Int J Clin Exp Pathol 2017;10(1):233-241
www.ijcep.com /ISSN:1936-2625/IJCEP0042997

Original Article

Relationship between expression of MAS-related GPR family member D and clinicopathological characteristics in pancreatic cancer

Dan-Ming Wei[1*], Ting-Qing Gan[2*], Lin Shi[3], Wan-Ying Li[1], Meng-Jie Yin[1], Ting-Ting Xie[1], Jia-Ying Lin[1], Gang Chen[1], Yi-Wu Dang[1*], Dian-Zhong Luo[1*]

Departments of [1]Pathology, [2]Medical Oncology, First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi Zhuang Autonomous Region, People's Republic of China; [3]Department of Pathology, First Affiliated Hospital of Guangxi University of Science and Technology, Guangxi Zhuang Autonomous Region, People's Republic of China. [*]Equal contributors.

Received October 27, 2016; Accepted October 27, 2016; Epub January 1, 2017; Published January 15, 2017

Abstract: *Objective:* MAS related GPR family member D (MRGPRD), as a member of MAS related GPR family, was found in nociceptive neurons, muscle, hart and testicle. Moreover, high expression of MRGPRD has been observed in lung cancer. However, the relationship between MRGPRD expression and pancreatic cancer (PC) has not been reported. Hence, in this study, we evaluated MRGPRD expression in PC tissues in order to explore its clinicopathological significance. *Methods:* This study involved 241 samples, which included 157 samples of PC, 66 of matched tumor-adjacent tissues and 18 of benign pancreatic lesions. Immunohistochemical staining was applied to detect the protein expression of MRGPRD and its clinical significance. Furthermore, data mining was conducted in Gene Expression Omnibus (GEO) and The Cancer Genome Atlas (TCGA) public database to confirm the clinical significance of MRGPRD. *Results:* The evaluation showed that 100 among 157 (63.7%) cases of PC positively expressed MRGPRD, which was significantly higher as compared to that in tumor-adjacent tissues (11/66, 16.7%) and (2/18, 11.1%) benign pancreatic lesions (both, P<0.001). More importantly, the high expression of MRGPRD was found to be related to neural invasion (r=0.362, P=0.017), clinical TNM stage (r=0.386, P<0.001) and lymph node metastasis (r=0.419, P<0.001) in PC. Moreover, 6% genetic alteration was noted based on TCGA database in 185 PC, including three cases of amplification, seven cases of mRNA upregulation and one case of missense mutation. *Conclusion:* High expression of MRGPRD might play vital roles in the neural invasion and lymph node metastasis of PC. However, this finding needs to be confirmed with larger size of patients.

Keywords: MRGPRD, pancreatic cancer, immunohistochemistry, neural invasion, TNM stage, lymph node metastasis

Introduction

Pancreatic cancer (PC) is one of the most aggressive human malignancies worldwide, as 50% of the cases present with metastatic disease and 35% with locally advanced disease when being diagnosed [1, 2]. The poor prognosis of PC is believed to be manifested in an overall median survival of 4.4 months, and a 5-year survival of 9.7% [1, 3-6]. Diagnostic problems for PC have arisen due to the nonspecific symptoms [7-9]. And there has been no effective screening process for PC by far. More importantly, the etiology of PC remains largely unknown [4, 10-12]. Thus, it is of great importance to seek for potential biomarkers for PC, as well as to explore the molecular mechanism in the tumorigenesis and progression of PC.

Human MAS related GPR family member D (MRGPRD), also known as MRGD; TGR7 (Gene ID: 116512 Location: 11q13.3) belongs to the MAS related GPR family. MRGPRD has found to be mainly expressed in the dorsal root ganglia (DRG) [13]. Interestingly, the role of MRGPRD in malignancies has also been investigated. Nishimura S and colleagues [14] reported that overexpression of MRGPRD in murine fibroblast

Table 1. Expression of MRGPRD in different pancreatic tissues

	The expression of MRGPRD				
	Total	Negative (%)	Positive (%)	Chi square value	*P*-value
Benign pancreatic lesions	18	16 (88.9)	2 (11.1)	18.365	P<0.001[a]
Tumor-adjacent tissues	66	55 (83.3)	11 (16.7)	0.334	P=0.725[b]
Pancreatic cancer	157	57 (36.3)	100 (63.7)	41.107	P<0.001[c]

a: Benign pancreatic lesions VS Pancreatic cancer; b: Benign pancreatic lesions VS Tumor-adjacent tissues; c: Pancreatic cancer VS Tumor-adjacent tissues.

