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ORIGINAL ARTICLE

Impact of IL-18 gene promoter polymorphisms on renal cell carcinoma occurrence and prognosis in Chinese Han population*

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Abstract

Objective Genetic polymorphisms in various inflammatory cytokines have been associated with the risk and growth or invasiveness of renal cell carcinoma (RCC). However, the molecular basis of RCC pathogenesis is unclear. The aim of this study was to explore a possible association between two IL-18 gene promoter polymorphisms, –137G/C and –607C/A, and RCC occurrence and prognosis in a Chinese Han population.

Methods Chinese Han patients with RCC (n = 175) and age-matched healthy controls (n = 200) were analyzed by single nucleotide polymorphism genotyping during follow-up.

Results IL-18-137G allele frequency was significantly higher in patients with lymph node metastasis (Odds ratio [OR], 3.52; 95% confidence interval [CI], 0.97–16.17; P = 0.045). The *IL-18-607 CC* genotype was associated with distant metastasis (OR, 2.81; 95% CI, 1.35–6.24; P = 0.025). The IL-18-137 G allele was correlated with more advanced tumor stage (OR, 1.83; 95% CI, 1.05–3.72; P = 0.026) and higher tumor grade (OR, 2.23; 95% CI, 0.78–4.12; P = 0.041). The IL-18-607 CC genotype frequency was significantly higher in patients with more advanced cancer stage (OR, 2.92; 95% CI, 1.80–6.87; P = 0.001) and higher tumor grade (OR, 2.21; 95% CI, 1.25–12.25; P = 0.035). The IL-18-607 allele was associated with more advanced cancer stage (OR, 2.47; 95% CI, 1.38–3.83; P = 0.002).Carriers of the GG genotype with the –137G/ C polymorphism had a 2.165-times higher risk of RCC progression than carriers of the GC genotype (Hazard ratio = 2.15, 95% CI, 1.270–3.687).

Conclusion The IL-18-137 G allele was correlated with more advanced stage, higher tumor grade, and lymph node metastasis. *IL-18* gene promoter polymorphism -137G/C may thus influence the prognosis of RCC patients.

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Key words: *interleukin-18*; renal cell carcinoma; polymorphism; prognosis

Renal cell carcinoma (RCC) is the most common renal tumor and accounts for 2%–3% of all malignancies. RCC is two times more frequent in men than in women, and higher RCC incidence is observed beginning in the sixth decade[1]. Considerable recent evidence has associated increased tumor risk with inflammation, and clinical and experimental studies have associated tumor progression with the upregulation of proinflammatory molecules, especially during late stages of the disease [2].Cytokines are produced by a variety of hemopoietic and nonhemopoietic cell types that mediate and regulate immunity, inflammation, and hemopoiesis. The interaction between a tumor and the immune system and the production of cytokines by the tumor itself can result in differences in local and systemic levels of cytokines in cancer patients [3]. In this context, genetic polymorphisms

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in different inflammatory cytokines have been associated with cancer risk and the growth or invasiveness of RCC [4]. However, the molecular basis of RCC pathogenesis is unclear.

Interleukin-18 (*IL-18*) is an 18-kDa cytokine that belongs to the IL-1 (IL-1) superfamily and is produced by various immune and non-immune cells [5–7]. The expression and secretion of *IL-18* is a crucial event against the oncogenesis of oral carcinoma cells because of its ability to modulate cell cycle progression or trigger an apoptotic pathway [5–7]. We have previously demonstrated a correlation between the levels of serum *IL-18* and disease severity in patients with RCC and prostate cancer [8–9]. In some animal model systems, transfection of the *IL-18* gene into tumor cells enhanced both specific and non-specific antitumor immune responses, which indicates that the transfection of *IL-18* into dendritic cells should induce highly effective antitumor immune responses [10]. These findings provide evidence of an association between susceptibility to cancer and *IL-18* gene expression.

