Original Article

The association of *interleukin-6* gene polymorphism and risk of colorectal cancer in Chinese patients

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Background: Clinical and experimental data have strongly revealed a vital role of interleukin-6 (IL-6) in the development of both sporadic and colitis-associated colorectal cancer (CRC) development. The aim of our study is to discover the association between CRC risk in Chinese people and one variant (*rs1800795*) in *IL-6* gene which was reported to significantly associate with CRC risk in Caucasian population.

Methods: We included 186 CRC patients and 200 age- and gender- matched control individuals from the Wuxi Traditional Chinese Hospital. We used one customized assay of IL6-174G/C from Applied Biosystems to genotype one *IL-6* gene polymorphisms (*rs1800795*) through real time-RCR method. All statistical analyses were conducted with SPSS 17.0 by Student's *t*-test, χ^2 test, Fisher's exact test or logistic regression.

Results: Finally, our studies showed the C allele would significant increase the CRC risk in female [odds ratio (OR): 1.741, 95% confidence interval (CI): 1.037, 2.924, P value: 0.035] and non-smokers (OR: 2.425, 95% CI: 1.626, 3.617, P value: <0.001). And the significant associations exited in the genotype distributions of *rs1800795* polymorphism and CRC risk in non-smokers (P value: <0.001), drinkers (P value: 0.026) and the samples of non-high fat diet (P value: 0.006). Our studies showed significant positive relations between *rs1800795* polymorphism and CRC risk in tumor node metastasis (TNM) stage I (OR: 4.841, 95% CI: 4.220, 5.554, P value: <0.001) and TNM stage II (OR: 1.138, 95% CI: 1.034, 1.252, P value: 0.008). The further study of CRC subtypes indicated that *rs1800795* polymorphism indicated a better prognosis in rectum patients.

Conclusions: This study is the first report of *IL-6* gene polymorphisms among CRC patients from China. The results indicated that screening the *rs1800795* polymorphism in specific groups would be a promising method to predict the risk of CRC. However, more large size of population needed to verify these results, and further studies needed to be conducted to explore its potential mechanism.

Keywords: Interleukin-6 (IL-6); *rs1800795*; polymorphism; colorectal cancer (CRC)

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, and a number of 530,000 patients died of CRC each year (1). There are numerous factors influencing the development of CRC, including genetic, environmental, smoking, drinking and the aberrant inflammation of gastrointestinal tract (2). Of note, it is proved that tumor-associated inflammation significantly affected cancer development (3). Among the various inflammation-associated factors, the role of interleukin-6 (IL-6) in CRC tumorigenesis has been well-established.

IL-6 is a pleiotropic inflammatory cytokine which plays a vital role not only in immune and inflammatory response, but also the development of malignancy (4). Moreover, it is

reported that the increased production of IL-6 is observed in tumor itself and the serum of CRC patients (5). In addition, IL-6 expression shows a close relation to tumor stage, size, metastasis and survival of CRC patients (6). And these results may result from its role in producing pro-inflammatory cytokines and modulating Th17 and Treg cells in CRC (7). The role of *rs1800795*, a well-studied *IL-6* polymorphism, has been discussed in vast areas (8-21). Our team has conducted a meta-analysis to explore the relationship between *IL-6* polymorphisms and CRC risk, and we discovered that *IL-6 rs1800795* polymorphism significantly increased the risk of CRC in allele additive model in Europe [odds ratio (OR): 1.07, 95 % confidence interval (CI): 1.01, 1.14] (22). However, few studies were carried out to explore the relationship between the *IL-6 rs1800795* polymorphism and CRC risk in Chinese population. Hence, the aim of this study is to discover the association between one variant (*rs1800795*) in *IL-6* gene and CRC risk in Chinese population.