Table 2. Relationship between the expression of MRGPRD and clinical characteristics of pancreatic cancer (PC) patients

	The expression of MRGPRD in PC				
	Total	Negative (%)	Positive (%)	Chi square value	*P*-value
Sex	157				
Male	90	34 (37.8)	56 (62.2)	0.198	P=0.738
Female	67	23 (34.3)	44 (65.7)		
Age (years)	157			3.268	P=0.095
≤58	87	37 (42.5)	50 (57.5)		
>58	70	20 (28.6)	50 (71.4)		
Lifetime (months)	49			0.282	P=0.708
≤18	40	14 (35.0)	26 (65.0)		
>18	9	4 (44.4)	5 (55.6)		
Differentiation grade	151			0.169	P=0.953
I	44	15 (34.1)	29 (65.9)		
II	64	24 (37.5)	40 (62.5)		
III	43	16 (37.2)	27 (62.8)		
Histology	157			1.222	P=0.784
Adenocarcinoma	153	56 (36.6)	97 (63.4)		
Anaplastic carcinoma	2	0 (0.0)	2 (100.0)		
Adenosquamous carcinoma	2	1 (50.0)	1 (50.0)		
Neural Invasion	49			6.422	P=0.017
(-)	36	17 (47.2)	19 (52.8)		
(+)	13	1 (7.7)	12 (92.3)		
Position	49			0.55	P=1.000
Pancreatic head	40	15 (37.5)	25 (62.5)		
Pancreatic body/tail	9	3 (33.3)	6 (66.7)		
Size (cm)	49			0.99	P=0.759
≤4	15	6 (40.0)	9 (60.0)		
>4	34	12 (35.3)	22 (64.7)		
CA199 (u/ml)	49			3.115	P=0.127
≤37	9	1 (11.1)	8 (88.9)		
>37	40	17 (42.5)	23 (57.5)		
CEA (ng/ml)	49			0.142	P=0.767
≤55	31	12 (38.7)	19 (61.3)		
>55	18	6 (33.3)	12 (66.7)		
TNM		157		30.181	*P<0.001
1	75	43 (57.3)	32 (42.7)		
2	15	5 (33.3)	10 (66.7)		
3	57	8 (14.0)	49 (86.0)		
4	10	1 (10.0)	9 (90.0)		

T staging	157			4.409	P=0.200
T1	49	22 (44.9)	27 (55.1)		
T2	77	28 (36.4)	49 (63.6)		
T3	31	7 (22.6)	24 (77.4)		
N staging	157			27.625	P<0.001
N0	92	49 (53.3)	43 (46.7)		
N1	65	8 (12.3)	57 (87.7)		
M Staging	157			3.196	P=0.095
M0	147	56 (38.1)	91 (61.9)		
M1	10	1 (10.0)	9 (90.0)		

*TNM1 vs TNM2: P=0.155; TNM1 vs TNM3: P<0.001; TNM1 vs TNM4: P=0.006; TNM2 vs TNM3: P=0.127; TNM2 vs TNM4: P=0.345; TNM3 vs TNM4: P=1.000. T staging: tumor size and extent. N staging: Lymphatic metastasis. M staging: Distant metastasis.

cell line NIH3T3 could induce focus formation and multi-cellular spheroid formation, and also promote in vivo tumorigenesis in nude mice. Nishimura S, et al [14] and our previous work [15] both found that high expression of MRGPRD was observed in clinical lung cancer tissues and MRGPRD expression was closely related to the progression of lung cancer. However, the clinical role of MRGPRD remains much unknown in PC. Thus, we evaluated MRGPRD expression and its clinical significance in PC tissues with immunohistochemistry and public data.

Material and methods

Tissue samples

In present study a total of 241 patients who underwent curative surgical operations without chemotherapy or radiotherapy before surgery were selected from the First Affiliated Hospital of Guangxi Medical University, the First Affiliated Hospital of Guangxi University of Science and Technology, and Fanpu Biotech, Inc (PAC481 and PAC961, Guilin, China). All samples were fixed in formaldehyde and embedded in paraffin. These samples included 153 adenocarcinomas, 2 anaplastic carcinomas, 2 adenosquamous carcinomas, 66 matched tumor-adjacent tissues and 18 benign pancreatic lesions. The differentiation of PC sample was determined according to the World Health Organization (WHO) Classification of Tumors. The clinical characteristics included age, gender, tumor location and stage (**Tables 1**, **2**). The study was approved by the Research Ethics Committees of the Affiliated Hospital of Guangxi University of Science and Technology and the First Affiliated Hospital of Guangxi Medical University, China. Informed written consents were gained from all patients who participated in the current study.