The *IL-18* gene is located on chromosome 11q22. Two functional gene polymorphisms, *-607A/C* and *-137G/C*, are found in its promoter region [11]. Giedraitis *et al* analyzed the *IL-18* gene promoter sequence and found a change from the *C* allele to the *A* allele at position –607 and a change from the G allele to the *C* allele at position –137 of the *IL-18* promoter region[11]. Estimation of the transcription activity of *IL-18* gene promoter fragments showed that C allele of *–607A/C* or *G* allele of *–137G/C* caused higher activity of *IL-18*. Individuals with the CC homozygote of *–607A/C* or the *GG* homozygote of *–137G/C* polymorphism exhibited somewhat higher levels of *IL-18* mRNA compared with individuals with other genotypes [12]. *IL-18* gene polymorphisms have been recently investigated in several cancers, including nasopharyngeal carcinoma [12], prostate cancer [13], cervical cancer[14], and breast cancer [15]. However, these studies yielded different or even controversial results.

We have previously described an effect of *IL-18* polymorphisms at –607 and –137 on clinical characteristics of prostate cancer patients [16]. In this study, we investigated the role of *IL-18* gene promoter polymorphisms in the occurrence of RCC and prognosis to provide data for screening high-risk Han Chinese individuals.

Materials and methods

Study subjects

The study included 175 patients diagnosed with renal clear-cell carcinoma (RCC) at the Department of Urology of The Affiliated Hospital of Nantong University (China) between 2005 and 2015. All patients had undergone radical or partial nephrectomy. Their mean age was 68 years (range, 58–85 years). Clinicopathological characteristics are shown in Table 1. Two consulting pathologists retrospectively and independently reviewed the hematoxylin and eosin stained tissue slides according to the World Health Association classification. The Fuhrman scale was used to assess nuclear grade. Tumor stage was assigned according to the 2002 TNM classification. Patients were actively followed-up from diagnosis to December 2005. Cancer characteristics according to the University of California, Los Angeles integrating staging system included TNM stage, histologic grade (Fuhrman), and performance status as prognostic factors. Only the first two parameters were assessed, because a performance status higher than zero was found in only a very low percentage of patients and was not deemed relevant for the statistical analysis. No other risk factors for an adverse prognosis were evaluated. The control group comprised 200 healthy blood donors with a mean age of 70 years. Control samples were collected between 2005 and 2015. All patients provided signed informed consent to participate in this study, which was approved by the ethics committee of our hospital.

Single nucleotide polymorphism (SNP) genotyping

After DNA extraction, samples were randomly placed in wells of 96-well plates and analyzed using real-time polymerase chain reaction (PCR). The PCR primer designs, reaction mixture composition, and reaction processes of this study were the same as those used in a previous study [16]. Standard samples were sequenced using a BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, USA) and ABI 3130 genetic analyzer (Applied Biosystems). Genotyping results of all samples

Table 1 Characteristics of patients

Characteristics	Median	Percentage
Age (years)	68 ± 9.8 (58–85)	
Gender		
Male	95	54.3
Female	80	45.7
Tumor stage		
pT1	55	31.4
pT2	70	40.0
pT3	15	8.6
pT4	35	20.0
Lymph node metastasis		
Negative	124	70.9
Positive	51	29.1
Metastasis		
Negative	118	67.4
Positve	57	32.6
Grade		
G1–2	98	56
G3–4	77	44

were obtained using the Gene Scanning v1.2 software by comparison with standard samples.

Statistical analyses

The observed genotype frequencies in the controls were tested for Hardy-Weinberg equilibrium. Possible significant difference in age was tested by the Student's t-test. The distribution of genotypes and allele frequencies between the two groups was analyzed by the chi-square analysis. Haplotype analysis was carried out using a related software platform. Odds ratio (OR) and 95% confidence interval (95% CI) calculations were conducted with the risk option of Crosstabs. Kaplan-Meier and multivariate Cox proportional hazard models were used to examine the relationship between the genotypes and progression-free survival time. Hazard ratios (HRs) and 95% CIs were calculated. A two-sided $P < 0.05$ was considered statistically significant.

