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ORIGINAL ARTICLE

Association of interleukin-6 and interleukin-10 expression, gene polymorphisms, and Takayasu arteritis in a Chinese Han population

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Abstract

Takayasu arteritis (TA) is a chronic inflammatory disease. Interleukin (IL)-6 and IL-10 are important cytokines involved in the immune response of TA in some ethnicities. We investigated whether the single-nucleotide polymorphism (SNP) of IL-6 and IL-10 genes and their expressions were associated with TA in a Chinese Han population. One hundred eighty-four TA patients and 235 healthy controls (HC) were recruited. DNA and RNA were extracted from peripheral blood cells. Genotyping of IL-6 and -10 was performed using polymerase chain reaction-ligase detection reaction (PCR-LDR). The mRNA levels of IL-6 and IL-10 were semi-quantified using reverse transcription polymerase chain reaction (RT-PCR) and real-time polymerase chain reaction (real-time PCR). Plasma levels of them were examined by enzyme-linked immunosorbent assay (ELISA). The mRNA levels of IL-6 in active phase of TA were higher than those in stable phase ($p = 0.015$); the IL-10 in active phase was lower compared with stable phase ($p = 0.046$). Plasma levels of IL-6 in TA were higher than those in HC ($p = 0.024$). Plasma levels of IL-10 showed no difference between the two groups ($p = 0.264$). Plasma levels of IL-6 in active phase were increased than those in stable phase ($p = 0.043$) while those of IL-10 were decreased in active phase ($p = 0.041$). We found no significant differences between TA and HC in the frequency of any of the variations in the SNPs of IL-6 and IL-10 genes. The expression levels of both cytokines were associated with the disease status, indicating that they may serve as potential biomarkers for monitoring disease activity.

Keywords Interleukin-6 · Interleukin-10 · mRNA · Single-nucleotide polymorphism · Takayasu arteritis

Introduction

Takayasu arteritis (TA) is a chronic systemic inflammatory disease of unclear etiology, characterized by stenosis, occlusion, or sometimes aneurysm of large elastic arteries, involving aorta, its main branches, and pulmonary arteries. Although TA has a global distribution, it appears more common in Asian populations [1, 2]. The incidence of TA was estimated 2.4 per million in South Korea, 1–2 per million in Japan, and 2.2 per million in Kuwait [3, 4]. Recent studies indicated that the incidence of TA in Europe ranges from 0.4 to 1.5 per million [4].

Studies regarding the etiology of TA remain rudimentary. Nevertheless, it is acknowledged that a cell-mediated inflammatory response in the arterial wall plays a crucial role in the pathogenesis of TA. Previous studies from our team had shown genetic predisposition and difference in plasma concentration of TA. Individuals with the human leukocyte antigen (HLA)-DRB1*04, HLA-DRB1*07, HLA-DPB1*09, and HLA-DPB1*1701 alleles might be at higher risk for developing TA [5, 6]. The plasma tumor necrosis factor alpha (TNF-α) concentrations were lower in the subjects carrying the -863A allele in the promoter of the TNF-α gene than those without it and increasing plasma level of TNF-α indicated patients in active stage of TA [7]. C-reactive protein and N-terminal pro-brain natriuretic peptide in peripheral blood concentration were increased remarkable with TA patients [8, 9]. Growing evidence suggests that interleukins, a cluster of important inflammatory cytokine, may play critical roles in the pathophysiology of TA. Interleukin (IL)-6 is the main focus of pro-inflammatory cytokines involved in TA. Almost all studies reported higher serum levels of IL-6 in TA patients compared with control subjects. In accordance, active phase was associated with higher IL-6 levels than the stable phase [10,

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11]. IL-10 is a vital anti-inflammatory cytokine that protects the host from excessive immune response in various pathological settings [12]. A lower messenger RNA (mRNA) level of IL-10 was confirmed in peripheral blood mononuclear cells (PBMCs) of India TA patients when their PMBCs were stimulated with phytohemagglutinin (PHA) + phorbol 12-myristate 13-acetate (PMA) [13]. Given the ethnic heterogeneity in TA, further investigation into the expression levels of IL-6 and IL-10 in Chinese Han populations may warrant better understanding of their role in TA.