Methods

Study population

This is a hospital-based case-control study conducted in Wuxi Traditional Chinese Hospital during October 2015 and July 2017. The inclusion criteria for CRC patients were as follows: positive results of colonoscopy and pathology for colon or rectum tumors. And the control samples should have no gastrointestinal disorders, and these control samples have been subjected to diagnostic colonoscopy and had eligible colonoscopy results with no malignant tumors, adenomatous polyps, or inflammatory ulcers. All subjects were self-reported born in China. The exclusion criteria were: a history of other cancer, HIV, HBV, HCV, or IV drug use, or a mental impairment. We also recorded the information of age, sex, disease stage, smoking, drinking and dietary habit from medical records and pathology reports.

All enrolled subjects were informed and gave written consent to participate in this study according to the Helsinki declaration, and this study protocol was also supported by the ethical committee of Wuxi Traditional Chinese Hospital.

Genotyping

We isolated genomic DNA from 5 mL of peripheral blood leukocytes using the standard phenol-chloroform method. Single nucleotide polymorphism (SNP) genotyping was conducted with predesigned TaqMan assays from Applied Biosystems by minor groove binder probes fluorescently labeled with FAM or VIC (Genesky Biotechnologies Inc., Shanghai, China). The probes and primers used for SNP genotyping are: *IL-6* 174 G_C (*rs1800795*), VIC-TCTTGCGATGCTAAA, FAM-TCTTGCCATGCTAAA, Forward primer: TGACGACCTAAGCTGCACTTTTC, Reverse primer: GGGCTGATTGGAAACCTTATTAAGA. Polymerase chain reactions were operated on a Tetrad DNA Engine PCR machine and read in an ABI PRISM 7900 Sequence detection system. In order to keep the quality in genotyping, we repeated the genotyping for three times until to explore the consistent results.

Statistical analysis

The statistical significance of age and body mass index (BMI) was calculated by the Student's *t*-test. The χ^2 test or Fisher's exact test was used for univariate analyses of allele and genotype distribution between CRC patients and control subjects. The multivariate analyses of the association between SNPs and CRC risk were evaluated with the OR with 95% CIs by logistic regression, adjusting for age, gender, and BMI. When the minor allele homozygote counts are 14 or more, we calculated in three kinds of logistic regression models (dominant, additive and recessive). When the minor allele homozygote count is less than 14, we only examined in the dominant genetic model. Hardy-Weinberg equilibrium (HWE) was performed to exclude deviations in control subjects by HWE version 1.20 (Columbia University, New York, NY). In addition, the statistical power was measured with the STPLAN 4.3 software under a given sample size and significance level (α=0.05). The results were considered significant when the P values are less than 0.05. All statistical analyses were conducted with SPSS 17.0.

Results

Characteristics of the study groups

A total of 186 CRC patients and 200 control samples were enrolled in our study, and all samples in our study are all Han ethnic (*Table 1*). The distribution of the included SNP was in HWE for control subjects (P=0.16). In addition,

Table 1 Characteristics of studied population

Variables	Controls (n=200)	Cases (n=186)	P value
Age (mean ± SD)[a]	51.58±9.35	60.82±9.81	0.390
BMI[a]	24.77±3.40	24.95±3.13	0.052
Gender[b], n			0.465
Male	112	111	
Female	88	75	
Smoking[b]			0.210
Smoker	33	40	
Non-smoker	167	146	
Drinking[b]			0.561
Drinker	16	18	
Non-drinker	184	168	
Diet habit[b]			0.377
High fat diet	47	51	
Non high fat diet	153	135	
Tumor location			–
Colon		115	
Rectum		71	
TNM stage			–
I		33	
II		70	
III		71	
IV		12	

[a], the statistical data were calculated by the Student's t-test; [b], the statistical data were calculated by χ^2 test or Fisher's exact test. BMI, body mass index.

rs1800795 had a power of 0.264 which is lower than 0.08. There are no significant differences in age (P=0.390), BMI (P=0.052), gender (P=0.465), smoking (P=0.210), drinking (P=0.561) or diet habit (P=0.377). The case group comprises of 115 colon cancer patients and 71 rectum cancer patients. Moreover, there are 33 patients in tumor Node Metastasis (TNM) stage I, 70 patients in TNM stage II, 71 patients in TNM stage III and 12 patients in TNM stage IV.