Results

Subject characteristics

The genotype distribution of the controls was in Hardy-Weinberg equilibrium ($P > 0.05$ for both polymorphisms). The mean ages for cases and controls were 68 ± 9.8 and 70 ± 9.7 years, respectively ($P = 0.12$). Based on the clinical findings, 125 patients were in pT1 or pT2, and 50 patients were in pT3 or pT4 (Table 1).

Association analysis of SNPs and RCC susceptibility

The results of association analyses of alleles and genotypes with RCC cancer susceptibility are shown in Table 2. No differences were observed between the genotype distribution of the two SNPs among the cases and controls ($P = 0.18$ and 0.53 for –137G/C, $P = 0.31$ and 0.54 for –607C/A). No significant associations were detected in the allele frequencies ($P = 0.15$ for –137G/C, $P = 0.55$ for –607C/A). On the basis of the haplotype analysis results shown in Table 3, no promising *P*-values were detected ($P > 0.05$ for all).

Association between cancer progression and genotypes

The associations of the *IL-18* genotypes with tumor grade and stage are shown in Table 4. Genotype GG of *IL-18*-137 was associated with more advanced cancer stage (OR, 2.81; 95% CI, 1.23–5.47; $P = 0.008$) and higher (G3–G4) tumor grade (OR, 3.12; 95% CI, 1.16–8.17; $P = 0.021$). The *IL-18*-137 G allele was correlated with more advanced stage (OR, 1.83; 95% CI, 1.05–3.72; $P = 0.026$) and higher tumor grade (OR, 2.23; 95% CI, 0.78–4.12; $P = 0.041$). The *IL-18*-607 CC genotype was significantly more frequent in patients with more advanced cancer stage (OR, 2.92; 95% CI, 1.80–6.87; $P = 0.001$) and higher tumor grade (OR, 2.21; 95% CI, 1.25–12.25; $P = 0.035$). The *IL-18*-607 C allele was associated with more advanced cancer stage (OR, 2.47; 95% CI, 1.38–3.83; $P = 0.002$).

Table 2 Genotypes and allele frequencies of IL-18 promoters in relation to the occurrence of RCC

Polymorphisms	Cases *n* (%)	Controls *n* (%)	χ^2	*P**	OR	95% CI
–137 C/G						
Genotype						
GG	141 (80.6)	152 (76.0)			1.0	
CG	34 (19.4)	46 (23.0)	1.72	0.18	0.80	0.48–1.12
CC	0 (0.0)	2 (1.0)			0.53	
Allele						
C	40 (11.4)	60 (15.0)			1.00	
G	310 (88.6)	340 (85.0)	2.24	0.15	0.76	0.85–1.27
-607 A/C						
Genotype						
CC	82 (46.7)	47 (23.5)			1.00	
AC	78 (44.6)	99 (49.5)	1.12	0.31	0.85	0.54–1.86
AA	45 (25.7)	54 (27.0)	0.48	0.53	0.81	0.65–1.31
Allele						
C	170 (48.6)	210 (52.5)			1.00	
A	185 (52.4)	190 (47.5)	0.45	0.55	0.95	0.87–1.59

OR = odds ratio; CI, confidence interval; * x^2 Test or Fisher's exact test

Table 3 Haplotype frequencies of IL-18 promoters in RCC and controls

Haplotype	Cases *n* (%)	Controls *n* (%)	OR	95% CI	*P**
–607C/–137G	165 (47.1)	184(46.0)	1.00		
–607C/–137C	7 (2.0)	6(1.5)	1.12	0.49–2.56	0.78
–607A /–137G	147 (42.0)	168(42.0)	0.99	0.45-2.05	0.89
–607A /–137C	3 (8.9)	42(10.5)	0.75	0.53-1.09	0.95

OR = odds ratio; CI: confidence interval; * x^2 Test or Fisher's exact test

Association results of the *IL-18* genotypes with lymph node metastasis and distant metastasis are shown in Table 5. The *IL-18*-137G allele was significantly more frequent in patients with lymph node metastasis (OR, 3.52; 95% CI, 0.97–16.17; $P = 0.045$). The *IL-18*-607 CC genotype was associated with distant metastasis (OR, 2.81; 95% CI, 1.35–6.24; $P = 0.025$).

