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Original Article

Study on correlation between IL-33 serum level, IL-33 gene single nucleotide polymorphism and systemic lupus erythematosus

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Abstract: Objective: To compare the alleles and genotype frequencies of IL-33 rs1891385 SNP loci as well as the expression level of IL-33 in peripheral serum between patients with systemic lupus erythematosus and healthy controls, and investigate the correlation between IL-33 rs4012455 SNP loci, level of IL-33 in serum and systemic lupus erythematosus disease. Methods: A total of 77 patients with systemic lupus erythematosus who were hospitalized in Department of Rheumatism and Immunology of our hospital were in included in the study as case group. 71 cases of healthy volunteers were enrolled as normal control group. Peripheral venous blood was collected and DNA was extracted from the subjects. TaqMan probe and PCR ABI7300 were used to detect the alleles and genotype frequencies of IL-33 rs1891385 SNP loci in subjects of both groups. The χ^2 test or exact probability method were used to compare the distribution of alleles and genotype frequencies between two groups; Stata 10.1 software was used for analysis of Hardy Weinberg equilibrium. ELISA kit was used to detect the expression level of IL-33, and SPSS 17.0 statistics software was used for analysis where $P<0.05$ was considered as significant differences. Results: The genotype frequencies of AA, AC and CC were 31%, 47.9% and 21.1% in the control group, and 35.1%, 45.5% and 19.4% in the case group. With C/C genotype as a reference, there was no statistically significant difference in genotype frequency distribution between two groups. The genotype frequencies of A and C alleles were 59.7% and 40.3% in case group, and 56.3% and 43.7% in the control group; with no significant differences in allele frequency distribution. IL-33 rs1891385 A allele frequency in serositis patients was lower than that in non-serositis patients (OR=0.527, P=0.017). However, A allele frequency had no statistical correlation with other clinical manifestations of SLE such as discoid erythema, zygomatic erythema, arthritis, and oral ulcer. There was no significant difference in the level of serum IL-33 between the case group and the normal group, but there was statistical difference in the serum IL-33 level between the patients with nephritis and patients without nephritis. IL-33 level was correlated with some laboratory test indexes in patients with SLE. Conclusion: There was no statistical correlation between rs IL-33 1891385 gene polymorphism and SLE genetic susceptibility. A allele in rs1891385 may play a protective role in SLE patients with comorbid serositis, and the expression level of serum IL-33 was correlated with part inspection indexes in SLE patients.

Keywords: Systemic lupus eythematosus (SLE), IL-33, single nucleotide, polymorphism

Introduction

Systemic Lupus Erythematosus (SLE) is a kind of systemic multi-organ autoimmune connective tissue disease [1]. At present, the pathogenesis of SLE has not been fully clarified. It is generally believed that the pathogenesis of SLE includes environment, genetic and endocrine factors. Studies suggest that immune system disorders play an important role in the development of SLE [2, 3]. Cytokines play a promoting role in the activation, maturation and differentiation of a variety of immune cells, not only involved in the immune regulation of systemic lupus erythematosus, but also involved in the inflammatory response of tissue injury. Abnormal expression of cytokines and network imbalance exist in the pathogenesis progress of SLE. Studies have shown that IL-6, IL-17, IL-10, TNF-α and other cytokines are associated with the development of SLE, and some cytokines can be used as the biological signs of SLE and potential therapeutic targets [4, 5].

IL-33 is recently discovered as a new member of the IL-1 subfamily [6], with a regulatory role

for a variety of immune cells. Recent studies have shown that IL-33/ST2 pathway plays an important role in the occurrence and development of systemic vasculitis [7, 8]. Mutations of IL-33 rs1891385 A to C may affect the expression of IL-33. Previous studies have indicated that IL-33 rs1891385 polymorphism is associated with susceptibility to ankylosing spondylitis [9]. However, there is no report about the correlation between IL-33 gene polymorphism (rs1891385) and SLE at present. Therefore, this research aims to compare IL-33 gene single nucleotide polymorphism and serum IL-33 expression between SLE patients and normal controls, explore the association between IL-33 and systemic lupus erythematosus, and provide experimental basis for regarding IL-33 as biological monitoring index of SLE onset and potential therapeutic targets.