Immunohistochemistry

The sections were firstly deparaffinized in xylene and then rehydrated by gradient alcohol, and then exposed to citrate buffer for 10 min. A pressure cooker was used for antigen retrieval. Subsequently, the slides were incubated with 0.3% H_2O_2 for 20 min to block endogenous peroxidase activity. Primary rabbit polyclonal antibody specific for MRGPRD was purchased from Biorbyt LLC (California, United States, Catalog Number: orb85117, dilution 1:150) and the synthetic 18 amino acid peptide is from 3rd cytoplasmic domain of human MRGPRD. BLAST analysis of the peptide immunogen shows no homology with other human proteins. Primary MRGPRD antibody was applied at 37°C for 60 minutes, followed by secondary antibody (Zhongshan Gene Bridge Biotechnology Company, Beijing, China). Color was generated by 3'3-diaminobenzidine (DAB) according to the manufacturer's protocols.

The sections were assessed independently by two pathologists without knowledge of the clinical characteristics. The expression of MRGPRD was scored according to the assessment of both the positive cell percentage and the staining intensity. The percentage of positive cell was marked as 0=none, 1="<10% of cells", 2="10-50% of cells", 3="51-80% of cells", 4=">80%"; the degree of intensity was classified into four groups of 0-3 as follows: 0=nega-

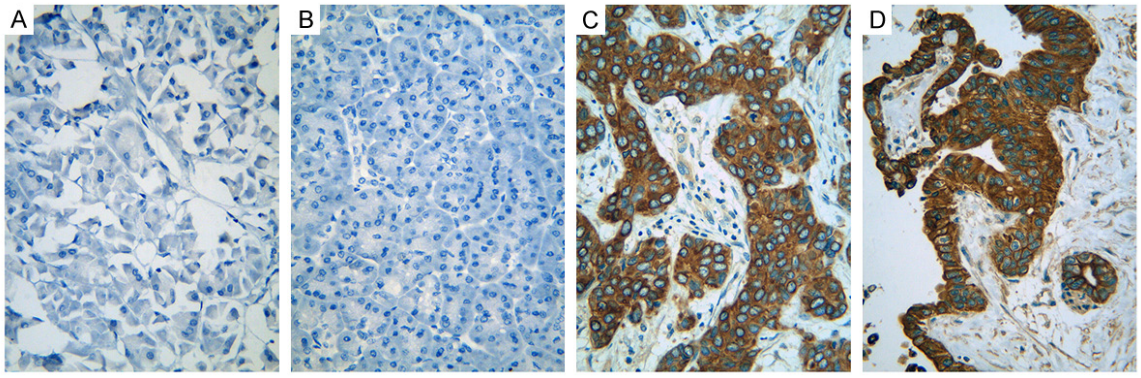

Figure 1. MRGPRD protein expression in pancreatic cancer (PC) and non-cancerous pancreatic tissues. Immunohistochemistry was performed to detect the expression of MRGPRD in tumor-adjacent tissues (A), normal pancreatic tissue (B) and PC tissues (C: Grade II, TNM 3; D: Grade III, TNM 4). ×400.

