The Role of *IL-10* Promoter Polymorphisms in Renal Cell Carcinoma

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Abstract. *Background/Aim: Renal cell carcinoma (RCC) accounts for approximately 3% of all cancer-related mortalities worldwide and the risk factors for the development of RCC have not yet been fully elucidated. Mounting proteomic evidence suggests that inflammatory process plays a role in RCC etiology and interleukin-10 (IL-10) is an important immunosuppressive cytokine. However, little is known on the contribution of IL-10 genotypes to RCC. This study aimed at evaluating the contribution of IL-10 promoter A-1082G (rs1800896), T-819C (rs3021097), A-592C (rs1800872) genetic polymorphisms to the risk of RCC in Taiwan. Materials and Methods: Associations of the three IL-10 polymorphic genotypes with the risk of RCC were examined among 92 RCC patients and 580 age- and gender-matched cancer-free controls by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methodology. Results: The pilot results showed that the percentages of TT and TC for IL-10 T-819C genotypes were significantly higher in the RCC patient group than those in the healthy control group. The CC genotype carriers were of lower risk for RCC (odds ratio (OR)=0.33, 95% confidence interval (CI)=0.12-0.93, p=0.0369). There is no difference in the distribution of A-1082G or A-592C genotype between the RCC and control groups. Conclusion: The CC genotype of IL-10 T-819C genotype may have a protective effect on RCC risk in Taiwan. Further investigation with larger sample size in addition to genotype-phenotype correlation and intracellular mechanisms are our future work.*

Renal cell carcinoma (RCC) has a worldwide incidence with more than 270,000 new cases and 100,000 deaths annually (1). The incidence of RCC has kept its increasing step in the world (2). After Japan, Taiwan has the second-highest prevalence rate of end-stage renal disease in the world. Epidemiological investigations have shown that cigarette smoking, hypertension, obesity, occupational exposures, diet and family history of cancer are associated with RCC (3-5). However, only few exposed individuals develop RCC during their lifetime, suggesting that genomic factor(s) may be involved in the etiology of RCC. For urologists, RCC remains unpredictable of its behavior and tumor stage and grade are not satisfying parameters for prognosis of RCC patients.

Interleukin-10 (IL-10), also known as human cytokine synthesis inhibitory factor (CSIF) and produced by activated T cells, monocytes, B cells and thymocytes, was found to be an important immuno-regulatory cytokine playing a modulating role in activating and suppressing immuno-responses (6). The expression of IL-10 not only directs the differentiation and proliferation of several immune cells but has both tumor-promoting and tumor-inhibiting properties. The significance of IL-10 is based on the fact that it may play a critical role in tumor development and metastasis (7). The genetic polymorphisms found in the regulatory sites, especially the promoter region of *IL-10* gene, are believed to affect the expression of IL-10 protein and possibly be associated with RCC susceptibility and prognosis. In the literature, there exist two reports examining the contribution of *IL-10* genotypes to RCC. In 2005, Havranek and his

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colleagues found that AA genotypes at *IL-10* A-1082G were associated with higher risk of RCC among citizens in London (8). In 2009, Romero and his colleagues also revealed that *IL-10* genotypes were associated with clear-cell RCC susceptibility among Spanish people (9). In that report, the genotypes of three *IL-10* polymorphic sites at promoter region were examined, A-1082G (rs1800896), T-819C (rs3021097) and A-592C (rs1800872), where the A allele of *IL-10* A-1082G was not associated with higher susceptibility, while associated with advanced disease stage, larger tumor size, and presence of adenopathy (9).

The GG genotype at *IL-10* A-1082G is contributing to enhanced expression of IL-10 at the protein level (9-11). However, another study of IL-10 expression in peripheral blood lymphocytes from patients with RCC showed no statistical difference in IL-10 expression among the patients of GG, AA or AG genotypes at *IL-10* A-1082G (8). In 2013, Yao and his colleagues proposed that the genotypes of *IL-10* at T-819C and A-592C sites may also influence the expression of *IL-10* mRNA (12). To validate the role of these *IL-10* genotypes at promoter site in determining the risk for RCC, we sought to investigate the association of the genotypes at the promoter region of *IL-10*, A-1082G (rs1800896), T-819C (rs3021097) and A-592C (rs1800872) with RCC risk in a Taiwanese population.

