215-233.
7) Filipowicz W, Bhattacharyya SN, Sonenberg N. Mechanisms of posttranscriptional regulation by microRNAs: are the answers in sight? Nat Rev Genet 2008; 9: 102-114.
8) Brennecke J, Hipfner DR, Stark A, Russell RB, Cohen SM. Bantam encodes a developmentally regulated microRNA that controls cell proliferation and regulates the proapoptotic gene hid in Drosophila. Cell 2003; 113: 25-36.
9) Tölle A, Ratert N, Jung K. miRNA panels as biomarkers for bladder cancer. Biomark Med 2014; 8: 733-746.
10) Chai C, Song LJ, Yang B, Han SY, Li XQ, Li M. Circulating miR-199a-3p in plasma and its potential diagnostic and prognostic value in glioma. Eur Rev Med Pharmacol Sci 2016; 20: 4885-4890.
11) Lan H, Lu H, Wang X, Jin H. MicroRNAs as potential biomarkers in cancer: opportunities and challenges. Biomed Res Int 2015; 2015: 125094.
12) Ludwig N, Nourkami-Tutdibi N, Backes C, Lenhof HP, Graf N, Keller A, Meese E. Circulating serum miRNAs as potential biomarkers for nephroblastoma. Pediatr Blood Cancer 2015; 62: 1360-1367.
13) Zhou GH, Yang WH, Sun B. Clinical impact of serum miR-661 in diagnosis and prognosis of non-small cell lung cancer. Eur Rev Med Pharmacol Sci 2017; 21: 5696-5701.
14) Miyamae M, Komatsu S, Ichikawa D, Kawaguchi T, Hirajima S, Okajima W, Ohashi T, Imamura T, Konishi H, Shiozaki A, Morimura R, Ikoma H, Ochiai T, Okamoto K, Taniguchi H, Otsuji E. Plasma microRNA profiles: identification of miR-744 as a novel diagnostic and prognostic biomarker in pancreatic cancer. Br J Cancer 2015; 113: 1467-1476.
15) Morimura R, Komatsu S, Ichikawa D, Takeshita H, Tsujiura M, Nagata H, Konishi H, Shiozaki A, Ikoma H, Okamoto K, Ochiai T, Taniguchi H, Otsuji E. Novel diagnostic value of circulating miR-18a in plasma of patients with pancreatic cancer. Br J Cancer 2011; 105: 1733-1740.
16) Abue M, Yokoyama M, Shibuya R, Tamai K, Yamaguchi K, Sato I, Tanaka N, Hamada S, Shimosegawa T, Sugamura K, Satoh K. Circulating miR-483-3p and miR-21 is highly expressed in plasma of pancreatic cancer. Int J Oncol 2015; 46: 539-547.
17) Shin VY, Ng EK, Chan VW, Kwong A, Chu KM. A three-miRNA signature as promising non-invasive diagnostic marker for gastric cancer. Mol Cancer 2015; 14: 202.
18) Chan CM, Lai KKY, Ng EKO, Kiang MN, Kwok TWH, Wang HK, Chan KW, Law TT, Tong DK, Chan KT, Lee NP, Law S. Serum microRNA-193b as a promising biomarker for prediction of chemoradiation sensitivity in esophageal squamous cell carcinoma patients. Oncol Lett 2018; 15: 3273-3280.
19) Ding Y, Gu XY, Xu F, Shi XY, Yang DZ, Zhong J, Wang SM. MicroRNA expression profiling of mature ovarian teratomas. Oncol Lett 2012; 3: 35-38.
20) Zhu J, Huang X, Su G, Wang L, Wu F, Zhang T, Song G. High expression levels of microRNA-629, microRNA-525-5p and microRNA-516a-3p in paediatric systemic lupus erythematosus. Clin Rheumatol 2014; 33: 807-815.
21) Zhang S, Ouyang X, Jiang X, Gu D, Lin Y, Kong SK, Xie W. Dysregulated serum MicroRNA expression profile and potential biomarkers in hepatitis C virus-infected patients. Int J Med Sci 2015; 12: 590-598.
22) Yan H, Li Q, Wu J, Hu W, Jiang J, Shi L, Yang X, Zhu D, Ji M, Wu C. MiR-629 promotes human pancreatic cancer progression by targeting FOXO3. Cell Death Dis 2017; 8: e3154.
23) He XY, Yuan YZ. Advances in pancreatic cancer research: moving towards early detection. World J Gastroenterol 2014; 20: 11241-11248.
24) Lin QJ, Yang F, Jin C, Fu DL. Current status and progress of pancreatic cancer in China. World J Gastroenterol 2015; 21: 7988-8003.
25) Parikh DA, Durbin-Johnson B, Urayama S. Utility of serum CA19-9 levels in the diagnosis of pancreatic ductal adenocarcinoma in an endoscopic ultrasound referral population. J Gastrointest Cancer 2014; 45: 74-79.
26) Javle M, Li Y, Tan D, Dong X, Chang P, Kar S, Li D. Biomarkers of TGF-β signaling pathway and prognosis of pancreatic cancer. PLoS One 2014; 9: e85942.
27) Fu Z, Qian F, Yang X, Jiang H, Chen Y, Liu S. Circulating miR-222 in plasma and its potential diagnostic and prognostic value in gastric cancer. Med Oncol 2014; 31: 164.
28) Cai H, Zhao H, Tang J, Wu H. Serum miR-195 is a diagnostic and prognostic marker for osteosarcoma. J Surg Res 2015; 194: 505-510.
29) Shao L, Shen Z, Qian H, Zhou S, Chen Y. Knockdown of miR-629 inhibits ovarian cancer malignant behaviors by targeting testis-specific y-like protein 5. DNA Cell Biol 2017; 36: 1108-1116.
30) Jingushi K, Ueda Y, Kitae K, Hase H, Egawa H, Ohshio I, Kawakami R, Kashiwagi Y, Tsukada Y, Kobayashi T, Nakata W, Fujita K, Uemura M, Nonomura N, Tsujikawa K. miR-629 targets TRIM33 to promote TGFβ/Smad signaling and metastatic phenotypes in ccRCC. Mol Cancer Res 2015; 13: 565-574.
31) Wang J, Song C, Tang H, Zhang C, Tang J, Li X, Chen B, Xie X. miR-629-3p may serve as a novel biomarker and potential therapeutic target for lung metastases of triple-negative breast cancer. Breast Cancer Res 2017; 9: 27.