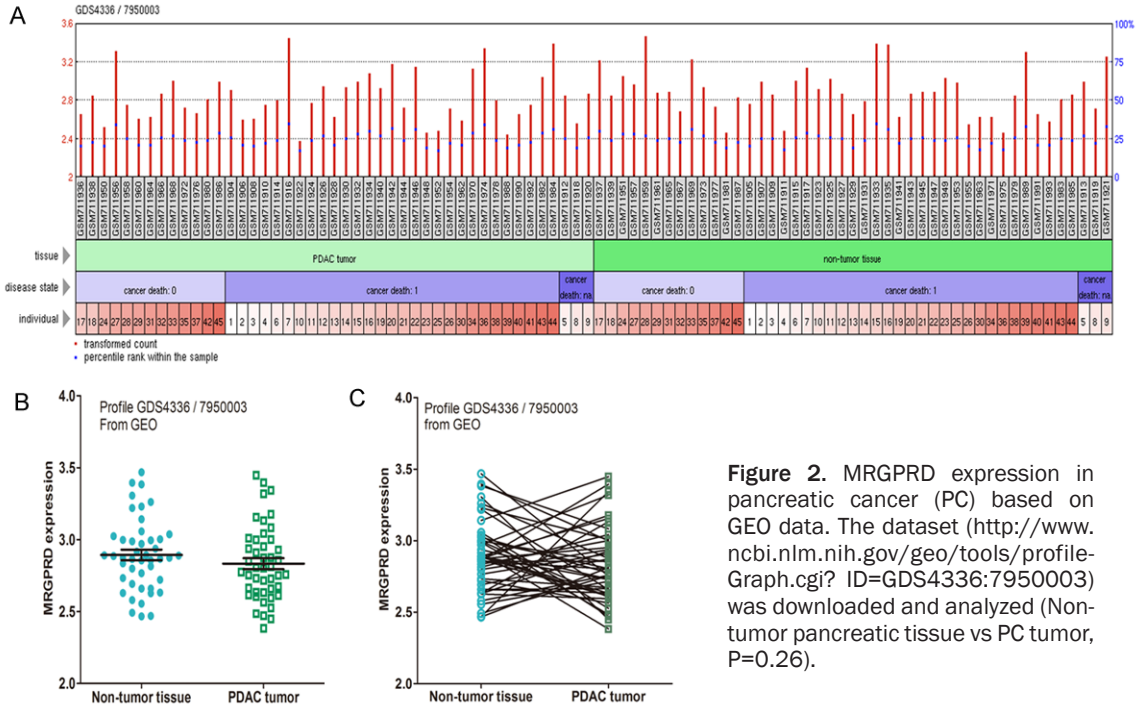

Figure 2. MRGPRD expression in pancreatic cancer (PC) based on GEO data. The dataset (http://www.ncbi.nlm.nih.gov/geo/tools/profileGraph.cgi? ID=GDS4336:7950003) was downloaded and analyzed (Non-tumor pancreatic tissue vs PC tumor, P=0.26).

tive, 1=weak, 2=intermediate, 3=strong. The final scores were determined by multiplying the scores of positive cell percentage by the scores of staining intensities. A score of 0-2 was regarded as being negative stained with MRGPRD or low expression, while >2 as positive staining of MRGPRD.

GEO profile collection and analysis

PC expression profiling studies were searched from the Gene Expression Omnibus database (GEO, http://www.ncbi.nlm.nih.gov/geo). The key words used for searching were: "pancreatic cancer" AND MRGPRD. We only retained original experimental articles that analyzed gene expression profiling between PC and normal control tissues in human studies. Studies were included in the analysis if they met the following criteria: 1. Conformed to standard of PC diagnosis. 2. Having access to the main data content information.

The Cancer Genome Atlas (TCGA) data evaluation

Furthermore, data mining was also conducted in The Cancer Genome Atlas (TCGA) public