Association between cancer survival and genotypes

In this study, disease progress is represented as progression-free survival. The mean and median progression-free survival values were 20.68 ± 13.77 and 18 months, respectively. The distinction of cancer progress among the different genotypes in the two SNPs is described in Table 6. Carriers of the GG genotype in -137G/C had a 2.165-times higher risk of progress compared with GC carriers (HR = 2.15, 95% CI = 1.270-3.687) (Table 6, Fig. 1).

Table 4 Associations of IL-18 genotypes with tumor stage, and grade

IL-18 Polymorphisms	Tumor pT1 (%)	Stage pT2–4 (%)	OR	95% CI	*P**	Tumor pT1 (%)	Stagep T2–4 (%)	OR	95% CI	*P**
-137 C/G										
CC	7 (5.8)	3 (5.9)	1.33	0.22–7.81	0.625	4 (4.1)	6 (7.8)	1.48	0.25–19.27	0.643
CG	58 (48.4)	15 (29.4)	1.00			54 (55.1)	15 (19.5)	1.00		
GG	55 (45.8)	33 (64.7)	2.81	1.23–5.47	0.008	40 (40.8)	56 (72.7)	3.12	1.16–8.17	0.021
Allele										
C	35 (29.2)	32 (24.8)	1.00			40 (40.8)	21 (27.3)	1.00		
G	85 (70.8)	97 (75.2)	1.83	1.05–3.72	0.026	58 (55.7)	56 (72.7)	2.23	0.78–4.12	0.041
–607 A/C										
Genotype										
AA	14 (11.7)	4 (7.8)	0.75	0.24–2.47	0.627	9 (9.2)	8 (10.4)	1.21	0.28–5.21	0.762
AC	72 (60.0)	22 (43.1)	1.00			69 (70.4)	39 (50.6)	1.00		
CC	34 (28.3)	25 (49.1)	2.92	1.80–6.87	0.001	20 (20.4)	30 (39.0)	2.21	1.25–12.25	0.035
Allele										
A	57 (43.2)	45 (35.4)	1.00			35 (26.9)	23 (17.7)	1.00		
C	75 (56.8)	82 (64.6)	2.47	1.38–3.83	0.002	95 (73.1)	107 (82.3)	1.78	0.77–4.62	0.163

95%CI = 95% confidence interval; * x^2 Test or Fisher's exact test

Table 5 Associations of IL-18 genotypes with lymph node metastasis, metastasis

IL-18 Polymorphisms	Lymph node metastasis		OR	95% CI	*P**	Metastasis		OR	95% CI	*P**
	Negative (%)	Positive (%)				Negative (%)	Positive (%)			
–137 C/G										
CC	7 (6.7)	1 (2.0)	0.95	0.78–1.22	0.662	3 (2.5)	2 (3.5)	2.51	0.42–14.27	0.437
CG	41 (39.4)	24 (47.1)	1.00			42 (25.1)	11 (19.3)	1.00		
GG	56 (53.9)	26 (50.9)	1.89	0.43–8.35	0.416	62 (52.5)	44 (77.2)	1.88	0.93–5.27	0.163
Allele										
C	65 (43.3)	17 (16.7)	1.00			42 (25.1)	19 (16.7)	1.00		
G	85 (56.7)	85 (56.7)	3.52	0.97–16.17	0.045	125 (74.9)	95 (83.3)	1.67	0.82–3.40	0.327
–607 A/C										
Genotype										
AA	10 (9.6)	2 (4.0)	0.97	0.89–1.03	0.343	8 (6.8)	2 (3.5)	2.47	0.57–6.15	0.158
AC	55 (52.9)	17 (33.3)	1.00			69 (58.5)	23 (40.4)	1.00		
CC	39 (37.5)	32 (62.7)	2.62	0.58–9.17	0.82	41 (34.7)	32 (56.1)	2.81	1.35–6.24	0.025
Allele										
A	60 (46.2)	20 (19.6)	1.00			61 (34.7)	33 (28.9)	1.00		
C	70 (53.8)	82 (80.4)	2.58	0.79–8.63	0.066	115 (65.3)	81 (71.1)	1.55	0.93–3.55	0.247