Gene polymorphism of IL-6 (rs7805828 and rs1546766) was identified as contributing genetic factors for large-vessel arteritis such as giant cell arteritis [14]. In the setting of TA, GG genotype of rs1800795, a single-nucleotide polymorphism (SNP) in the promoter of the IL-6 gene, is more frequent in TA patients in a Turkey population [15]. Recently, a genome-wide association study identified susceptibility loci in IL-6 in TA patients from Turkey and North America [16]. The impact of gene polymorphism of IL-6 on TA in Asian populations, however, was less understood. To the best of our knowledge, whether the SNPs of IL-10 gene correlate with TA also remains unknown. These findings prompted us to further investigate genetic contributions of IL-6 and IL-10 to TA in Chinese Han populations.

The present study investigated the gene polymorphism of IL-6 and IL-10, as well as mRNA and protein expression levels of IL-6 and IL-10 in Chinese Han TA patients.

Material and methods

TA patients and control subjects

This study was designed as a case-control study. The study recruited 184 TA patients and 235 age- and sex-matched healthy controls (HC) in Fuwai Hospital between 2007 and 2010. All patients met the American College of Rheumatology 1990 criteria [17]. TA was classified into four types according to the criteria [18]: type I, arteritis affecting the aortic arch and its major branches; type II, arteritis affecting the thoracic and abdominal aorta; type III, arteritis affecting the whole aorta; and type IV, arteritis affecting the pulmonary artery. The disease activity was assessed according to the NIH criteria [19]. Active phase was defined as a patient presented new onset or appeared at least two of the following features: (1) systemic symptoms without infection; (2) characteristics of vascular ischemia or inflammation, such as bruit, claudication, vascular pain, or asymmetry in pulses or blood pressure; (3) an increase in ESR; and (4) typical angiographic sign. The study was conducted in compliance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the Fuwai Hospital, all participants signed an informed consent.

SNP selection and genotype determination

Genomic DNA was extracted from PBMCs by the salting-out method. We selected tagger SNPs from HapMap database (http://hapmap.ncbi.nlm.nih.gov/) that used a clustering approach (tag SNP Data) to bin SNPs with similar r^2 for one threshold (0.8). One tag SNP was chosen for each cluster bin (frequency > 5%). One common polymorphism of IL-6 gene (rs1800796) and three common polymorphisms of IL-10 gene (rs1800872, rs3790622, rs3021094) were genotyped using Ligase detection reaction. Replicate quality control samples were included and genotyped with more than 99% concordance. Successful rate of genotyping ranged from 96 to 97%.

RNA extraction, RT-PCR, and real-time PCR

Total RNA was extracted from PBMCs using Trizol reagent (Invitrogen) and RNA was used for reverse transcription (RT) (Invitrogen, Super Script III First-strand Synthesis System for RT-PCR) according to the manufacturer's protocols. Real-time PCR analysis for IL-6 and IL-10 cDNA was performed using a BIO-RAD Option 2. β-actin (housekeeping gene) was used as the internal quality control. All experiments were done in triplicates. The data was presented as the fold change in the gene expression normalized to an endogenous reference gene and relative to the healthy control. The threshold cycle (C_T) indicated the fractional cycle number at which the amount of amplified target reached a fixed threshold. ΔC_T was equal to the difference in threshold cycles for target and reference. For the healthy control sample, $\Delta\Delta C_T$ equaled 0 and 2^0 equaled 1, so that the fold change in gene expression relative to the healthy control equaled 1, by definition. For the TA samples, evaluation of $2^{-\Delta\Delta CT}$ indicated the fold change in gene expression relative to the healthy control. $2^{-\Delta\Delta CT} = 2^{-[(CT,\ Target\text{-}CT,\ Actin)\ patient - (CT,\ Target\text{-}CT,\ Actin)\ control]}$. The mean and SD were then determined from the triplicate samples at each time. We quantified gene expression using a $2^{-\Delta\Delta CT}$ method, which is analysis of relative gene expression [20].

Measurement of plasma interleukin-6 and interleukin-10

Blood samples were obtained from TA patients and controls. Plasma specimens were separated by centrifugation at 3000 rpm for 10 min and stored at − 80 °C. Commercial enzyme-linked immunosorbent assay (ELISA) kits were used for the measurements of plasma IL-6 and IL-10 concentrations according to the manufacturer's instructions (R&D Systems, Minneapolis, MN, USA). No significant cross-reactivity or interference was observed. The coefficient of variation of intra-assay and inter-assay was less than 10%.

