Effect of IL-1β, IL-8, and IL-10 polymorphisms on the development of myocardial infarction

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ABSTRACT. Myocardial infarction (MI) is currently a leading cause of death worldwide, and is caused by various environmental and genetic factors. We therefore conducted a case-control study to investigate the association between polymorphisms in interleukins IL-1β, IL-8, and IL-10 and MI risk. This study recruited 260 MI patients and 285 control subjects. Genotyping of IL-1β +3954C/T, IL-8 -251T/A, IL-10 -1082A/G, and IL-10 -819C/T were assessed using the polymerase chain reaction-

restriction fragment length polymorphism method. By comparing the risk factors of MI between the case and control groups, we discovered that MI patients were more likely to have smoking and drinking habits, have a history of hypertension and diabetes, have higher triglycerides and low-density lipoprotein cholesterol levels, and a lower high-density lipoprotein cholesterol level (P < 0.05). Unconditional regression analyses showed that subjects carrying the GG genotype of the IL-10 -1082A/G polymorphism were associated with increased risk of MI, and the OR (95%CI) was 2.04 (1.15-3.65). Our study found that the IL-10 -1082A/G polymorphism plays an important role in influencing the development of MI.

Key words: Myocardial infarction; Interleukin factors; Polymorphism

INTRODUCTION

Myocardial infarction (MI) is a common neurological disease and a leading cause of death worldwide. The etiology of MI is complicated and not completely understood. Several factors are considered important in the development of MI, including genetic and environmental influences (Lopez et al., 2006). The main environmental factors for MI include hypertension, hypercholesterolemia, diabetes, obesity, and smoking (Lopez et al., 2006). Moreover, studies have reported that genetic polymorphisms play an important role in the development of MI (Ianni et al., 2012; Konenkov et al., 2012; Arun Kumar et al., 2015).

The inflammatory mechanism can contribute to the process of MI, and cytokines are the main mediators of the inflammatory response. Inflammation also contributes to ischemic events through the promotion of atherosclerosis (Ross, 1999). Therefore, functional polymorphisms in inflammatory genes could influence the development and outcome of MI.

Previous studies have reported that C-reactive protein and interleukin (IL)-6 are risk factors for cardiovascular disease (Danesh et al., 2000; Hirschfield and Pepys, 2003), and IL-10 and tumor necrosis factor-α are associated with development of cardiovascular outcomes in adults (Kritchevsky et al., 2005). However, few studies have reported the association between *IL-8* gene polymorphisms and MI risk. Therefore, we conducted this case-control study to investigate the association between IL-1β, IL-8, and IL-10 polymorphisms and MI risk.

MATERIAL AND METHODS

Patients

We recruited 260 MI patients and 285 control subjects. The MI patients were recruited from visitors to the First People's Hospital of Wenling. MI patients were confirmed through computed tomography, magnetic resonance imaging, angiography, or duplex sonography by well-trained physicians. Patients were excluded from our study if they presented accidental or iatrogenic stroke, transient ischemic attack, brain tumors, or other cerebrovascular disorders. The controls were recruited from people who visited our hospital for a general health check-

up. Controls who had a history of stroke, ischemic heart diseases, neurological diseases, or any severe underlying diseases were excluded from our study. The study was approved by the First People's Hospital of Wenling, and all subjects gave their informed consent prior to inclusion in the study.

The clinical and pathological data were retrospectively collected from medical records. We used a questionnaire that enquired about social and demographic characteristics and risk factors for MI, including gender, age, hypertension, diabetes, cholesterol levels, body mass index, smoking, and physical exercise frequency.

