Polymorphisms in the Promoter Region of RANTES and the Regulatory Region of Monocyte Chemoattractant Protein-1 Among Chinese Children with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** Chemokines play an important role in the physiology and pathophysiology of acute and chronic inflammatory processes. We investigated whether chemokines such as RANTES (regulated upon activation, normally T cell expressed and secreted) promoter and monocyte chemoattractant protein-1 (MCP-1) regulatory polymorphisms were associated with systemic lupus erythematosus (SLE) in Chinese children.

Methods. Forty-six patients with SLE and 107 healthy children of comparable ages were studied for genotypes with polymerase chain reaction-based assays.

Results. The frequency and distribution of genotypes of the –28(C/G) RANTES gene polymorphism were significantly different between the 2 groups ($p < 0.001$), and the RANTES –28G allele was significantly more frequent in patients with SLE than in healthy controls (23.9% vs 11%; $p = 0.006$, OR 2.37, 95% CI 1.25–4.28). There was no significant difference in the frequency or in the distribution of genotypes of the –2518(A/G) MCP-1 and the –403(G/A) RANTES gene polymorphisms between patients and controls ($p = 0.32$ and $p = 0.19$, respectively). The RANTES –28G allele was also significantly associated with higher initial levels of antinuclear antibody, lower levels of C3, and higher incidences of central nervous system lupus.

Conclusion. In the Chinese population, children with RANTES –28C/G polymorphisms have increased risk of developing SLE. Healthy controls with the C/G or G/G genotype were 2.37 times more likely to have SLE compared to those with the C/C genotype. (J Rheumatol 2004;31:2062–7)

Key Indexing Terms:
CHEMOKINE CYTOKINE POLYMORPHISM CHINESE LUPUS SYSTEMIC LUPUS ERYTHEMATOSUS CENTRAL NERVOUS SYSTEM

Chemotactic cytokines (chemokines) are small signaling proteins that are released by a variety of cells and are involved in the pathophysiology of inflammatory processes, through the process of attracting and stimulating specific subsets of leukocytes, adhesion of cells, and penetration across the endothelial cells. Chemokines, such as regulated upon activation, normally T cell expressed and secreted (RANTES) and monocyte chemoattractant protein-1 (MCP-1), are responsible for the recruitment of monocytes and T lymphocytes in both the acute and chronic phases of inflammation[1]. The RANTES and MCP-1 genes are located on human chromosome 17[2,3]. RANTES is associated with Th1 cytokine-related immune response *in vitro* and MCP-1 contributes more to the Th2 than Th1 cytokine-mediated inflammation *in vivo*[4,5].

RANTES is produced from various cell types, including CD8+ T cells, CD4+ T cells, monocyte/macrophages, and renal tubular epithelium after cellular activation by stimuli and cytokines such as tumor necrosis factor-α (TNF-α) and interleukin 1ß (IL-1ß) stimulation[6-8]. Although RANTES has some attractive effect on neutrophils[9] and eosinophils[10], its action largely causes the selective migration of monocytes and memory T lymphocytes[11]. There are 2 functional polymorphisms in the proximal promoter region of the RANTES gene (–28 C to G and –403 G to A) that increase transcriptional activity and subsequent RANTES expression in human cell lines[12,13]. Yao, *et al*[14] showed that the RANTES –28G allele is associated with asthma severity in Chinese children, while Liu, *et al*[12] reported that the

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RANTES –28G allele increases RANTES expression in individuals with human immunodeficiency virus (HIV-1), thus delaying the progression of HIV-1 disease. Nickel, *et al*[13] have reported that the RANTES –403A allele is associated with increased susceptibility to atopic dermatitis in German children. These studies imply that the polymorphisms in the promoter of RANTES play an important role on the pathogenesis of inflammatory disease.

The MCP-1 –2518G allele in the regulatory region increases transcriptional activity[15]. MCP-1 is suggested to be responsible for tissue inflammation in autoimmune diseases because of its tissue expression in human and experimental autoimmune models[16-19].

Development of systemic lupus erythematosus (SLE) is influenced by multiple genetic and environmental factors. It is a disorder of immune regulation manifested by polyclonal B cell activation, leading to the production of autoantibodies, activation of the complement system, and generation and deposition of immune complexes. These stimuli also induce the infiltration of mononuclear leukocytes. The migration of mononuclear leukocytes through vessels and tissues is dependent in part on chemokines in the inflammatory response[20-22].

Given the importance of MCP-1 and RANTES in inflammation, we hypothesized that RANTES promoter and MCP-1 regulatory polymorphisms that influence the expression of these chemokines are risk factors for SLE. We investigated the frequency of the RANTES –28C/G and –403G/A and MCP-1 –2518A/G polymorphisms in a cohort of Chinese children.