95% CI = 95% confidence interval; * x^2 Test or Fisher's exact test

Discussion

The etiology of renal cancer is highly complex and involves both environmental and genetic factors. In addition, genetic polymorphisms in genes encoding cytokines can influence their expression or function, and polymorphisms in genes that regulate the intensity of immune responses may contribute to the pathogenesis of renal cancer and thus influence the clinical outcome of patients [17]. *IL-18*, a proinflammatory cytokine that belongs to the IL-1 family of ligands, induces interferon-gamma (IFN-γ) production in T cells and natural killer cells, which is important in the T helper-cell type 1 response[3, 4]. An antitumor effect of *IL-18* has been demonstrated and *IL-18* has been considered for use

Table 6 Survival analysis of the selected SNPs in patients (n = 127)

Polymorphisms	Genotypes *n* (%)	Developed *n* (%)	HR	95% CI
IL-18-607C/A				
GG	32 (25.2)	19 (20.0)	1.00	0.67–1.74
TT	89 (70.1)	72 (75.8)	1.05	0.08–1.79
GT	6 (4.7)	4 (4.2)	0.23	
IL-18-137G/C				
GC	26 (20.5)	28 (29.5)	1.00	
GG	101 (79.5)	67 (70.5)	2.36	1.26–3.89

HR = hazard ratio; 95% HCI = 95% confidence interval

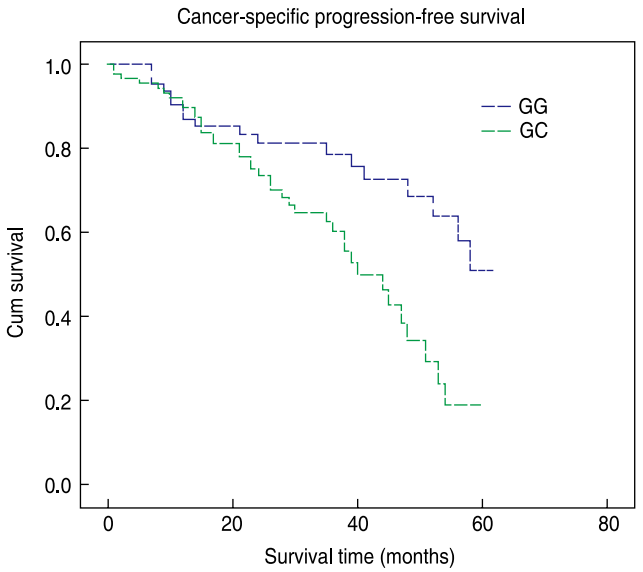

Fig. 1 Progression-free survival time of RCC patients carrying GG or GC genotypes of the SNP-137G/C. Cum = cumulative

in cancer immunotherapy or gene therapy[18]. On the contrary, we have reported that *IL-18* can increase tumor growth via increasing the stimulation of vascular endothelial growth factor and the immune response and can also stimulate solid tumor metastasis [8,19]. Considering the above findings, the purpose of this study was to investigate whether the *IL-18* promoter (–607) C/A and (–137) G/C gene polymorphisms have any association with the risk for RCC. The *IL-18* promoter region is composed of five single nucleotide positions, among which only –137G/C and –607C/A have confirmed impact on *IL-18* activity and expression in tissues [20]. Different haplotypes of *IL-18* polymorphisms might lead to different expression levels of *IL-18* mRNA[20]. For example, –137G/–607C causes a higher level of *IL-18* mRNA synthesis [20], while the haplotype (–137C/–607A) causes a lower promoter activity.

