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Original Article

The polymorphisms of oncostatin M receptor gene associated with increased risk of lung cancer

Yue Zhong[1,3], Ji Li[2], Yaping Zhang[1], Wei Qiu[1], Yan Luo[3]

Departments of [1]Ultrasound, [2]Cardiothoracic Surgery, The First People Hospital of Neijiang, Neijiang 641000, Sichuan Province, P. R. China; [3]Department of Ultrasonography, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, P. R. China

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Abstract: Oncostatin M receptor (OSMR) played an important role in tumorigenesis by inhibiting proliferation of tumor cells. But the relationship between OSMR polymorphism and lung cancer has not been reported yet. Two OSMR polymorphisms (rs2278329 and rs2292016) were detected by SNP genotype assay in 388 lung cancer patients and 490 healthy controls. The results indicated that GA/AA genotypes of rs2278329 is related closely to increased lung cancer risk in dominant model (OR = 2.04, P < 0.001). The A allele of rs2278329 was also associated with increased risk of lung cancer (OR = 1.45, P < 0.001). And GT/TT genotypes of rs2292016 was related closely to poor survival of squamous carcinoma patients (P = 0.025). Cox multiple-variate logistic regression analysis indicated that rs2279329 related closely to better prognosis in squamous carcinoma patients. Our research confirmed that OSMR GT+TT of rs2292016 associated with poor prognosis, while GA+AA of rs2278329 related to better survival of squmous carcinoma patients.

Keywords: IL-32, single-nucleotide polymorphism, lung cancer, prognosis, survival status

Introduction

Lung cancer is the leading cause of malignant-related deaths all over the world. The death rate of lung cancer in China was 610.2 per 100,000 [1]. Nearly 60% of patients diagnosed with lung cancer die within 1-year and 75% die within 2-year, and the total 5-year survival rate was only less than 16% [2]. The reason of poor survival was due to the advanced stage in lung cancer diagnosis. Early detection of lung cancer was difficult by the inaccessibility of the lungs and the consequent risks in obtaining lung tissues for pathological diagnosis [3]. CT screening played an important role in early lung cancer diagnosis, however, high false-positive rates was the major problem in CT-mediated early lung cancer screening [4]. The National Lung Screening Trial (NLST) in United States confirmed the role of CT in reducing the mortality of lung cancer, but 96% of the positive screening results in the low dose CT was found to be false-positive [5].

Oncostatin M receptor (OSMR) was a member of the interleukin 6 (IL6) receptor families [6]. By oncostatin M (OSM) binding, OSMR could activate MAPK/Erk and PI3K/Akt cascades and induce the transcription of context-dependent target genes [7, 8]. OSMR signaling was important in inflammation, haematopoiesis and was increasingly recognized as an important contributor in cancer progression [9, 10]. OSMR was widely expressed in many tumor cells, including melanoma, hepatocellular and prostate carcinoma [11-13]. In breast cancer, enhanced OSMR expression related closely to shorter recurrence-free and overall survival and with chemotherapy resistance in oestrogen receptor-negative tumors [14, 15]. OSMR could induce cell detachment, anchorage-independent growth, migration and invasion in breast cancer cells by promoting epithelial-mesenchymal transition [16]. OSM-OSMR interactions also could increase the angiogenesis phenotype in an endothelial-fibroblast co-culture model system [17].

Table 1. Description of the study population

Variables	Number	Percent
Age, median (range)	58 (31-86)	
Total patients	388	
Sex		
Male	268	69.1
Female	120	30.9
Smoking status		
Never	121	31.2
Former	115	29.6
Current	152	39.2
Stage		
I	119	30.7
II	97	25.0
III	114	29.4
IV	19	4.9
Unknown or not available	39	10.1
Histology		
Adenocarcinoma	206	53.1
Squamous	161	41.5
Other	21	5.4
Grade		
Poorly differentiated	101	26.0
Moderately differentiated	126	32.5
Well differentiated	16	4.1
Unknown or not available	145	37.4

However, the role of OSMR polymorphisms in lung cancer susceptibility has not been reported yet. In this study, we analyzed the association between OSMR polymorphisms (rs2278329 and rs2292016) and lung cancer risk, patients' clinical characteristics (histological types, stages and metastasis), as well as relationship with survival in lung cancer patients.

Materials and methods

Patients

A total of 388 lung cancer patients who were admitted to West China Hospital were enrolled in this study (flow diagram of participants).