Genotyping analysis

All study participants were asked to provide 5 mL venous blood, which was collected in ethylenediaminetetraacetic acid-coated tubes and stored at -20°C until required. Genomic DNA was extracted from peripheral blood lymphocytes and analyzed using a TIANamp Blood DNA Kit (Tiangen Biotech Co., Ltd., Beijing, China). Genotyping of IL-1β +3954C/T, IL-8 -251T/A, IL-10 -1082A/G, and IL-10 -819C/T were assessed by the polymerase chain reaction-restriction fragment length polymorphism method. Primers and probes of IL-1β +3954C/T, IL-8 -251T/A, IL-10 -1082A/G, and IL-10 -819C/T were designed using the Sequenom Assay Design 3.1 software. The cycling program for the polymerase chain reaction was as follows: denaturation at 95°C for 10 min, followed by 40 cycles at 95°C for 30 s, 62°C for 30 s, 72°C for 30 s, and extension at 72°C for 10 min. Genotyping was repeated in 5% of samples to check for accuracy.

Statistical analysis

Frequencies were used to describe the distribution of categorical variables and median and interquartile range was used for continuous variables. Differences in frequency distributions of the selected demographic variables and risk factors for MI were evaluated between the patients with MI and the control subjects using the chi-square test or Student t-test. The Hardy-Weinberg equilibrium for genotype distribution in the controls was tested by a goodness-of-fit chi-square test. Logistic regression was taken to assess the association between IL-1β +3954C/T, IL-8 -251T/A, IL-10 -1082A/G, and IL-10 -819C/T polymorphisms and MI risk, and the odds ratios (ORs) and 95% confidence intervals (95%CIs) of the results were determined. $P < 0.05$ was considered a statistically significant difference. Statistical analyses were conducted using SPSS version 16.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

The 260 MI patients comprised 204 males and 56 females, and the mean age was 53.81 ± 9.54 years. The 285 controls comprised 219 males and 66 females, and the mean age was 53.51 ± 10.25 years (Table 1). By comparing the risk factors of MI between the two groups, MI patients were more likely to have a habit of smoking and drinking, have a history of hypertension and diabetes, and have higher triglycerides, total cholesterol and low-density lipoprotein cholesterol levels, and a lower high-density lipoprotein cholesterol level ($P < 0.05$).

Table 1. Clinical characteristics of patients.

Characteristics	MI cases (%)	Controls (%)	χ^2 or t-test	P value
Age (years)				
<50	93 (25.83)	102 (35.79)	0.00	0.99
≥50	167 (46.39)	183 (64.21)		
Gender				
Male	204 (78.46)	219 (76.84)	0.21	0.65
Female	56 (21.54)	66 (23.16)		
Smoking status				
Never	124 (47.69)	176 (61.75)	10.86	<0.05
Current or former	136 (52.31)	109 (38.25)		
Drinking status				
Never	99 (38.08)	159 (55.79)	17.11	<0.05
Current or former	161 (61.92)	126 (44.21)		
Hypertension				
No	104 (40.00)	190 (66.67)	38.92	<0.05
Yes	156 (60.00)	95 (33.33)		
Diabetes				
No	150 (57.69)	223 (78.25)	26.59	<0.05
Yes	110 (42.31)	62 (21.75)		
Triglycerides (mM)	4.26 ± 0.81	3.83 ± 0.71	6.60	<0.05
Total cholesterol (mM)	5.06 ± 1.31	4.78 ± 1.20	2.60	<0.05
LDL-C (mM)	3.34 ± 0.91	2.71 ± 0.88	8.21	<0.05
HDL-C (mM)	1.08 ± 0.29	1.35 ± 0.53	7.28	<0.05

MI = myocardial infarction; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

The genotype distributions of IL-10 -1082A/G and IL-10 -819C/T were found to be in line with the Hardy-Weinberg equilibrium in the control group, but the IL-1β +3954C/T and IL-8 -251T/A distributions were not.

Unconditional regression analyses showed that subjects carrying the GG genotype of IL-10 -1082A/G were associated with increased risk of MI, and the OR (95%CI) was 2.04 (1.15-3.65) (Table 2). However, we found that IL-1β +3954C/T, IL -8-251T/A, and IL-10 -819C/T were not correlated with MI risk.

Table 2. Association between IL-1β +3954C/T, IL-8 -251T/A, IL-10 -1082A/G, and IL-10 -819C/T polymorphisms and myocardial infarction (MI) risk.