Statistical analysis

Continuous data are presented as mean ± standard deviation (SD), and categorical data are expressed as total number (percentage). Each polymorphism was examined in the control population to confirm that the distribution of the genotypes conformed to Hardy-Weinberg expectations. The minor allele frequency (MAF) and distribution of genotypes in TA and healthy controls were compared using chi-square test. The odds ratio (OR) was calculated with a 95% confidence interval (CI). The Kolmogorov-Smirnov test was used to evaluate continuous data with non-normal distribution. Independent *t* test was used to assess the difference between groups. A two-sided level of $p < 0.05$ was considered statistically difference using SPSS software package (version 17.0).

Result

Participant characteristics

A total of 184 TA patients and 235 HC of Han Chinese ancestry were recruited for this study. The mean age of TA patients was 34.2 ± 12.6 years and 77.2% were women. Based on NIH criteria, 88 patients were included in the active phase and 96 patients in the stable phase. Table 1 presents demographic and clinical data of the patient and control groups.

mRNA expression of IL-6 and IL-10

We first determined the mRNA expression levels of Han Chinese TA patients in both active and stable phases. We randomly selected 31 patients from the active group and stable group, respectively. Total RNA was extracted from PBMCs and the $2^{-\Delta\Delta CT}$ method was employed for relative quantification of mRNA. The relative quantitative mRNA levels of IL-6 is significantly higher in active phase (3.68 ± 0.25) compared with the stable phase ($p = 0.015$). Conversely, active phase (0.56 ± 0.12) is associated with lower mRNA levels of IL-10 compared with those in the stable phase ($p = 0.046$) (Fig. 1).

Plasma level of IL-6 and IL-10

Next, we examined the plasma concentration of IL-6 and IL-10 in all TA patients, including both active and stable phases (Fig. 2). The mean plasma level of IL-6 in the TA group was significant higher than that in the HC group (8.65 ± 5.75 pg/ml vs 4.77 ± 2.51 pg/ml; $p = 0.024$), whereas no significant difference in plasma levels of IL-10 was observed between the two groups (17.96 ± 9.6 pg/ml vs 30.07 ± 16.31 pg/ml; $p = 0.264$). Further analysis revealed that the active phase is associated with elevated plasma levels of IL-6 than those in stable phase (9.20 ± 4.75 pg/ml vs 5.32 ± 3.16 pg/ml; $p = 0.043$). In contrast, the plasma levels of IL-10 were significantly lower in the active phase than those in the stable phase (17.45 ± 9.0 pg/ml vs 20.93 ± 11.59 pg/ml; $p = 0.041$).

IL-6 and IL-10 genotyping

Given the altered mRNA and plasma levels of IL-6 and IL-10 in TA patients and controls, we further evaluated whether this observation is associated with the frequency of SNP variants in IL-6 and IL-10 genes. The distributions of the IL-6 and IL-10 gene genotypes and alleles are listed in Table 2. Intriguingly, although the minor allele frequency (MAF) of G allele of rs1800796 in IL-6 gene was higher in TA (33.2%) as compared to healthy controls (30.6%), the difference was not statistically significant ($p = 0.461$, OR (95% CI) = 0.893 (0.663–1.204)). Similarly, despite the observation of a rising trend of GG genotype and a declining trend of CC and CG genotype of SNP rs1800796 in TA patients as compared to control subjects (13.6% vs 9.8%,47.3% vs 48.5%,

Table 1 Characteristics of patients with TA and controls

	All TA $n = 184$	Active TA $n = 88$	Stable TA $n = 96$	Controls $n = 235$
Age (year)	34.2 ± 12.6	32.7 ± 12.9	35.3 ± 12.4	38.0 ± 8.2
Female, *n* (%)	142 (77.2)	79 (89.8)	80 (83.3)	156 (66.4)
ESR (mm/h)	18.7 ± 13.2	32.3 ± 15.1*#	7.2 ± 4.9	6.5 ± 4.6
CRP (mg/l)	6.5 ± 3.3	9.4 ± 5.0*#	3.4 ± 2.4	2.1 ± 1.4
Clinical classification, *n* (%)				
Type I	50 (27.2)	20 (22.7)	35 (36.4)	–
Type II	38 (20.7)	25 (28.4)	13 (13.5)	–
Type III	87 (47.3)	32 (36.4)	55 (57.3)	–
Type IV	9 (5.0)	9 (10.2)	0 (0)	–