Among 388 samples, 231 were tissue samples from patients which diagnosed in 2007 and had complete follow-up visiting and 5-year survival data. The other 157 were blood sample which collected from patients who diagnosed as lung cancer during 2013-2015. All clinical data were obtained from medical records within 2 weeks of the date of diagnosis. Date of death was obtained during subsequent follow-up visit or through telephonic inquiry. The overall survival time was calculated as time from the date of diagnosis to the date of death or last follow up visit (if the exact date of death was unavailable). Controls were 490 healthy individuals had routine examinations in our hospital. The standards of enrolled healthy control were absent of clinical symptom of lung cancer, had no history of malignancy and had no record of lung diseases. The basic characteristics of patients were presented in **Table 1**. This study was conducted in agreement with Declaration of Helsinki and performed with the approval of ethics committee of West China Hospital, all persons signed informed consent to participate in this study.

DNA isolation and genotyping classification

Genomic DNA was extracted by the use of whole-blood DNA extraction kit from Tiangen (Beijing, China) following the manufacturer's instruction. Genotyping of OSMR polymorphisms were performed using the TaqMan® SNP Genotyping Assay (Applied Biosystems, ABI, Foster City, CA) with the Assay ID C__15965230_10 for rs2278329 and C__15966926_10 for rs2292016. In order to distinguish the SNP at the end of real-time PCR, the allelic A probe for rs2278329 and allelic G probe for rs2292016 were labeled with the fluorescent VIC dye, and the others with the fluorescent FAM dye. TaqMan probe real-time PCR was carried out as follows: 20 ng of genomic DNA was amplified in a total volume of 10 μl reaction mixture containing 5 μl 2 × TaqMan Universal PCR Master Mix, 0.5 μl 20 × SNP Genotyping Assay. Real-time PCR conditions were as follows: 95°C for 10 min, followed by 59 cycles at 92°C for 15 seconds, 60°C for 1 min. About 15% of the samples were randomly selected to carry out the repeated assays.

Statistical methods

Statistical analyses were performed using SPSS version 16.0 software. Genotype frequencies of these two tag SNPs were obtained by directed counting. Hardy-Weinberg equilibrium was evaluated by chi-square test. Genotypic association test in a case-control pattern assuming codominant, dominant, recessive, or overdominant genetic models was performed

Table 2. Distribution of the *OSMR* SNPs among cases and controls and their associations with lung cancer risk

		rs2278329					rs2292016			
		Cases	Controls	OR (95% CI)[a]	*P* value[a]		Cases	Controls	OR (95% CI)[a]	*P* value[a]
Model	Genotype					Genotype				
Codominant	GG	126 (32.5%)	226 (46.1%)	1.00	**< 0.001**	GG	161 (41.5%)	211 (43.1%)	1.00	0.33
	GA	212 (54.6%)	217 (44.3%)	**2.04 (1.45-2.86)**		GT	180 (46.4%)	219 (44.7%)	1.28 (0.93-1.82)	
	AA	50 (12.9%)	47 (9.6%)	**2.01 (1.18-3.45)**		TT	47 (12.1%)	60 (12.2%)	0.92 (0.68-1.85)	
Dominant	GG	126 (32.5%)	226 (46.1%)	1.00	**< 0.001**	GG	161 (41.5%)	211 (43.1%)	1.00	0.16
	GA/AA	262 (67.5%)	264 (53.9%)	**2.04 (1.47-2.79)**		GT/TT	227 (58.5%)	279 (56.9%)	1.25 (0.91-1.72)	
Recessive	GG/GA	338 (87.1%)	443 (90.4%)	1.00	0.25	GGGT	341 (87.9%)	430 (87.8%)	1.00	0.94
	AA	50 (12.9%)	47 (9.6%)	1.33 (0.81-2.17)		TT	47 (12.1%)	60 (12.2%)	0.98 (0.61-1.59)	
Overdominant	GG/AA	176 (45.4%)	273 (55.7%)	1.00	**< 0.001**	GG/TT	208 (53.6%)	271 (55.3%)	1.00	0.15
	GA	212 (54.6%)	217 (44.3%)	**1.75 (1.27-2.38)**		GT	180 (46.4%)	219 (44.7%)	1.25 (0.89-1.41)	
	Allele					Allele				
	G	464 (59.8)	669 (68.3)	1.00	**< 0.001**	G	502 (64.7)	641 (65.4)	1.00	0.75
	A	312 (40.2)	311 (31.7)	**1.45 (1.12-1.76)**		T	274 (35.3)	339 (34.6)	1.03 (0.85-1.26)	

[a]Adjusted by age, sex and smoking status. Boldfaced values indicate a significant difference at the 5% level.