Material and methods

Study objects

From December 2014 to March 2015, 77 patients with SLE were admitted to rheumatology department in our hospital. Their diagnosis was in accordance with the SLE diagnostic criteria established by the American College of Rheumatology (ACR) in 1997. These patients included 39 males and 38 females, aged 47-75, (61.7±14.7) years old on average, with a disease duration of 0.7 to 15 years, and (27±5.4) months on average. The patients with other systemic diseases, confusion or coma, or those that can not cooperate were excluded in the study. In addition, 71 healthy volunteers in health examination center of our hospital were selected as normal control group, including 33 males and 38 females matched age and gender with the case group. Inclusion criteria in normal control group: do not meet any diagnostic criteria for SLE; no long-term drugs application of immunosuppressive agents, hormones ect.; no family history of autoimmune disease; no major disease; no significant difference in gender and age between two groups. Patients in both groups had informed consent to this study.

Methods

Genomic DNA extraction: 5 ml peripheral venous blood in subjects was collected; DNA was extracted and purified with EDTA anticoagulation, proteinase K digestion and salting out extraction method, and frozen in refrigerator under 80°C for standby.

Design and synthesis of primers: primers rank was designed according to the GenBank sequence, the forward primer: 5'-CCACATTATCCCTCACAGCACCTC-3', the reverse primer: 5'-AAGAGAACAATGGCTGGCAGGA-3', and they were used to be synthesized.

PCR reaction: dNTPs (2.5 mol/L) 0.5 μL, 0.4 μL for each primer, 10 * PCR buffer solution 2.5 μL, TaqDNA polymerase 0.3 μL, DNA template 1 μL, ddH2O 19.9 μL, applied in ABI 7300 PCR amplification instrument (USA) for amplification. Amplification conditions: 95°C pre-denaturation for 4 min, 94°C degeneration for 30 s, 55°C pre-annealing for 40 s, 72°C extension for 1 min, circulation for 40 times, and 72°C extension for 7 min finally.

PCR-RFLP analysis of single nucleotide polymorphism in rs1891385 loci: PCR products were mixed into the restriction enzyme reaction system, reacted at 37°C for 18 h, and then 2% agarose gel electrophoresis was used to determine the genotype results. The wildtype was AA genotype; the mutant type was CC genotype; and the heterozygote type was AC genotype.

Sequencing verification: after the results were obtained by PCR-RFLP enzyme, 10 samples were selected randomly from each genotype, and the PCR products were sequenced by using positive and negative bidirectional sequencing methods for verification.

Determination of serum IL-33

5 mL venous blood was extracted in the fasting state from the patients in case group and normal control group. With the use of EDTA anticoagulant, serum was separated by 1500 rpm * 5 min, and then placed in -80°C refrigerator for standby use. Enzyme-linked immunosorbent assay (ELISA) was used to detect the concentration of serum IL-33. The sample, reference standard product, and HRP-labeled detection antibody were added in turn to microwells precoated with IL-33 antibody. Then they were incubated and washed thoroughly. The OD value of each microwell was determined at 450 nm wavelength after coloration, and the stan-

Table 1. Clinical characteristics of systemic lupus erythematosus

Clinical characteristics	Positive cases	Proportion (%)
Discoid erythema	8	10.39
Malar erythema	35	45.45
Arthritis	47	61.04
Oral ulcers	16	20.78
Serositis	13	16.9
Nervous system damage	11	14.29
Renal injury	33	42.86

Table 2. Comparison of genotype and allele frequency of IL33 gene rs1891385 loci between two groups

rs4012455	Cases (n=77/%)	Controls (n=71/%)	P	OR (95% CI)
Genotype				
A/A	27 (35.1)	22 (31.0)	0.348	0.851 (0.462-1.127)
A/C	35 (45.5)	34 (47.9)	0.186	0.825 (0.618-1.286)
C/C	15 (19.4)	15 (21.1)	1.00	
Alleles				
A	46 (59.7)	40 (56.3)	0.448	1.239 (0.944-1.135)
C	31 (40.3)	31 (43.7)	1.0	-

dard curve was drawn to calculate the concentration of each sample.

The statistical analysis

SPSS 19.0 software was used for statistical data analysis, and measurement data were expressed with mean±standard deviation. The two groups were compared by using t test, and whether the IL-33 rs1891385 genotype of both groups complies with HWE was verified by using Stata 11.0 software. The correlation between distribution difference, allele and genotype frequency of IL-33 rs1891385 and common clinical manifestations of SLE was verified by using χ^2 test or Fisher exact test. $P<0.05$ was considered with statistically significant difference.