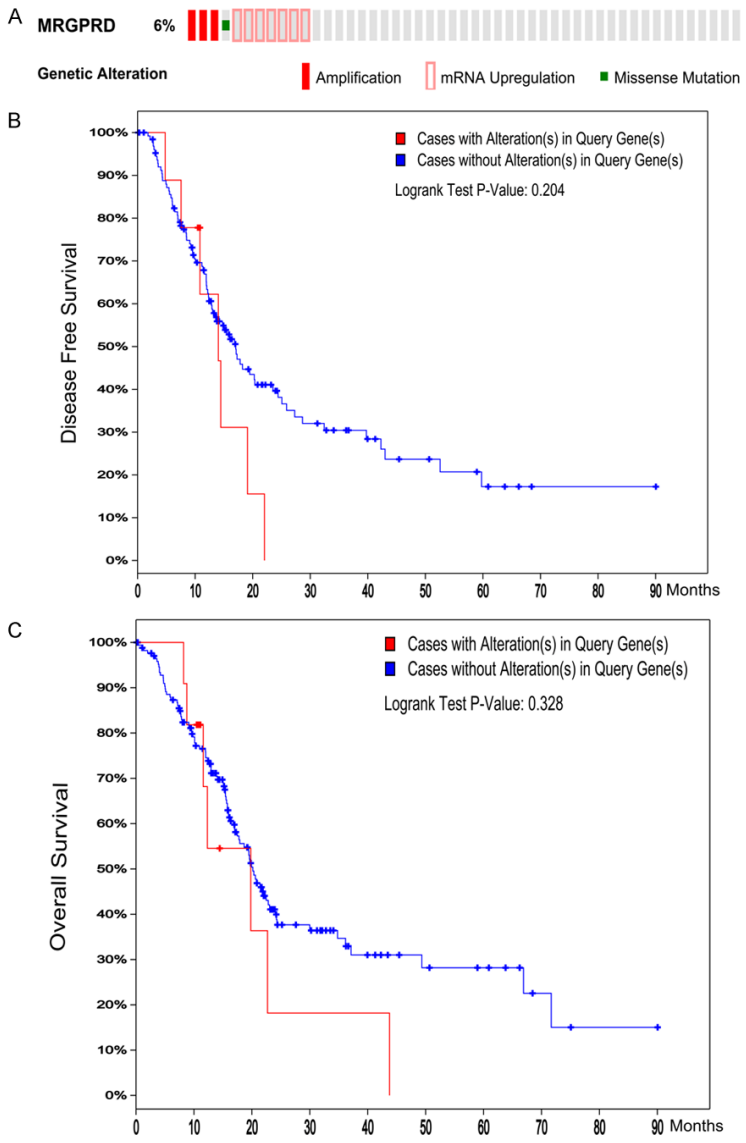

Figure 3. Clinical significance of MRGPRD alteration from TCGA in patients with pancreatic cancer (PC). A: The OncoPrint of genetic alterations of MRGPRD, including amplification, mRNA upregulation, and missense mutation, was displayed in PC by cBioPortal (www.cbioportal.org). B: Disease free survival (DFS): seven cases relapsed of 11 cases with alterations with the median survival as 19.81 months, while 92 cases relapsed among 173 cases without alterations, whose median disease free time was 20.17 months (P=0.204). C: Overall survival (OS): seven cases were deceased in nine cases with alterations with median disease free survival of 14.03 month, and 77 cases were relapsed in 132 cases without alterations, whose median survival time was 17.05 months (P=0.328). The survival was analyzed by Kaplan-Meier Estimate.

database to confirm the clinical significance of MRGPRD via cBioPortal (www.cbioportal.org).

Statistical analysis

The SPSS22.0 software was used for data analysis. The Chi-squared test was employed to compare the expression of MRGPRD protein with different groups for clinicopathological parameters. Spearman correlation test was conducted to assess the relationship between MRGPRD protein expression and several indicators of tumor progression, including the status of neural invasion, clinical TNM stage, lymph node metastasis, etc. Kaplan-Meier (K-M) test was performed to explore the relationship between MRGPRD alteration or mRNA regulation and survival. Differences with *P* value<0.05 were considered to be statistically significant.

Results

High expression of MRGPRD in PC

The signaling of MRGPRD protein was found in the cytoplasm of PC cells. The immunohistochemical evaluation showed that 100 among 157 (63.7%) cases of PC positively expressed MRGPRD, which was significantly higher as compared to that in tumor-adjacent tissues (11/66, 16.9%) and (2/18, 11.1%) benign pancreatic lesions (both, P< 0.001, **Figure 1**).

Correlations between the expression of MRGPRD and clinical characteristics in PC

Significant higher expression of MRGPRD was found in PC with neural invasion (92.3%), as compared to that without neural invasion (52.8%, P=0.017). Furthermore, remarkably higher expression of MRGPRD was observed in cases of both TNM stage 3 and 4 (86.0% and 90%) than that in TNM stage 1 (42.7%, both P<0.01). When the T, N and M staging were analyzed separately, we found that the expression of MRGPRD was obviously higher in the patients

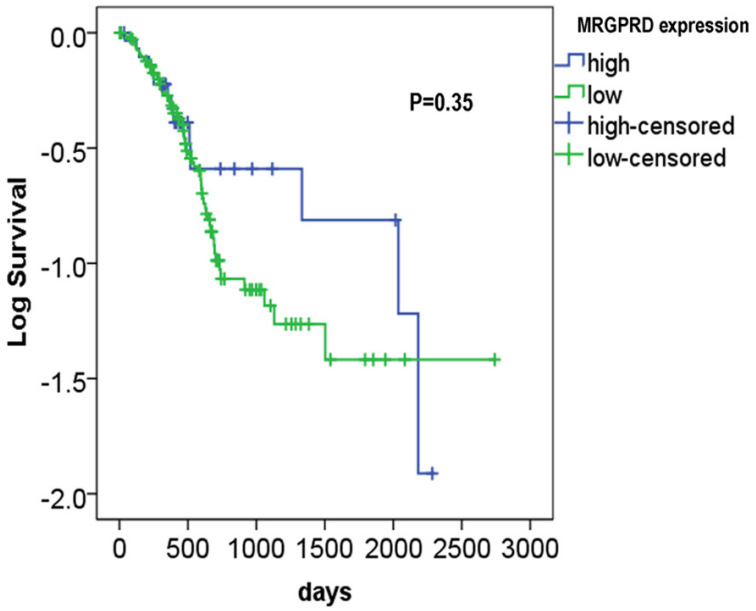

Figure 4. Relationship between MRGPRD mRNA upregulation and survival in pancreatic cancer based on TCGA data. Kaplan-Meier (K-M) test was performed to explore the relationship between MRGPRD mRNA upregulation and survival.

with lymph node metastasis (87.7%) than that without lymph node metastasis (46.7%, P<0.001, **Table 1**). More importantly, the spearman correlation analyses revealed that the high expression of MRGPRD was positively related to neural invasion (r=0.362, P=0.017), clinical TNM stage (r=0.386, P<0.001) and lymph node metastasis (r=0.419, P<0.001) in PC. No significant relationship was noted between MRGPRD expression and other parameters of PC, including sex, age, lifetime, differentiation, histology, position, size, CA199, CEA, T staging or M staging (**Table 2**).