Table 3. Association between clinical characteristics of patients with lung cancer and rs2278329

Characteristics	Cases No.	Genotype No. (%)			*P*-value	Allele No. (%)		*P*-value	OR (95% CI)
		GG	GA	AA		G	A		
Gender									
Male	268	91 (34.0)	144 (53.7)	33 (12.3)		326 (60.8)	210 (43.4)		
Female	120	35 (29.2)	68 (56.7)	17 (14.2)	0.62	138 (57.5)	102 (42.5)	0.38	0.87 (0.64-1.19)
Age									
≤ 58	184	59 (32.1)	99 (53.8)	26 (14.1)		217 (59.0)	151 (41.0)		
> 58	204	67 (32.8)	113 (55.4)	24 (11.8)	0.79	247 (60.5)	161 (39.5)	0.66	1.07 (0.80-1.42)
Histology									
Adenocarcinoma	205	69 (33.7)	113 (55.1)	23 (11.2)		251 (61.2)	159 (38.8)		
Squamous	179	56 (31.3)	96 (53.6)	27 (15.1)	0.52	208 (58.1)	150 (41.9)	0.38	0.88 (0.66-1.17)
Differentiation									
Poor	106	32 (30.2)	56 (52.8)	18 (17.0)		120 (56.6)	92 (43.4)		
Moderate-well	139	41 (29.5)	82 (59.0)	16 (11.5)	0.43	164 (59.0)	114 (41.0)	0.60	1.10 (0.77-1.58)
Clinical stage									
I-II	168	49 (29.2)	97 (57.7)	22 (13.1)		195 (58.0)	141 (42.0)		
III-IV	103	27 (26.2)	60 (58.2)	16 (15.5)	0.79	114 (55.3)	92 (44.7)	0.54	0.90 (0.63-1.27)

Table 4. Association between clinical characteristics of patients with lung cancer and rs2292016

Characteristics	Cases No.	Genotype No. (%)			*P*-value	Allele No. (%)		*P*-value	OR (95% CI)
		GG	GT	TT		G	T		
Gender									
Male	268	114 (42.5)	124 (46.3)	30 (11.2)		352 (65.7)	184 (34.3)		
Female	120	47 (39.2)	56 (46.7)	17 (14.2)	0.66	150 (62.5)	90 (37.5)	0.39	0.87 (0.64-1.20)
Age									
≤ 58	184	81 (44.0)	81 (44.0)	22 (12.0)		243 (66.0)	125 (34.0)		
> 58	204	80 (39.2)	99 (48.5)	25 (12.2)	0.62	259 (63.5)	149 (36.5)	0.46	0.89 (0.67-1.20)
Histology									
Adenocarcinoma	205	84 (41.0	96 (46.8)	25 (12.2)		264 (64.4)	146 (35.6)		
Squamous	179	76 (42.5)	82 (45.8)	21 (11.7)	0.96	234 (65.4)	124 (34.6)	0.78	1.04 (0.78-1.41)
Differentiation									
Poor	106	42 (39.6)	48 (45.3)	16 (15.1)		132 (62.3)	80 (37.7)		
Moderate-well	139	56 (40.3)	66 (47.5)	17 (12.2)	0.81	178 (64.0)	100 (36.0)	0.69	1.08 (0.75-1.56)
Clinical stage									
I-II	168	70 (41.7)	77 (45.8)	21 (12.5)		217 (64.6)	119 (35.4)		
III-IV	103	37 (35.9)	54 (52.4)	12 (11.7)	0.56	128 (62.1)	78 (37.9)	0.57	0.90 (0.63-1.29)

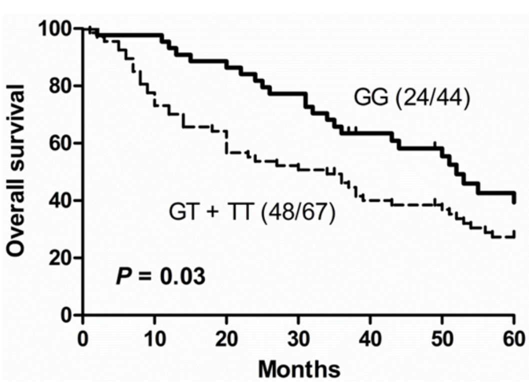

Figure 1. The association analysis between rs2292016 and survival functions in squamous carcinoma patients.

using SNPstats. If binary, the application assumes an unmatched case-control design and unconditional logistic regression models are used. If the response is quantitative, then a unique population is assumed and linear regression models are used to assess the proportion of variation in the response explained by the SNPs. Kaplan-Meier test was used to calculate the survival status of different genotype groups, and Log-rank test was used to compare the survival among all groups. Cox logistic regression was introduced to complete multi-variate analysis adjusted by gender, age, histology, differentiation status, clinical stage and smoking history.