Results

The clinical data of study and HWE test

The main clinical manifestations of SLE patients were: renal injury (33 cases, 42.86%), malar erythema (35 cases, 45.45%), arthritis (47 cases, 61.04%), discoid erythema (8 cases, 10.39%), oral ulcers (16 cases, 20.78%) (**Table 1**). The results of Hardy-Weinberg equilibrium test in two groups suggested that rs1891385 genotype frequencies of case group and control group were consistent with HWE equilibrium (case group: $\chi^2=1.186$, $P=0.295$; control group: $\chi^2=0.002$, $P=0.985$).

Comparison of genotype and allele frequency distribution of IL-33 gene rs1891385 locus between two groups of patients

IL-33 gene rs1891385 loci were genotyped by using ABI 7300 PCR amplification device, and the results were as follows: the genotype frequency of group A/A, A/C and C/C in two groups: normal control group-31.0% (22 cases), 47.9% (34 cases) and 21.1% (15 cases); case group-35.1% (27 cases), 45.5% (35 cases) and 19.4% (15 cases). With genotype C/C as a reference, the distribution of genotype frequencies between the two groups was not statistically significant. With C allele as a reference, the difference in allele frequency distribution was also not statistically significant (**Table 2**).

Relationship between polymorphism of IL-33 gene rs1891385 and clinical characteristics of SLE

There was no statistical association between clinical characteristics of Malar erythema, arthritis and dlisoid lupus and rs1891385 alleles ($P>0.05$). 13 patients in case group had serositis in case group, with A allele frequency of 61.5%, and in 64 patients without serositis, A allele frequency was 73.4%. A allele frequency in patients with serositis was lower than that in patients without serositis, with statistically significant difference between two groups (OR= 0.527, 95% CI=0.312-0.908, and $P=0.017$). See **Table 3**.

Detection of the serum IL-33 level in two groups

ELISA results showed that the concentration of IL-33 in peripheral serum was 57.25±10.25 pg/mL in patients with SLE, and was 54.32±11.04 pg/mL in normal control group, with no statistically significant difference (t=-1.864, $P=0.071$).

Table 3. Correlation analysis between allele frequency of rs1891385 and SLE clinical characteristics

Clinical characteristics		Allele frequency (%)		OR (95% CI)	P
		A	C		
Dlisoid lupus	+	6 (75%)	2 (25%)	0.784 (0.601-1.156)	0.382
	-	50 (72.5%)	19 (27.5%)		
Malar erythema	+	24 (68.6%)	11 (31.4%)	1.410 (0.976-2.261)	0.087
	-	29 (69.0%)	13 (31%)		
Arthritis	+	34 (72.3%)	13 (27.7%)	0.965 (0.748-1.237)	0.815
	-	22 (73.3%)	8 (26.7%)		
Oral ulcer	+	12 (75%)	4 (25%)	1.128 (0.827-1.547)	0.412
	-	44 (72.1%)	17 (27.9%)		
Serositis	+	8 (61.5%)	5 (38.5%)	0.527 (0.312-0.908)	0.017
	-	47 (73.4%)	17 (26.6%)		
Nervous system damage	+	7 (63.6%)	4 (36.4%)	0.735 (0.514-1.082)	0.076
	-	44 (66.7%)	22 (33.3%)		
Renal injury	+	24 (72.7%)	9 (27.3%)	0.918 (0.714-1.158)	0.497
	-	31 (70.5%)	13 (29.5%)		