Materials and Methods

Study population. The hospital-based case-control study recruited 92 RCC patients and 580 cancer-free controls, frequency matched by age and sex, while none of the subjects are relatives to each other with any biological relationship. All the RCC patients were diagnosed and histopathologically confirmed and without any prior history of other cancers. All the age- and gender-matched cancer-free controls were genetically unrelated to the RCC patients and had no individual history of cancer. Extra exclusion criteria of the controls were that if they had symptoms suggestive of RCC, such as hematuria. Each patient donated 3-5 ml venous blood after providing a written informed consent. The study was approved by the Institutional Review Board of China Medical University. The details of the characteristics for all the participants are summarized and compared in Table I.

Genotyping protocol. The total genomic DNA of each subject was extracted from the leucocytes of peripheral blood and stored as previously published (13-15). The polymerase chain reaction (PCR) cycling conditions were: one cycle at 94˚C for 5 min; 35 cycles of 94˚C for 30 sec, 55˚C for 30 sec and 72˚C for 30 sec, and a final extension at 72˚C for 10 min. Pairs of PCR primer sequences and restriction enzyme for each DNA product of *IL-10* genotyping work are all listed in Table II. The PCR products were cut by proper restriction enzymes and the reaction was incubated for 2 h at 37˚C. Then, 10 μl of product was loaded into a 3% agarose gel for electrophoresis.

Statistical analyses. To ensure that the controls used were representative of the general population and to exclude the possibility of genotyping error, the deviation of the genotype frequencies of *IL-10* single nucleotide polymorphisms in the control subjects from those expected under the Hardy-Weinberg equilibrium was assessed using the goodness-of-fit test. Pearson's Chi-square test or Fisher's exact test (when the expected number in any cell was less than five) was used to compare the distribution of the *IL-10* genotypes between cases and controls. The associations between the *IL-10* polymorphisms and RCC risk were estimated by computing odds ratios (ORs) and their 95% confidence intervals (CIs) from unconditional logistic regression analysis with the adjustment for possible confounders. $p<0.05$ was considered statistically significant; all statistical tests were two-sided.

Table I. *Distributions of the frequencies of selected characteristics among the RCC cases and healthy controls.*

Characteristics	Cases (n=92)		Controls (n=580)		*p*-Value
	N	%	N	%	
Age (year) (mean±SD)	58.8±11.7		58.3±11.5		0.8971
≤60	47	51.1%	307	52.9%	0.8223
>60	45	48.9%	273	47.1%	
Gender					
Male	59	64.1%	371	64.0%	1.0000
Female	33	35.9%	209	36.0%	
Smoking status					
Smokers	41	44.6%	220	37.9%	0.2499
Non-smokers	51	55.4%	360	62.1%	
Alcohol drinking status					
Drinkers	37	40.2%	209	36.0%	0.4848
Non-drinkers	55	59.8%	371	64.0%	
Hypertension					
Yes	61	66.3%	302	52.1%	0.0130*
No	31	33.7%	278	47.9%	
Diabetes					
Yes	21	22.8%	104	17.9%	0.2523
No	71	77.2%	476	82.1%	
Family cancer history					
Yes	6	6.5%	17	2.9%	0.1125
No	86	93.5%	563	97.1%	

*Statistically significant.

Results

Basic characteristic indexes compared between the RCC case and control groups. The frequency distributions of the characteristics for the control and case subjects are summarized in Table I. There were no differences between the case and control groups on age, sex, smoking or alcohol drinking status, diabetes or family history of cancer ($p>0.05$). However, there were more subjects with hypertension (66.3%) among the RCC cases than the controls (52.1%); this difference was significant ($p=0.0130$).