Table 5. Association between SNPs in OSMR and patient's survival

SNP/genotype	Adenocarcinoma			Squamous carcinoma		
	Alive/dead, *N*	HR (95% CI)[a]	*P*	Alive/dead, *N*	HR (95% CI)[a]	*P*
rs2278329						
GG	16/17			12/17		
GA	26/45			22/45		
AA	8/7			5/10		
Dominant		1.04 (0.51-2.12)	0.92		**0.45 (0.21-0.97)**	**< 0.05**
Recessive		1.42 (0.61-3.30)	0.42		0.96 (0.38-2.42)	0.96
Overdominant		0.84 (0.45-1.56)	0.58		1.78 (0.91-3.49)	0.09
rs2292016						
GG	19/27			20/24		
GT	23/34			14/40		
TT	8/8			5/8		
Dominant		0.94 (0.54-1.65)	0.83		1.30 (0.64-2.62)	0.47
Recessive		1.30 (0.58-2.91)	0.52		0.92 (0.34-2.50)	0.87
Overdominant		0.82 (0.48-1.43)	0.49		1.31 (0.67-2.54)	0.43

N corresponds to the number of individuals. [a]Adjusted by gender, age, histology, differentiation, clinical stage and smoking status. Boldfaced values indicate a significant difference at the 5% level.

Results and discussion

Rs2278329 related closely to increase risk of lung cancer

In this study, tow SNPs of OSMR, rs2278329 and rs2292016 were genotyped in 388 lung cancer patients and 490 healthy controls. Three genotypes of each SNP were identified. Genotype frequencies of these two SNPs in both patients and controls were in agreement with the expectation under the Hardy-Weinberg equilibrium. All genotype and allele frequencies of OSMR SNPs in lung cancer patients and controls were shown in **Table 2**. The results indicated that the distribution of allele or genotype of rs2292016 had no significant difference between patients and controls. Significant difference in genotype distribution of rs2278329 was observed between lung cancer patients and controls in codominant model ($P < 0.001$, GA: OR = 1.75, 95% CI = 1.32-2.33; AA: OR = 1.92, 95% CI = 1.20-3.03), dominant model (OR = 1.79, 95% CI = 1.35-2.33, $P < 0.001$) and overdominant model (OR = 1.52, 95% CI = 1.16-2.00, $P = 0.002$), which suggested that GA/AA genotypes of rs2278329 was related closely to increased risk for lung cancer patients. In allele analysis of rs2278329, allele A was associated with increased risk for lung cancer ($P < 0.001$, OR = 1.45, 95% CI = 1.12-1.76), all these results confirmed the role of rs2278329 in predicting the risk of lung cancer initiation.

Rs2278329 and rs2292016 had no relationship with clinical characteristics of lung cancer

Further analysis was conducted to uncover the relationship between these two SNPs and specific clinical characteristics of lung cancer patients. We analyzed the genotype distribution of OSMR SNPs in lung cancer patients' characteristics including gender, age, histological classification, differentiation status and clinical stages. The results indicate that neither rs2278329 nor rs2292016 had significant relationship with lung cancer characteristics (**Tables 3** and **4**).

Rs2278329 confers better prognosis in squamous carcinoma patients

The lung cancer patients enrolled in this study included 120 adenocarcinoma (ADC) and 111 squamous carcinoma (SCC) with complete follow-up. The single variate analysis indicated rs2292016 had no relationship with urvival status of ADC patients. But in SCC analysis, GT/TT genotype was related closely to poor survival status ($P < 0.03$), which confirmed the important role of rs2292016 in predicting the poor prognosis in lung squamous carcinoma patients (**Figure 1**). Cox logistic regression was then per-