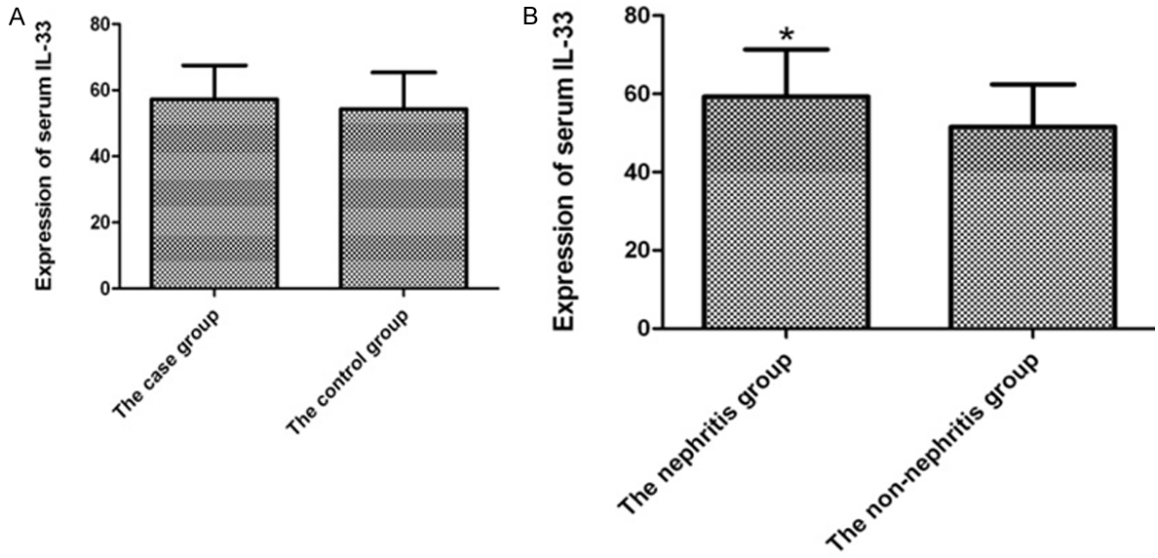

Figure 1. Comparison of serum IL-33 level between different groups. A: Cases group vs control group; B: Nephritis group vs non-nephritis group. **P<0.05.*

The concentration of IL-33 in serum was 59.32±12.02 pg/mL in SLE+ nephritis group and 51.54±10.86 pg/mL in non-nephritis group, with statistical difference between two groups (t=-2.554, *P*=0.010). See **Figure 1** and **Table 4** for details.

Correlation between the serum IL-33 level and clinical characteristics in patients with SLE

The serum IL-33 level was compared between the negative group and the positive group, and the results showed that except renal injury (*P=0.007*), other clinical characteristics had no significant difference between two groups (*P>0.05*). See **Table 5** for details.

Correlation between serum IL-33 level and other laboratory parameters in patients with SLE

Pearson correlation analysis results indicated that: the expression levels of serum IL-33 were correlated with anti-dsDNA antibody (r=0.762, *P*=0.000), complements reduction (r=0.572,

Table 4. Comparison of serum IL-33 level between different groups

Group	Number	The serum IL-33 level (pg/mL)	T	P
Case group	77	57.25±10.25	-1.864	0.071
Control group	71	54.32±11.04		
Nephritis group	33	59.32±12.02	-2.554	P=0.010
Non-nephritis group	44	51.54±10.86		

Table 5. Correlation between the serum IL-33 level and clinical characteristics of SLE

Clinical characteristics	+/-	Serum IL-33 level	T	P
Dlisoid lupus	+	46.19±10.76	0.117	0.907
	-	47.39±11.62		
Malar erythema	+	47.18±11.72	0.326	0.718
	-	46.95±11.97		
Arthritis	+	46.55±11.87	0.686	0.477
	-	48.39±11.47		
Oral ulcer	+	46.18±11.21	0.511	0.614
	-	47.56±12.11		
Serositis	+	38.97±11.68	1.264	0.203
	-	43.58±11.52		
Nervous system damage	+	41.64±10.04	1.189	0.214
	-	47.48±11.68		
Renal injury	+	47.45±11.21	-2.742	0.007
	-	37.11±11.67		

Table 6. Correlation between serum IL-33 level and laboratory parameters in patients with SLE

Clinical Indicators	Anti-dsDNA antibody	Complements reduction	Increased erythrocyte sedimentation rate	Proteinuria
r	0.762	0.572	0.665	0.814
P	0.000	0.001	0.000	0.000

P=0.001), increased erythrocyte sedimentation rate (r=0.665, *P*=0.000), and proteinuria (r=0.814, *P*=0.000) in SLE patients, but were not significantly correlated with anti-nuclear antibodies, anti-Sm antibodies, anti-SSA antibodies, anti-SSB antibodies and other indicators. See **Table 6**.