Univariate analysis

In the univariate analysis of the association between *rs1800795* polymorphism and CRC risk, our results showed the significant allele distributions in female (OR: 1.741, 95% CI: 1.037, 2.924, P value: 0.035) and non-smokers (OR: 2.425, 95% CI: 1.626, 3.617, P value: <0.001). Moreover, the significant findings were observed in genotype distribution of non-smokers (P value: <0.001), drinkers (P value: 0.026) and the samples of non-high fat diet (P value: 0.006) (*Table 2*). In addition, no significant results were seen in the allele or genotype distribution based on CRC kind or TNM stage (*Table 3*).

Multivariate analysis

In the multivariate analysis of the association between *rs1800795* polymorphism and CRC risk, we adjusted the results for age, sex and BMI. Finally, we did not find any significant association between *rs1800795* polymorphism and CRC risk in whole people (OR: 0.966, 95% CI: 0.894, 1.043, P value: 0.374), colon cancer samples (OR: 0.941, 95% CI: 0.866, 1.024, P value: 0.158) or rectum cancer patient (OR: 0.955, 95% CI: 0.871, 1.048, P value: 0.336). Our studies showed significant association between *rs1800795* polymorphism and CRC risk in TNM stage I (OR: 4.841, 95% CI: 4.220, 5.554, P value: <0.001) and TNM stage II (OR: 1.138, 95% CI: 1.034, 1.252, *P* value: 0.008) (*Table 4*). Moreover, we further explored the associations between SNP and CRC subtypes. Interesting, we found positive correlation between *rs1800795* polymorphism and rectum risk in TNM stage I (OR: 2.466, 95% CI: 2.033, 2.993, P value: <0.001) and TNM stage II (OR: 1.193, 95% CI: 1.055, 1.349, P value: 0.005). While negative correlation was reflected in TNM stage III (OR: 0.573, 95% CI: 0.499, 0.658, P value: <0.001) and TNM stage IV (OR: 0.216, 95% CI: 0.148, 0.316, P value: <0.001). In addition, results have shown significant association between *rs1800795* polymorphism and colon risk in TNM stage I (OR: 6.200, 95% CI: 5.219, 7.365, P value: <0.001), and TNM stage IV (OR: 2.094, 95% CI: 1.894, 2.315, P value: <0.001) (*Table 5*).

Discussion

The SNP *rs1800795* is a well-studied SNP, which has been widely discussed in wide districts except for China. To our knowledge, this is the first study to explore the association between *rs1800795* polymorphism and CRC risk. Our studies showed the C allele would significant increase the CRC risk in female and non-smokers. And the significantly associations existed in the genotype distribution of

Table 2 Allele and genotype distribution of *rs1800795* polymorphism among CRC patients and healthy control subjects

Variable	Controls (n=200)	Cases (n=186)	OR (95% CI)	P value
Allele			1.134 (0.823, 1.561)	0.443
G	299	269		
C	101	103		
Genotype				0.346
GG	108	98		
GC	83	73		
CC	9	15		
Male				
Allele			0.850 (0.563, 1.281)	0.437
G	156	162		
C	68	60		
Genotype				0.090
GG	49	60		
GC	58	42		
CC	5	9		
Female				
Allele			1.741 (1.037, 2.924)	0.035
G	143	107		
C	33	43		
Genotype				0.105
GG	59	38		
GC	25	31		
CC	4	6		
Smoker				
Allele			0.714 (0.346, 1.474)	0.362
G	45	60		
C	21	20		
Genotype				0.417
GG	15	24		
GC	15	12		
CC	3	4		

Table 2 (*continued*)

Table 2 (*continued*)

Variable	Controls (n=200)	Cases (n=186)	OR (95% CI)	P value
Non-smoker				
Allele			2.425 (1.626, 3.617)	*<0.001*
G	287	209		
C	47	83		
Genotype				*<0.001*
GG	122	74		
GC	43	61		
CC	2	11		
Drinker				
Allele			0.367 (0.128, 1.051)	0.052
G	18	28		
C	14	8		
Genotype				0.026
GG	5	13		
GC	8	2		
CC	3	3		
Non-drinker				
Allele			1.273 (0.908, 1.785)	0.161
G	281	241		
C	87	95		
Genotype				0.211
GG	103	85		
GC	75	71		
CC	6	12		
High fat diet				
Allele			1.022 (0.567, 1.844)	0.941
G	145	80		
C	39	22		
Genotype				0.183
GG	60	30		
GC	25	20		
CC	7	1		