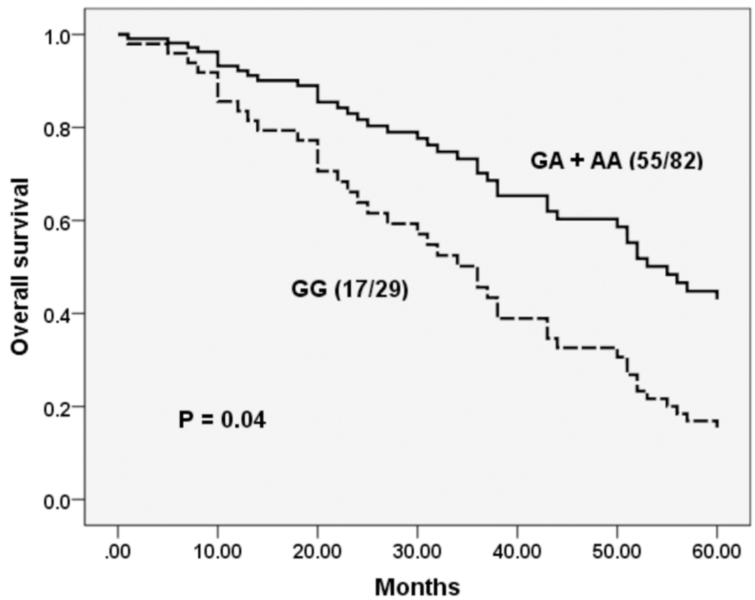

Figure 2. The association analysis between rs2278329 and survival functions in squamous patients by Cox logistic regression adjusted by gender, age, histology, differentiation status, clinical stage and smoking history.

formed to multi-variate analysis adjusted by gender, age, histology, differentiation status, clinical stage and smoking history (**Table 5**). And the results indicated that rs2292016 had no association with survival of both ADC and SCC patients, while rs2278329 conferred better survival of SCC patients (**Figure 2**), which suggested that rs22783329 could act as protection factor in SCC.

Discussion

Accumulate evidences confirmed that OSMR related closely to cancer. The OSM-OSMR signaling functions were identified as a potent suppressor of tumor cell including melanoma, glioblastoma, lung carcinoma, esophageal squamous carcinoma carcinomas and breast tumors [18-20]. It was reported that specific loss of OSMR subunit, in conjunction with a low level of histone acetylation in the promoter region of OSMR could dramatically inhibited the proliferation of metastatic melanoma cell lines by activating the STAT3 kinase pathway [10]. In breast tumor study, activation of OSMR inhibited proliferation of tumor cells and induced morphologic transformation partly by stimulating a specific stress/senescence program of gene expression mediated by JNK pathway [20]. In prostate cancer research, cell lines DU-145 and PC-3 were transfected with an androgen-responsive (AR) gene, the results indicated that overexpression of AR could increase the expression of OSMR, which indicated the role of OSMR in the drug treatment of prostate cancer [6]. Kim et al found that highly methylated OSMR was detected in primary colon cancer tissues (80%, 80/100) compared with adjacent normal tissues (4%, 4/100), methylation of OSMR was also detected in stool DNA from colon cancer patients, but generally absent from non-cancer patients [21] Moreover, the mRNA expression of OSMR was dramatically inhibited in colon cancer tissues as compared to normal tissues, all these results revealed a suppressive role for OSMR in colon cancer progression [21]. Other studies also demonstrated the important role of OSMR in suppression of tumor cell proliferation in glioblastoma, mammary tumors and lung cancer [22-24].

Our results suggested that GA genotype of rs2278329 related closely to occurrence of lung cancer. The A allele of rs2278329 was also associated with the increased risk of lung cancer occurrence. And GT/TT genotype of rs2292016 was related closely to poor survival status in squamous carcinoma patients. Multiple-variate analysis by Cox logistic regression suggested that rs2279329 conferred better prognosis in squamous carcinoma, which suggested the closely relationship between SNP of OSMR and lung cancer.

Conclusion

To our knowledge, this was the first report about the role of OSMR polymorphism in lung cancer. Our observations demonstrated that OSMR polymorphisms were deeply involved in lung cancer susceptibility and survival status. Further researches should be performed in understanding the mechanisms on how OSMR polymorphisms influence the carcinogenesis of lung cancer.

Disclosure of conflict of interest

None.

Address correspondence to: Yan Luo, Department of Ultrasonography, West China Hospital, Sichuan University, 37 Guo Xue Street, Chengdu 610041, Sichuan Province, P. R. China. Tel: +86-1360825-4072; E-mail: 13608254072@163.com

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