MATERIALS AND METHODS

Subjects. From 1994 to 2002, 46 children with SLE were enrolled for study: 40 girls and 6 boys with a mean age of 14.8 years (range 9–18 yrs). Diagnosis was made according to the revised American College of Rheumatology criteria for the classification of SLE[23]. As well, 107 healthy children of comparable ages were also enrolled as controls. There were no blood relations among the 46 patients with SLE and the 107 healthy children. Disease activity was determined using the SLE Disease Activity Index (SLEDAI)[24].

Our patients were divided into 2 groups: patients who showed a score ≥ 6 in the SLEDAI were defined as having active disease; patients who had a SLEDAI score < 6 were defined as inactive disease. Twenty-six patients had active disease and 20 had inactive disease. Among all patients, 21 had hypertension, defined when the average of 3 separate systolic blood pressures was > 95% for age and sex. Eight patients with SLE initially presented with neurologic involvement, with cerebral hypoperfusion confirmed by cranial single photon emission computed tomography[25]. Lupus nephritis in 26 patients was proven when one of the following criteria was observed: positive renal biopsy or persistent proteinuria > 0.5 g per day. The disease duration ranged from 12 months to 9 years (mean 50 ± 28.5 mo).

ELISA for RANTES chemokines. Blood samples from patients with SLE were centrifuged and serum was frozen at –80°C until testing. The serum concentrations of RANTES chemokines in patients with SLE were determined by a sandwich ELISA method (R&D Systems, Minneapolis, MN, USA)[26]. Optical density at 450 nm was measured on an automated plate reader (Model 35550-UV Microplate Reader; Bio-Rad, Hercules, CA, USA), and chemokine levels were determined by comparison to the standard curve obtained using commercial recombinant chemokines.

Genotyping. Total genomic DNA was extracted from white blood cells of SLE patients and healthy controls using the Easy Pure Genomic DNA Purification Kit (Bioman Scientific Co., Taipei, Taiwan).

The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay was used to genotype SLE patients and controls for RANTES and MCP-1[14,27]. The RANTES –28 genotype was determined using a *Hinc*II site introduced with a mismatch into the PCR primer next to the C/G transition. Amplification with the primers RANTES-50S: 5'-ACT CCC CTT AGG GGA TGC CCG T-3', which has a guanine instead of a cytosine (underlined), and RANTES124AS: 5'-GCG CAG AGG GCA GTA GCA AT-3' generated a 175 bp product. Digestion with *Hinc*II yields 152 and 23 bp fragments when C is at position –28.

The –403 genotype was determined using an *Rsa*I site introduced with a mismatch into the PCR primer next to the G/A transition. Amplification with the primers RANTES-581S: 5'-CAC AAG AGG ACT CAT TCC AAC TCA-3' and RANTES-376AS: 5'-GTT CCT GCT TAT TCA TTA CAG ATC GTA-3', which has a guanine instead of a thymine (underlined), generated a 206 bp product. Digestion with *Rsa*I yields 180 and 26 bp fragments when G is at position –403.

PCR amplification was carried out under the following cycling conditions: 94°C for 5 min followed by 35 cycles of 94°C for 1 min, 55°C for 1 min, and 72°C for 55 s, and a final extension at 72°C for 10 min. PCR products were digested, respectively, with *Hinc*II and *Rsa*I (Roche Diagnostics, Mannheim, Germany) at 37°C overnight. The products of each PCR and restriction enzyme digestion were examined following electrophoresis on a 3% agarose gel stained with ethidium bromide. The MCP-1 –2518 genotype was determined using a *Pvu*II site affected by the G/A polymorphism. Amplification with the primers MCP417S: 5'-TCT CTC ACG CCA GC ACT GAC C-3' and MCP650AS: 5'-GAG TGT TCA CAT AGG CTT CTG-3' generated a 234 bp product. Digestion with *Pvu*II yields 159 and 75 bp fragments when G is at position –2518.

PCR amplification was carried out under the following cycling conditions: 94°C for 5 min followed by 40 cycles of 94°C for 1 min, 52°C for 1 min, and 72°C for 45 s, and a final extension at 72°C for 10 min. PCR products were digested with *Pvu*II at 37°C overnight. The products were separated in 3% agarose gel and stained with ethidium bromide.

Statistical analysis. The genotypic and allelic frequencies for the different groups were calculated by direct counting. Statistical comparisons were by chi-square test for categorical data on 2 × 3 or 2 × 2 contingency tables, and by the Wilcoxon rank-sum test for continuous data using the SPSS statistical package (SPSS 10.0 for Windows; SPSS, Chicago, IL, USA). Odds ratios (OR) with 95% confidence intervals (CI) were measured for the risk of each genotype in SLE. A p value < 0.05 was considered statistically significant.