Table 2 (*continued*)

Table 2 (*continued*)

Variable	Controls (n=200)	Cases (n=186)	OR (95% CI)	P value
Non high fat diet				
Allele			1.053 (0.711, 1.560)	0.795
G	154	191		
C	62	81		
Genotype				0.006
GG	48	68		
GC	58	53		
CC	2	14		

CRC, colorectal cancer.

Table 3 Allele and genotype distribution of *rs1800795* polymorphism among CRC patients and healthy control subjects according to tumor location or TNM stages

Location	Variable	Controls (n=200)	Cases (n=186)	OR (95% CI)	P value
Colon	Allele			1.217 (0.846, 1.749)	0.289
	G	299	163		
	C	101	67		
	Genotype				0.211
	GG	108	59		
	GC	83	45		
	CC	9	11		
Rectum	Allele			1.005 (0.647, 1.562)	0.981
	G	299	106		
	C	101	36		
	Genotype				0.866
	GG	108	39		
	GC	83	28		
	CC	9	4		
TNM stage I	Allele			1.692 (0.976, 2.932)	0.059
	G	299	42		
	C	101	24		
	Genotype				0.098
	GG	108	12		
	GC	83	18		
	CC	9	3		

Table 3 (*continued*)

Table 3 (*continued*)

Location	Variable	Controls (n=200)	Cases (n=186)	OR (95% CI)	P value
TNM stage II	Allele			1.025 (0.659, 1.593)	0.913
	G	299	104		
	C	101	36		
	Genotype				0.616
	GG	108	39		
	GC	83	26		
	CC	9	5		
TNM stage III	Allele			1.005 (0.647, 1.562)	0.981
	G	299	106		
	C	101	36		
	Genotype				0.302
	GG	108	41		
	GC	83	24		
	CC	9	6		
TNM stage IV	Allele			1.219 (0.491, 3.024)	0.669
	G	299	17		
	C	101	7		
	Genotype				0.654
	GG	108	6		
	GC	83	5		
	CC	9	1		

CRC, colorectal cancer.

Table 4 The multivariate analysis of the association between *rs1800795* polymorphism and CRC risk adjusting for age, sex and BMI

Group	Model	P value*	OR (95% CI)*
Whole	Dominant	0.374	0.966 (0.894, 1.043)
Colon	Dominant	0.158	0.941 (0.866, 1.024)
Rectum	Dominant	0.336	0.955 (0.871, 1.048)
TNM stage I	Dominant	*<0.001*	*4.841 (4.220, 5.554)*
TNM stage II	Dominant	*0.008*	*1.138 (1.034, 1.252)*
TNM stage III	Dominant	0.248	0.783 (0.582, 3.129)
TNM stage IV	Dominant	0.668	0.782 (0.891, 2.398)

*, results were adjusted by age, sex and BMI. CRC, colorectal cancer; BMI, body mass index.

rs1800795 polymorphism and CRC risk in non-smokers, drinkers and the samples with non-high fat diet. Our studies showed significant positive relations between *rs1800795* polymorphism and CRC risk in TNM stage I and TNM stage II.