Data are mean ± SD or number (%). *$p < 0.05$ vs controls; #$p < 0.05$ vs stable. *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein

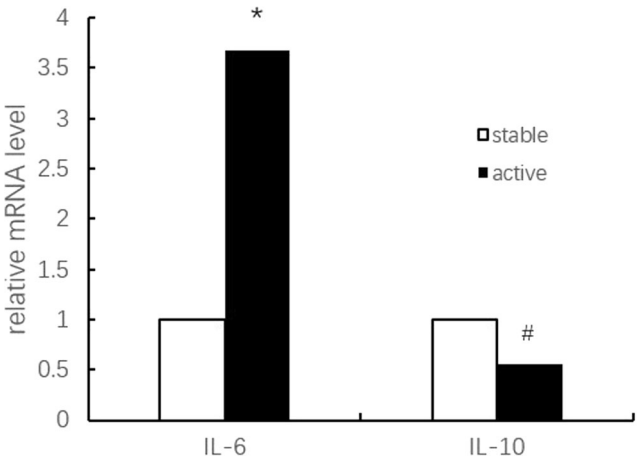

Fig. 1 mRNA of IL-6 and IL-10 expression in active and stable TA. *$p = 0.015$ vs stable, #$p = 0.046$ vs stable

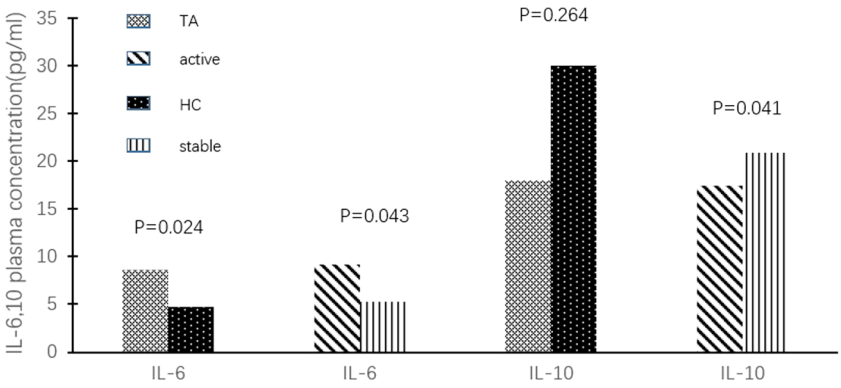

Fig. 2 IL-6 and IL-10 plasma concentration among TA, active TA, and stable TA. *$p = 0.024$ vs controls, = 0.043 vs stale, = 0.041 vs control in sequence; #$p = 0.264$ vs controls

and 39.1% vs 41.7% respectively), we did not find the SNP significantly associated with TA occurrence. In addition, we found no significant differences between TA patients and controls in MAF and the frequency of any of the five variations in the three SNPs of IL-10 gene we studied.

Discussion

TA is an immune-mediated vasculitis with ethnic heterogeneity in incidence and prevalence. Considering the heterogeneous epidemiology of TA globally and the population size of China, it is worthwhile to determine the role of IL-6 and IL-10 in Chinese Han population. Our study demonstrated that the mRNA and plasma expression levels of IL-6 and IL-10 associated with disease conditions in TA. However, SNPs on IL-6 and IL-10 genes did not correlate with TA occurrence and activity in a Chinese population.