MRGPRD expression in PC based on GEO and TCGA

Only one dataset (GEO ID: GSE28735) concerning MRGPRD expression in PC was obtained from GEO, which included 45 PC patients and 45 non-tumor controls (**Figure 2A**). Analysis on MRGPRD mRNA expression data of PC has not shown any significant difference between PC and control tissues (P=0.260, **Figure 2B**, **2C**).

We further investigated the clinical significance of MRGPRD with TCGA data. Genetic alteration of 6% was noted based on TCGA database in 185 PC via cBioPortal, including three cases of amplification, seven cases of mRNA upregulation (cut-off =2) and one case of missense mutation (**Figure 3A**). However, no difference of disease free survival or overall survival was found between the patients with and without genomic alterations (both P>0.05, **Figure 3B**, **3C**). We also assessed the relationship between MRGPRD mRNA level and survival. The mean survival time of the patients with high MRGPRD mRNA level was 1252.124±197.168 days, which was not significantly different from that with low MRGPRD mRNA level (1067.441±111.777 days, P=0.35, **Figure 4**). Since only four cases of non-cancerous pancreatic tissue were included in the TCGA data, we could not assess the difference of MRGPRD mRNA between non-cancerous pancreatic tissues and PC due to the small size. However, we showed the mRNA level of MRGPRD in all 33 types of cancers via the software of firebrowse (www.firebrowse.org, **Figure 5**).

Discussion

In the current study, we found that MRGPRD protein level was significantly up-regulated in PC tissues as compared to that in non-cancerous pancreatic tissues by immunohistochemistry. Furthermore, the high expression of MRGPRD was positively related to several parameters reflecting tumor progression.

The clinical role of MRGPRD in malignancies has not been well studied by far. Nishimura S et al [14] investigated the MRGPRD protein and mRNA expression level in the clinical samples of several cancers. They found that 67% (22/33) clinical lung cancer samples presented MRGPRD protein positive signaling as detected by immunohistochemistry, including 90% lung adenocarcinomas (9/10), 70% lung poorly-differentiated squamous cell carcinomas (7/10) and 60% well-differentiated squamous cell carcinomas (6/10). Nishimura S et al [14] also