Polymorphism	MI cases	Controls	OR (95%CI)[1]	P value
IL-1β +3954C/T				
CC	191 (73.46)	218 (76.49)	1.0 (Ref)	
CT	53 (20.38)	52 (18.25)	1.16 (0.74-1.83)	0.49
TT	16 (6.15)	15 (5.26)	1.22 (0.55-2.72)	0.6
IL-8 -251T/A				
TT	72 (27.69)	89 (31.23)	1.0 (Ref)	
TA	113 (43.46)	119 (41.75)	1.17 (0.77-1.79)	0.44
AA	75 (28.85)	77 (27.02)	1.20 (0.75-1.92)	0.41
IL-10 -1082A/G				
AA	118 (45.38)	155 (54.39)	1.0 (Ref)	
AG	100 (38.46)	103 (36.14)	1.28 (0.87-1.87)	0.26
GG	42 (16.15)	27 (9.47)	2.04 (1.15-3.65)	<0.05
IL-10 -819C/T				
CC	89 (34.23)	108 (37.89)	1.0 (Ref)	
CT	119 (45.77)	126 (44.21)	1.15 (0.77-1.70)	0.48
TT	52 (20.00)	51 (17.89)	1.24 (0.75-2.05)	0.38

[1]Adjusted for gender, age, smoking and drinking status, hypertension, diabetes, triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).

DISCUSSION

Cytokines are modulators of immune responses, and the balance between proinflammatory and anti-inflammatory stimuli plays an important role in the development of atherosclerosis. It is reported that locally higher secretion and concentrations of proinflammatory cytokines can cause severe damage to the epithelium of blood vessels and the surrounding tissues, and cytokines from lymphocytes within the inflamed site can induce more damage. Therefore, genetic polymorphisms of the functional cytokines are associated with increased risk of vascular lesions.

Our study found that the IL-10 -1082A/G polymorphism may be associated with MI risk. Previous studies have reported that the IL-10 -1082A/G polymorphism is associated with the risk of many blood vessel-related diseases, such as ischemic stroke (IS), deep venous thrombosis, and sepsis (Ouyang et al., 2013; Jin et al., 2014; Tang et al., 2014). Jin et al. (2014) conducted a meta-analysis of seven studies and found that the IL-10 -1082A/G polymorphism is associated with IS susceptibility in Asians and the -1082A allele may increase risk of IS in Asians. Tang et al. (2014) conducted a case-control study in a Chinese population and found that the IL-10 -1082A/G polymorphism is associated with risk of deep venous thrombosis. Another meta-analysis study of 11 studies investigated the association between the IL-10 -1082A/G polymorphism and susceptibility to sepsis, and it revealed that the IL-10 -1082A/G polymorphism has an association with susceptibility to sepsis (Ouyang et al., 2013). For the association between the IL-10 -1082A/G polymorphism and cardiovascular disease, one previous meta-analysis with 5006 patients and 3968 controls found that the A allele of the IL-10 -1082A/G polymorphism is associated with increased risk of cardiovascular disease (Wang et al., 2012). Few studies have reported the association between the IL-10 -1082A/G polymorphism and MI risk. Therefore, further well-designed studies are required to confirm the association between the IL-10 -1082A/G polymorphism and MI risk.

Several limitations in this study should be addressed. First, the case subjects and controls were recruited from one hospital, which may not have accurately represented the general population. Moreover, the genetic distributions of IL-1β +3954C/T and IL-8 -251T/A were not in Hardy-Weinberg equilibrium. Selection bias may have existed in our study. Second, the sample size of our study was relatively small, especially in the case subjects, which may have limited the statistical power to determine the difference between the groups. Third, some interaction between the IL-1β, IL-8, and IL-10 gene polymorphisms and environmental factors may have existed in our study, but we did not investigate their association. Therefore, further large sample size studies are required to verify the association between the IL-1β, IL-8, and IL-10 gene polymorphisms and risk of MI.

In conclusion, our study found that the IL-10 -1082A/G polymorphism plays an important role in influencing the development of MI. Further well-designed studies and studies with large sample sizes are required to confirm our results.

Conflicts of interest

The authors declare no conflict of interest.

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