Table II. *The primer sequences, polymerase chain reaction and restriction fragment length polymorphism conditions for identifying the interleukin-10 (IL-10) A-1082G, T-819C and A-592C genotypes among the investigated individuals.*

Polymorphism (locations)	Primer sequences	Restriction enzyme	SNP sequence	DNA fragment size (bp)
A-1082G (rs1800896)	F: 5'-CTCGCTGCAACCCAACTGGC-3'	*Mnl* I	A	139
	R: 5'-TCTTACCTATCCCTACTTCC-3'	G	106 + 33	
T-819C (rs3021097)	F: 5'-TCATTCTATGTGCTGGAGAT-3'	*Mae* III	T	209
	R: 5'-TGGGGGAAGTGGGTAAGAGT-3'	C	125 + 84	
A-592C (rs1800872)	F: 5'-GGTGAGCACTACCTGACTAG-3'	*Rsa* I	C	412
	R: 5'-CCTAGGTCACAGTGACGTGG-3'	A	236 + 176	

F and R indicate forward and reverse primers, respectively.

Association of IL-10 genotypes and RCC risk. The distributions of genetic frequencies for the IL-10 polymorphisms in the RCC cases and controls are presented and compared in Table III. The unadjusted ORs without adjusting those possible confounding factors (age, gender, smoking, alcohol drinking, hypertension, diabetes and family cancer history status) for the people carrying TC and CC genotypes at *IL-10* promoter T-819C were 0.62 (95% CI=0.38-1.02, p=0.0732) and 0.33 (95% CI=0.12-0.93, p=0.0369) respectively, compared to those carrying the TT wild-type genotype (Table III). The p for trend was significant (p=0.0262) (Table III). In the dominant model (TC plus CC *versus* TT), the association between *IL-10* promoter T-819C polymorphism and the risk for RCC was also statistically significant (OR=0.56, 95% CI=0.35-0.88, p=0.0130) (Table III). As for the two other polymorphic sites, the *IL-10* promoter A-1082G and promoter A-592C, the distributions of these polymorphisms were in Hardy-Weinberg equilibrium but there was no difference between RCC and control groups in the distribution in the genotype frequency at these SNPs (Table III). To sum up, these data indicated that variant C allele at *IL-10* promoter T-819C may play a protective role for RCC (Table III).

Association of IL-10 allelic types and RCC risk. The OR for the subjects carrying the C allele at *IL-10* promoter T-819C was 0.57 (95% CI=0.38-0.84, p=0.0004), compared to those carrying the T wild-type allele (Table IV). On the contrary, there is no differential distribution of allelic frequencies between RCC case and control groups as for the *IL-10* promoter A-1082G and promoter A-592C (Table IV).

Discussion

In this study, the association of *IL-10* polymorphism and RCC risk was investigated in Taiwan, where the prevalence of end-stage renal disease was second-highest all over the world after Japan. After genotyping, we found that individuals carrying the homozygous variant CC genotype were of significant lower risk of RCC compared to those carrying wild-type TT genotype on *IL-10* T-819C (Table III). We also investigated the association of *IL-10* T-819C C allele with RCC risk, finding that C allele at *IL-10* T-819C also contributed to a lower risk of RCC (Table IV). However, we did not examine the expression level of IL-10 among non-cancer renal tissues and tumor sites; we only compared the difference among the RCC patients with different genotypes at *IL-10* T-819C. We strongly believe that IL-10 expression will further strengthen the role of *IL-10* T-819C genotypes in RCC carcinogenesis. In 2012, we examined the *XRCC6* mRNA levels in the RCC samples according to their genotypes at *XRCC6* promoter T-991C, finding that C allele correlated to a lower expression level of *XRCC6* mRNA, that could have been responsible for decreased XRCC6 protein and lowered double-strand break (DSB) repair capacity (13).