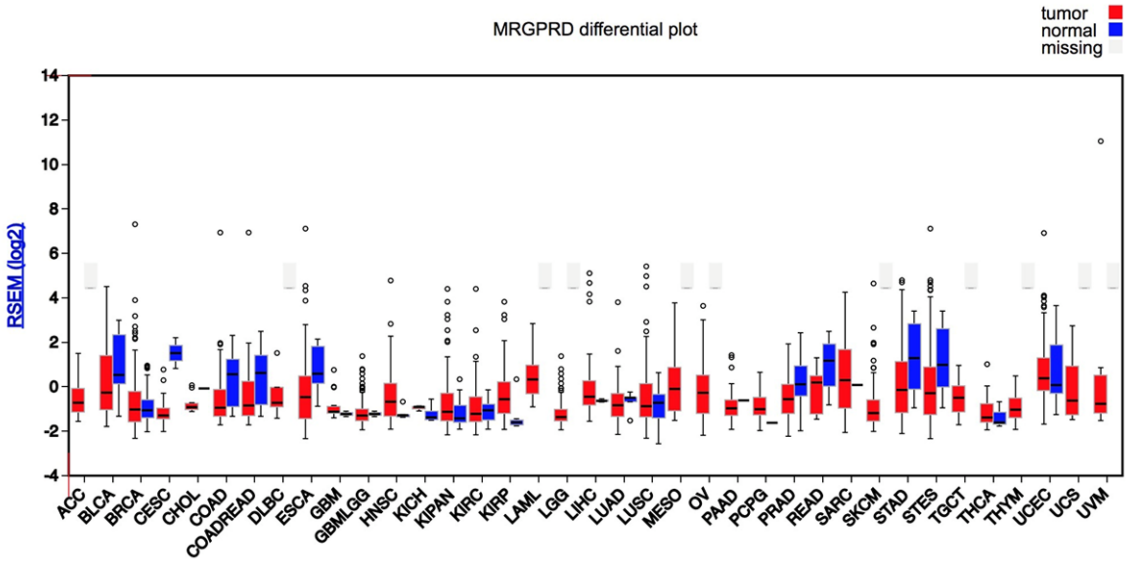

Figure 5. mRNA level of MRGPRD in all 33 types of cancers from TCGA. The mRNA level of MRGPRD in all 33 types of cancers from TCGA was shown by firebrowse (www.firebrowse.org). ACC: adrenocortical carcinoma, BLCA: bladder urothelial carcinoma, BRCA: breast invasive carcinoma, CESC: cervical squamous cell carcinoma and endocervical adenocarcinoma, CHOL: cholangiocarcinoma, COAD: colon adenocarcinoma, COADREAD: colon adenocarcinoma and rectum adenocarcinoma, DLBC: lymphoid neoplasm diffuse large B-cell lymphoma, ESCA: esophageal carcinoma, GBM: glioblastoma multiforme, GBMLGG: glioblastoma multiforme and brain lower grade glioma, HNSC: head and neck squamous cell carcinoma, KICH: kidney chromophobe, KIPAN: pan-kidney cohort (KICH+KIRC+KIRP), KIRC: kidney renal clear cell carcinoma, KIRP: kidney renal papillary cell carcinoma, LAML: acute myeloid leukemia, LGG: brain lower grade glioma, LIHC: liver hepatocellular carcinoma, LUAD: lung adenocarcinoma, LUSC: lung squamous cell carcinoma, MESO: mesothelioma, OV: ovarian serous cystadenocarcinoma, PAAD: pancreatic adenocarcinoma, PCPG: pheochromocytoma and paraganglioma, PRAD: prostate adenocarcinoma, READ: rectum adenocarcinoma, SARC: sarcoma, SKCM: skin cutaneous melanoma, STAD: stomach adenocarcinoma, STES: stomach and esophageal carcinoma, TGCT: testicular germ cell tumors, THCA: thyroid carcinoma, THYM: thymoma, UCEC: uterine corpus endometrial carcinoma, UCS: uterine carcinosarcoma, UVM: uveal melanoma.

examined MRGPRD gene expression by using quantitative RT-PCR. They found in the clinical samples of uterus or colon, MRGPRD mRNA expression in the cancer portion did not exceed three times the amount as compared to the normal tissues. As for lung cancers, the mean level of MRGPRD mRNA in the lung cancer tissues exceeded the amount equal to three times as much as that in the normal lung tissues, and for 12 among 33 lung pair samples, the MRGPRD mRNA expression in the lung cancer exceeded three times the amount in the paired normal lung tissues. Some other cancers, such as breast cancers (3 out of 16), esophageal cancers (2 out of 12), kidney cancers (1 out of 10) and stomach cancers (1 out of 25), also displayed three times higher expression in the cancer tissues compared to that in the normal controls. Furthermore, we previously also reported that the average level of MRGPRD mRNA in non-small cell lung cancer (NSCLC) tumor tissues (1.0682±0.6096) was significantly higher than that in the adjacent non-cancerous lung tissue (0.3994±0.2838, P<0.001). The area under curve (AUC) of receiver operating characteristic curve (ROC) of MRGPRD mRNA was 0.853 (95% CI: 0.808-0.898, P<0.001) to diagnose NSCLC [15], which was in agreement with what Nishimura S et al [14] reported. However, no study has covered the relationship between MRGPRD and PC. Herein, we, for the first time, reported that MRGPRD was over-expressed in PC tissues than that in the non-cancerous tissues. These results suggest that MRGPRD might play an oncogenic role in PC, similar as its role in lung cancer.

No investigation has been available concerning the correlation between MRGPRD and cancer deterioration except that we previously reported that the level of MRGPRD mRNA was positively correlated to lymph node metastasis, tumor size and clinical TNM stage. Furthermore, high MRGPRD expression was significantly cor-

related with poorer survival of NSCLS patients [15]. Consistently, in this study, the high expression of MRGPRD was found in PC with neural invasion, lymph node metastasis and TNM stage, which reflect largely the progression of tumor. This leads to the hypothesis that MRGPRD might be involved in cancer invasion and migration, playing again the similar role in lung cancer.

The mechanism of MRGPRD in the tumorigenesis and progression of malignancies remains basically unknown. Nishimura S et al [14] studied the *in vitro* and *in vivo* oncogenic function of MRGPRD using murine fibroblast cell line NIH3T3 stably expressed MRGPRD. They observed that overexpression of MRGPRD in NIH3T3 cells could induce focus formation and multi-cellular spheroid formation, and then could also promote tumor formation in nude mice. Furthermore, overexpression of MRGPRD in NIH3T3 cell could enhance the loss of contact inhibition, anchorage-independent growth and *in vivo* tumorigenesis. However, the exact mechanism of MRGPRD in PC needs *in vitro* and *in vivo* verification.

In summary, this study demonstrates that the expression of MRGPRD is upregulated in pancreatic tissues and there is a correlation between the expression of MRGPRD and tumor progression in PC tissues, which strongly indicates that MRGPRD might play an essential part in the carcinogenesis and development of PC. However, the tumorigenic function and mechanism of MRGPRD in PC remain unclear. Further investigations on MRGPRD are needed to reveal its functions on PC initiation or progression *in vitro* and *in vivo*.