In the present study, we found no association between *IL-18* polymorphisms and a higher risk of RCC. However, as in other studies [21], *IL-18* polymorphisms were found by us to be correlated with more advanced cancer stages. *IL-18* promoter polymorphisms have been associated with prostate carcinomas [22], although other authors found no association between *IL-18* polymorphisms and cancer risk [23]. In fact, *IL-18* activities are influenced by the tumor microenvironment. So, *IL-18* could exert its antitumor activity by augmenting IFN-γ production, particularly in the presence of IL-12 [24]. However, recent data also suggested a procancerous activity for this multifunctional cytokine under certain conditions depending on the tumor immune response at different tumor sites and probable genetic background [25]. In the present RCC patients, *IL-18* polymorphisms did not appear to be associated with RCC susceptibility. This discrepancy could be attributed to the different genetic backgrounds and environmental factors of patients, such as exposure to different carcinogens that initiate different cancers in different populations. In addition, the inadequate study design, involving nonrandom sampling and a limited sample size, should also be considered. The possible selection bias that might have been present in the hospital-based, case-control study is a relevant issue. Finally, we cannot exclude the fact that the observed association was due to a gene in linkage disequilibrium with the *IL-18* gene or the effect of *IL-18* on another peptide. However, once the tumor appears, high productive *IL-18* polymorphism promotes more advanced tumor grade, stage, and other features. These results may be explained by the fact that *IL-18* induces the production of angiogenic and growth factors [26].

We found that a genotype related to higher production of *IL-18* is associated with higher grade and stage of the tumor. *IL-18* activates vascular endothelial growth factor [26] and can activate angiogenesis in tumor nests [24]. Therefore, *IL-18* polymorphisms that increase its production would increase angiogenesis and provide adequate nutrients to transformed cells, promoting cancer development to a more advanced stage. *IL-18* is also correlated with the progression of the disease. High-production polymorphisms in *IL-18* are associated with differentiation of tumor cells, leading to a more advanced tumor grade and stage grouping. Therefore, *IL-18* can directly promote cancer cell proliferation by regulating proliferation stimulators. *IL-18* was recently implicated in the migration of breast cancer [15] and human melanoma cell lines through the generation of region of interest and the mitogen-activated protein kinase pathway [27]. Proinflammatory cytokines also induce adhesion receptors of endothelial cells for cancer cell attachment [28]. Gunel *et al* [29] showed that breast carcinoma patients with bone metastasis had higher serum *IL-18* levels compared with those with liver metastasis. Our results are similar to these findings. The clinical importance of these parameters is worth investigating in patients with RCC, especially for patients with metastasis. However, such studies should be conducted in a larger cohort of patients.

In the present study, polymorphisms related to *IL-18* production were associated with the development of metastasis and lymph node involvement. As metastasis is a highly complex process that may involve numerous genes, the analysis of the risk of a specific polymorphism leading to metastasis is difficult, as individual genes are likely to contribute only moderately to the risk [30]. This may explain the low correlation found in this study between *IL-18* production and metastasis. The association

between overall survival and *IL-18*-607 polymorphism was also analyzed. Our study showed that carriers of the GG genotype in -137G/C had a 2.165-times higher risk of progression compared with GC carriers. Because the median survival (30% mortality) was not achieved, we cannot confirm or rule out the statistical influence of this variable as a prognostic factor.

Our data demonstrated that the *IL-18*-137 G allele is correlated with a more advanced stage and higher tumor grade and lymph node metastasis. The *IL-18* -137G/C promoter polymorphism might contribute to the prognosis of RCC. However, there was no evidence to support an association between polymorphisms in the *IL-18* gene and RCC susceptibility in Han Chinese individuals, which does not imply exclusion of the contribution of other polymorphisms in *IL-18* to the risk of RCC. Further studies applying a more extensive array of *IL-18* gene SNPs, other independent large-size ethnic group cohorts, detailed clinical data, and long-term follow-up are needed to confirm our results.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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