Discussion

SLE is a kind of autoimmune disease mediated by CD_4^+ lymphocytes [10]. At present, its pathogenesis has not been fully clarified. Now it is mostly believed that it is related to genetic factors and environmental factors. Their interaction causes dysfunction of the body's cellular immune and humoral immune system, damages the body's normal mechanism of immune tolerance, causes the immune system to attack its own tissues and organs, and thus leading to the occurrence and development of SLE [11, 12]. The cytokines in the humoral immune system are a kind of micro molecular protein. They have a variety of physiological functions, playing an important role in the process of cell signal transduction, in cell proliferation and differentiation, as well as in the regulation of the immune system. The results show that there is a close relationship between the occurrence and development of SLE and cytokines, and the level of cytokines in most of SLE patients is abnormal [13, 14]. Clinical studies have reported that the levels of tumor necrosis factor-α (TNF-α), interferon, and interleukin in SLE patients are increased to different extents, and their levels were significantly positively correlated with the severity of SLE and the degree of activity [15-17]. Studies have shown that IL-1β is highly correlated with SLE disease activity, and it is significantly elevated in patients with SLE complicated with renal disease [18]. In the study of African American populations, IL-6 polymorphism is related with SLE susceptibility [19]. In the Korean population, systemic sclerosis may be associated with levels of IL-17 and IL-23 [20]. However, the role of IL-33 in the occurrence and development of SLE has not been reported.

IL-33 is one of the newest members of the IL-1 family, which was discovered in 2005 as a ligand of orphan receptor ST2. Human IL-33 gene is located on chromosome 9, and its mRNA expression is present in a variety of tissues and organs. In recent years, with the deepening of research, IL-33 is found to play multiple roles in the disease [21]. On one hand,

it can aggravate the pathological damage of inflammatory diseases mediated by Th2 and mast cells, and on the other hand, it promotes Th2 response to participate in the prevention and treatment of cardiovascular disease and parasitic infections. Other studies have shown that, in addition to participation in Th2-type immune response, IL-33 can also regulate Th1-type cytokines participation in the immune response of the disease [22, 23], indicating that IL-33 expression and function are present in a variety of immune cells, and involved in regulating multiple immune responses, with a wide range of biological effects. Currently, more and more studies show that IL-33 is present in a wide range of rheumatic diseases, suggesting that it plays a role in rheumatic diseases.

In this study, the gene frequency of AA, AC and CC was 31.0%, 47.9% and 21.1% respectively in the control group; 35.1%, 45.5% and 19.4% respectively in the case group. With genotype C/C as a reference, there was no significant difference in genotypes distribution Between two groups. The gene frequency of A and C allele was 59.7% and 40.3% in the case group, and was 56.3% and 43.7% respectively in the control group, with no significant difference in allele frequencies distribution between two groups. There were no significant differences in serum IL-33 level between SLE patients and control group, but the serum IL-33 level in nephritis patients was significantly higher than that in non-nephritis patients, which was basically consistent with other studies reported by Mok, et al. Kidney is the most commonly affected target organ, suggesting that IL-33 may be involved in the occurence and development of systemic lupus erythematosus. The analysis results of relationship between serum IL-33 expression levels and systemic lupus erythematosus clinical characteristics showed that, there was no significant difference in IL-33 levels among other subgroups except in renal injury. In further analysis of the relationship between serum IL-33 levels and systemic lupus erythematosus laboratory indicators, it was found that IL-33 level was significantly correlated with anti-ds-DNA antibodies (r=0.762, *P*=0.000), complement reduction (r=0.572, *P*=0.001), increased erythrocyte sedimentation rate (r=0.665, *P*=0.000), and proteinuria (r=0.814, *P*=0.000). However, the specific system needs further study. The studies by Yang et al [24] showed that serum IL-33 level was correlated with ESR and CRP in patients with systemic lupus erythematosus, suggesting that IL-33 was involved in acute phase response of systemic lupus erythematosus, but was not involved in the entire pathogenesis of systemic lupus erythematosus. Complement is one of the clinical indexes to assess the disease, remission and recurrence in patients with systemic lupus erythematosus disease. This study showed that IL-33 was related to disease activities, which was consistent with the results reported by Li et al [25].

In summary, although this study failed to find the correlation between IL-33 rs1891385 gene polymorphism and systemic lupus erythematosus, this could not suggest that this locus was not associated with systemic lupus erythematosus susceptibility: ① Population of this study was only restricted to Han population within this province, with certain personnel limitations; ② The study did not cover all of IL-33 gene SNP loci; ③ The sample size was still inadequate, and the correlation findings still need to be confirmed by further research. Therefore, we still need to further expand the sample size or use a large sample multi-center experiment to verify a major role of genetic variation in systemic lupus erythematosus pathogenesis, and provide experimental basis for early diagnosis of systemic lupus erythematosus.

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Disclosure of conflict of interest

None.

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