Acknowledgements

We would like to thank the Fund of Guangxi University Student Innovative Plan (201510-598014), the Fund of Guangxi Science Foundation (2014GXNSFBA118167, 2016GXNSFBA-380039), the Promoting Project of Basic Capacity for University Young and Middle-aged Teachers in Guangxi (KY2016LX031), the Fund of the Innovation Project of Guangxi Graduate Education (2016) and Natural Science Foundation of China (NSFC 81560448). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. We acknowledge the cBioPortal for Cancer Genomics site (http://www.cbioportal.org/), the TCGA Research Network for generating TCGA datasets (http://cancergenome.nih.gov/) and also Gene Expression Omnibus (GEO, https://www.ncbi.nlm.nih.gov/gds).

Disclosure of conflict of interest

None.

Address correspondence to: Yi-Wu Dang and Dian-Zhong Luo, Department of Pathology, First Affiliated Hospital of Guangxi Medical University, 6 Shuangyong Road, Nanning, Guangxi Zhuang Autonomous Region, People's Republic of China. Tel: +86-771-5356534; E-mail: dangyiwu@126.com (YWD); 13878802796@163.com (DZL)

References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.

[2] Tang B, Li Y, Qi G, Yuan S, Wang Z, Yu S, Li B and He S. Clinicopathological significance of CDKN2A promoter hypermethylation frequency with pancreatic cancer. Sci Rep 2015; 5: 13563.

[3] Wolfgang CL, Herman JM, Laheru DA, Klein AP, Erdek MA, Fishman EK and Hruban RH. Recent progress in pancreatic cancer. CA Cancer J Clin 2013; 63: 318-348.

[4] Tu C, Zheng F, Wang JY, Li YY and Qian KQ. An updated meta-analysis and system review: is gemcitabine+fluoropyrimidine in combination a better therapy versus gemcitabine alone for advanced and unresectable pancreatic cancer? Asian Pac J Cancer Prev 2015; 16: 5681-5686.

[5] Han W, Cao F, Chen MB, Lu RZ, Wang HB, Yu M, Shi CT and Ding HZ. Prognostic value of sPARC in patients with pancreatic cancer: a systematic review and meta-analysis. PLoS One 2016; 11: e0145803.

[6] Huang S, Zheng J, Huang Y, Song L, Yin Y, Ou D, He S, Chen X and Ouyang X. Impact of S100A4 expression on clinicopathological characteristics and prognosis in pancreatic cancer: a meta-analysis. Dis Markers 2016; 2016: 8137378.

[7] Zhang Y, Yang J, Li H, Wu Y, Zhang H and Chen W. Tumor markers CA19-9, CA242 and CEA in the diagnosis of pancreatic cancer: a meta-analysis. Int J Clin Exp Med 2015; 8: 11683-11691.

[8] Cao Z, Tian R, Zhang T and Zhao Y. Localized autoimmune pancreatitis: report of a case

clinically mimicking pancreatic cancer and a literature review. Medicine (Baltimore) 2015; 94: e1656.
[9] Chen C, Wu CQ, Chen TW, Tang MY and Zhang XM. Molecular Imaging with MRI: potential application in pancreatic cancer. Biomed Res Int 2015; 2015: 624074.
[10] Goral V. Pancreatic cancer: pathogenesis and diagnosis. Asian Pac J Cancer Prev 2015; 16: 5619-5624.
[11] Hu H, Jiao F, Han T and Wang LW. Functional significance of macrophages in pancreatic cancer biology. Tumour Biol 2015; 36: 9119-9126.
[12] Ogrendik M. Oral bacteria in pancreatic cancer: mutagenesis of the p53 tumour suppressor gene. Int J Clin Exp Pathol 2015; 8: 11835-11836.
[13] Luo W, Wickramasinghe SR, Savitt JM, Griffin JW, Dawson TM and Ginty DD. A hierarchical NGF signaling cascade controls ret-dependent and ret-independent events during development of nonpeptidergic DRG neurons. Neuron 2007; 54: 739-754.
[14] Nishimura S, Uno M, Kaneta Y, Fukuchi K, Nishigohri H, Hasegawa J, Komori H, Takeda S, Enomoto K, Nara F and Agatsuma T. MRGD, a MAS-related G-protein coupled receptor, promotes tumorigenisis and is highly expressed in lung cancer. PLoS One 2012; 7: e38618.
[15] Li Z, Xie Y, Zhong T, Zhang X, Dang Y, Gan T and Chen G. Expression and clinical contribution of MRGD mRNA in non-small cell lung cancers. J BUON 2015; 20: 1101-1106.