IL-6 is an important element of immune and inflammatory system, and it is also a key growth factor for malignancy (4). A recent study reported that the level of IL-6 was significantly higher in CRC tissues compared with noncancerous tissues, furthermore, the level of IL-6 was linked to invasion depth and lymph node metastasis in CRC (23). The team of Hara M discovered that the CRC patients with high serum IL-6 levels would have poorer overall survival and progression-free survival in comparison to those with low serum IL-6 levels, and a Cox proportional

Table 5 The multivariate analysis between *rs1800795* polymorphism and the risk of CRC subtypes adjusting for age, sex and BMI

Group	Model	P value*	OR (95% CI)*
Rectum			
TNM stage I	Dominant	*<0.001*	*2.466 (2.033, 2.993)*
TNM stage II	Dominant	*0.005*	*1.193 (1.055, 1.349)*
TNM stage III	Dominant	*<0.001*	*0.573 (0.499, 0.658)*
TNM stage IV	Dominant	*<0.001*	*0.216 (0.148, 0.316)*
Colon			
TNM stage I	Dominant	*<0.001*	*6.200 (5.219, 7.365)*
TNM stage II	Dominant	0.704	0.979 (0.877, 1.093)
TNM stage III	Dominant	*<0.001*	*0.531 (0.470, 0.601)*
TNM stage IV	Dominant	*<0.001*	*2.094 (1.894, 2.315)*

*, results were adjusted by age, sex and BMI. CRC, colorectal cancer; BMI, body mass index.

hazards regression analysis indicated that the CRC patients with high serum IL-6 levels may have an independent risk factor for a poor outcome (24). In addition, a review survey by Knüpfer and Preiss reported a close association between IL-6 expression and tumor stage, size, metastasis and survival of patients with CRC (6). Beside the findings about the close association between IL-6 and CRC clinically, a number of studies also explored its potential concrete molecular mechanisms. The current findings indicated that IL-6 functions in recruitment of immune cells and modulating Th17 and Treg cells in CRC (7). An increasing number of studies indicated CRC cells secreting IL-6 via STAT3 and JAK phosphorylation to enhance the phagocytic capacity and migration of macrophages in the tumor microenvironment (25-30), and modulating IL-6 would be a promising method to treat CRC (31-35). All these above studies indicated a close relation between IL-6 and CRC.

Based on the marked association between IL-6 and CRC, many researchers turned to reveal the relation between *IL-6* polymorphism and CRC risk. To date, several *IL-6* SNPs have been explored their association and CRC risk (8-21). Of note, *rs1800795* is the most well studies SNP. *Rs1800795* is located in promoter region of the gene (-174 n) and it is responsible for binding of certain transcriptional factors affecting transcription, RNA elongation, splicing, or maturation (36-39). Therefore, mutations in *rs1800795* may also influence the expression of *IL-6*. To date, *rs1800795* has been discussed its role in Spain (8,21), USA (9,13,17,20), Denmark (10,12), Greece (11), Sweden (14), France (15), Czech (16), Croatia (18) and Canada (19). However, no studies have been explored in China. In this study, this is the first study to explore the association between *rs1800795* polymorphism and CRC risk in Chinese. Our studies showed the C allele would significantly increase the CRC risk in female and non-smokers. And the significant associations existed in the genotype distribution of *rs1800795* polymorphism and CRC risk in non-smokers, drinkers and the samples with non-high fat diet. These studies indicated the distributions of allele and genotype in specific groups are significantly different, which indicated screening the *rs1800795* polymorphism in specific groups would be a promising method to predict the risk of CRC. In addition, our studies showed significant positive relations between *rs1800795* polymorphism and CRC risk in TNM stage I and TNM stage II in multivariate analysis after adjusting for the results for age, sex and BMI, these results indicated that *rs1800795* polymorphism may be a useful marker for CRC prognosis.

However, there are some limitations in our study. First, the size of enrolled samples is relatively small. Relatively small sample size is more likely to be lack of sufficient statistical power to verify the true positive findings if the result is negative. While when the result is positive, the outcome would be changed by chance due to the small sample size; then, further studies needed to be conducted to explore the role of *rs1800795* mutations in CRC development and progression.

This study is the first report of *rs1800795* polymorphisms in *IL-6* gene among CRC patients from China. However, more large size of population needed to verify these results, and further studies needed to be conducted to explore its potential mechanism.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.03.37). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All enrolled subjects were informed and gave written consent to participate in this study according to the Helsinki declaration (as revised in 2013), and this study protocol was also supported by the ethical committee of Wuxi Traditional Chinese Hospital (approval ID: 2016122003).

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