IL-6 is a pro-inflammatory cytokine synthesized primarily in activated T cells, monocytes/macrophages, and endothelial cells, which participates in B and T cell activation, fibroblast proliferation, and acute-phase protein synthesis [21]. In our study, we investigated plasma interleukin profiles in TA and evaluated their potential use in understanding disease

Table 2 Frequencies of IL-6 and IL-10 gene genotypes and alleles between TA and controls

Genotype and allele	TA *n* (%)	HC *n* (%)	*p* value	χ^2	OR (95% CI)
IL-6 rs1800796					
CC	87 (47.3)	114 (48.5)	0.466	1.529	
CG	72 (39.1)	98 (41.7)			
GG	25 (13.6)	23 (9.8)			
C	246 (66.8)	326 (69.4)	0.461	0.544	0.893 (0.663–1.204)
G	122 (33.2)	144 (30.6)			
IL-10 rs1800872					
AA	77 (41.8)	105 (44.7)	0.79	0.472	
AC	88 (47.8)	106 (45.1)			
CC	19 (10.3)	24 (10.2)			
A	241 (65.5)	316 (67.2)	0.556	0.346	0.916 (0.683–1.227)
C	127 (34.5)	154 (32.8)			
IL-10 rs3790622					
CC	140 (76.1)	189 (80.4)	0.735	0.614	
CT	43 (23.4)	44 (18.7)			
TT	1 (0.5)	2 (0.9)			
C	326 (88.6)	421 (89.6)	0.621	0.245	0.894 (0.574–1.293)
T	42 (11.4)	49 (10.4)			
IL-10 rs3021094					
AA	57 (31.0)	72 (30.6)	0.909	0.192	
AC	92 (50)	114 (48.5)			
CC	35 (19.0)	49 (20.9)			
A	206 (56.0)	259 (55.1)	0.761	0.093	1.044 (0.791–1.379)
C	162 (44.0)	211 (44.9)			

pathogenesis and monitoring disease activity. We found that all the patients with TA had elevated plasma concentration of IL-6 compared to control subjects. Plasma levels of IL-6 in the active phase were higher than those in the stable phase. In accordance with our findings, studies from other research groups also demonstrated a similar trend in IL-6 expression patterns in TA [10, 22, 23]. What is more, IL-6 was also highly expressed in affected vessel from TA patients with active disease compared to TA patients in remission [23]. Indeed, IL-6 may exert central regulatory effects in the pathophysiology of TA. More importantly, the constellation of these data suggests IL-6 as a potential biomarker for monitoring disease activity in multiple ethnic groups including Chinese Han population.

IL-10 plays a key role in downregulating the immune and inflammatory responses in vasculitis pathogenesis by inhibiting the production of the pro-inflammatory cytokines and mediators from macrophages and dendritic cells [24]. Active phase of TA patients was associated with lower IL-10 level compared to those in stable phase and long-term remission of TA was associated with increasing IL-10 level [25]. We also found a marked decreased in plasma levels of IL-10 in the active phase of TA compared with the stable phase. This indicated an inverse association between IL-10 and disease activity in TA.

Our data conflicts with a previous study showing that SNP rs1800795 on IL-6 genes was linked to TA in a Turkish population [15]. We revealed that SNPs on both IL-6 and IL-10 genes showed negative correlation with TA in a Chinese Han population. Although this may result from limited sample size and difference in methodological procedures, it also supports the hypothesis that ethnic heterogeneity plays a critical role in the disease. In line with our study, the SNP rs1800795 (IL-6 gene) exhibited no susceptibility to TA in an Asian Indian population [26]. Furthermore, in a recent study, Wen et al. demonstrated that SNP rs2069837 on IL-6 gene also showed no between-group differences [27]. Intriguingly, we for the first time have shown that SNPs on IL-10 did not significantly correlate with TA. However, whether this finding applies to other ethnic groups remains to be explored. Together, these results indicate that, at least in Chinese Han ethnic, SNPs on both IL-6 and IL-10 did not impact on genetic susceptibility to TA. Notably, it also suggested that ethnic variation should be considered when interpreting the clinical significance of SNPs on other genes in TA patients.

In conclusion, we confirmed the relevance of these two cytokines and TA disease activity in a Chinese Han population, suggesting that IL-6 and IL-10 may be used as potential biomarkers for disease activity monitoring. Additionally, no evidence for association between SNPs on IL-6 and IL-10 genes and the presence of TA in the Chinese Han population studied was observed. To verify that genetic variations contributed to differences in TA onset and progression, larger study sample size from multiple ethnicities is needed in future studies.

Compliance with ethical standards

The study was conducted in compliance with the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the Fuwai Hospital; all participants signed an informed consent.

Disclosures None.

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