From the viewpoint of epidemiology, the feasibility of collecting enough RCC samples, that are relatively rare among the cancers, for population-based or hospital-based case-control study limits the scientists to access the contribution of genotypes to RCC. In this study, we have collected 92 RCC samples and strengthened the analyzing power by 580 non-cancer controls (Table I). In the literature, the sample size of RCC patients in Japan was 71 (16) and that in Turkey was 41 (17), much less than the sample size (n=92) of the current study. Enlarged samples are valuable for further stratifying analysis of the contribution of *IL-10* genotypes to cancer stages and prognosis, such as survival rates. Also, the multi-interactions of genotype and these factors listed in Table I could be further revealed. Among different types of cancers, there are some epidemiological studies investigating the association between *IL-10* promoter polymorphisms, which may alter the function of this cytokine itself and its downstream signaling and cellular behavior, resulting in the development of human disorders. In literature, the genotypes at *IL-10* A-1082G were reported to be associated with lymphoma (18), gastric cancer (19-21), oral cancer (22), nasopharyngeal carcinoma (23), papillary thyroid cancer (24) and lymphoid leukemia (25). As for *IL-10* T-819C, its genotypes were associated with lung cancer (26, 27), gastric cancer (28) and adult leukemia (12, 29). Concerning *IL-10* A-592C, its genotypes were associated with

Table III. *Distributions of interleukin-10 (IL-10) genotypic frequencies among the RCC cases and controls.*

	RCC Cases (%)	Controls (%)	Crude OR (95% CI)	*p*-Value[a]
A-1082G				
AA	71 (77.2)	414 (76.6)	1.00 (reference)	
AG	16 (17.4)	107 (18.4)	0.94 (0.52-1.67)	0.9364
GG	5 (5.4)	29 (5.0)	1.08 (0.40-2.88)	0.8805
AG+GG	21 (22.8)	136 (23.4)	0.97 (0.57-1.63)	0.8958
p_{trend}				0.9598
T-819C				
TT	62 (67.4)	310 (53.4)	1.00 (reference)	
TC	26 (28.3)	209 (36.0)	0.62 (0.38-1.02)	0.0732
CC	4 (4.3)	61 (10.6)	0.33 (0.12-0.93)	0.0369*
TC+CC	30 (32.6)	270 (46.6)	0.56 (0.35-0.88)	0.0130*
p_{trend}				0.0262*
A-592C				
AA	61 (66.3)	371 (64.0)	1.00 (reference)	
AC	27 (29.3)	185 (31.9)	0.89 (0.55-1.44)	0.7199
CC	4 (4.4)	24 (4.1)	1.01 (0.34-3.02)	1.0000
AC+CC	31 (33.7)	209 (36.0)	0.90 (0.57-1.44)	0.7506
p_{trend}				0.8871

OR, Odds ratio; CI, confidence interval. [a]Based on Chi-square test with Yate's correction or Fisher's exact test; *p<0.05.

Table IV. *Allelic frequencies for interleukin-10 (IL-10) polymorphisms in the RCC and control groups.*

Polymorphic site Allele	RCC Cases (%) N=184	Controls (%) N=1160	Odds Ratio (95% CI)	*p*-Value[a]
A-1082G				
Allele A	158 (85.9)	995 (85.8)	1.00 (reference)	0.9730
Allele G	26 (14.1)	165 (14.2)	1.07 (0.69-1.65)	
T-819C				
Allele T	150 (81.5)	829 (71.5)	1.00 (reference)	0.0004*
Allele C	34 (18.5)	331 (28.5)	0.57 (0.38-0.84)	
A-592C				
Allele A	149 (81.0)	927 (79.9)	1.00 (reference)	0.7371
Allele C	35 (19.0)	233 (20.1)	0.93 (0.63-1.39)	

OR, Odds ratio; CI, confidence interval. [a]*p*-Value based on Chi-square test with Yate's correction or Fisher's exact test; *p<0.05.

lung cancer (26), gastric cancer (30, 31), esophageal cancer (32) and adult leukemia (29). It is worth noticing that we found that individuals carrying the homozygous variant CC genotype at *IL-10* T-819C were of significant lower risk of RCC. This finding was not similar to the previous reports focusing on the contribution of genotypes of *IL-10* A-1082G to RCC (8, 9). This inconsistency may be explained by the different background between Caucasians and Asians and needs to be validated in more populations.

In conclusion, our present study indicated that the promoter *IL-10* T-819C genotypes is associated with Taiwan RCC susceptibility and this *IL-10* polymorphism may lead to different expression levels of the IL-10 mRNA and protein, thus altering the downstream bioactivity of other immunologic proteins. Further functional studies are warranted to reveal the role of *IL-10* in RCC carcinogenesis.

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