RESULTS

Table 1 shows the distribution of gene polymorphisms in the 2 groups of children. Significant difference was observed in the frequencies of the –28G polymorphism in the gene promoter region of the RANTES between SLE cases and controls (23.9% vs 11.7%; p = 0.006, OR 2.37, 95% CI 1.25–4.28), and the distribution of the genotype frequencies of –28(C/G) RANTES gene polymorphism were significantly different in the cases and in the controls (p < 0.001). Healthy controls with C/G or G/G genotype were 2.37 times more likely to have SLE compared to those with C/C genotype. There was no other significant difference in the frequency of genotypes of the –2518(A/G) MCP-1 and the –403(G/A) RANTES gene polymorphisms between SLE

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Table 1. Genotype and allele frequencies for MCP-1 –2518, RANTES –28, and RANTES –403 in children with SLE and healthy controls.

Polymorphism	N	Genotype			p	Allele Frequencies	Difference Between Allele Frequencies	
							p	OR (95% CI)*
MCP-1 –2518 A/G (%)		A/A	A/G	G/G		G		
SLE	46	10 (22)	25 (54)	11 (24)	0.321	51%	0.96	0.99 (0.61–1.61)
Control	107	30 (28)	44 (41)	33 (31)		51.4%	1.0	—
RANTES –28 C/G (%)		C/C	C/G	G/G		G		
SLE	46	34 (74)	2 (4)	10 (22)	< 0.001	23.9%	0.006	2.37 (1.25–4.28)
Control	107	83 (77.6)	23 (21.5)	1 (0.9)		11.7%	1.0	—
RANTES –403 G/A (%)		G/G	G/A	A/A		A		
SLE	46	19 (41)	22 (48)	5 (11)	0.192	35%	0.073	1.62 (0.95–2.75)
Control	107	60 (56)	41 (38)	6 (6)		24.8%	1.0	—

* OR (odds ratio) for the C/G or G/G genotype indicates that persons who have either of these genotypes are 2.37 times more likely to have SLE; reference group (controls) designated with an OR of 1.0. MCP-1: Monocyte chemoattractant protein-1; RANTES: regulated upon activation normal T cell expressed and secreted.

patients and controls. Although the difference in the allelic frequency of the RANTES –403A polymorphism was near the significant level (p = 0.073, OR 1.62, 95% CI 0.95–2.75), there was no difference in the distribution of genotype frequencies between cases and controls.

Clinical characteristics were compared between the SLE patients with –28 C/C RANTES gene and patients with –28 C/G or G/G gene polymorphisms (Table 2). Patients with the C/G or G/G genotype at RANTES –28 had significantly higher initial mean levels of antinuclear antibody (ANA) and lower initial mean levels of C3 (28.5 vs 43 mg/dl; p = 0.044) than patients with the C/C genotype. There was no significant difference in the levels of initial anti-dsDNA (p = 0.10), C4 (p = 0.093), and SLEDAI score (p = 0.37) between the 2 groups. The SLE patients with –28 C/G or G/G gene polymorphisms had a significantly higher rate of central nervous system (CNS) lupus, although there was no significant difference in the distribution of the different genotypic frequencies of –2518 MCP-1, –28 RANTES, and –403 RANTES in SLE patients with or without hypertension, lupus nephritis, arthritis, and rashes.

Serum levels of RANTES in patients with SLE were also measured. There was no significant difference in the serum levels of RANTES between the SLE patients with the –28 C/C RANTES gene and patients with –28 C/G or G/G gene polymorphisms (16.01 ± 12.74 vs 16.67 ± 10.57 ng/ml; p = 0.87). Moreover, these patients with various genotypes of RANTES –403 had similar serum RANTES levels. The serum RANTES levels in patients with active SLE were also not significantly higher than in those with inactive SLE (17.62 ± 13.83 vs 14.40 ± 9.43 ng/ml; p = 0.37).

DISCUSSION

The genetic basis of SLE is currently unclear. Gaffney, *et al*[28] reported that one of the multiple genes, such as 6p11–p21, 16q13, 14q21–23, and 20p12, in the HLA region may influence susceptibility to SLE. To our knowledge, this is the first study to describe a genetic association between RANTES –28 promoter region polymorphisms and the risk of susceptibility to SLE.

The prevalence of RANTES –28G varies among different ethnic groups. The frequency of the RANTES –28G allele for our Chinese children was 11.7%, lower than that described for a Japanese population (16.6%)[12]. McDermott, *et al*[29] reported that the RANTES –28G allele was relatively uncommon in Caucasians (4%). In this study,

Table 2. Comparison of initial laboratory examination and clinical severity in genotype of RANTES –28 for children with SLE.

Clinical Characteristics	RANTES –28 Genotype CC, n = 34	CG/GG, n = 12	p
Anti-dsDNA Ab (< 35 IU/ml)	699 ± 732	1057 ± 723	0.103
ANA (homogeneous)	630 ± 510	1056 ± 371	0.011
ANA (speckled)	831 ± 501	1184 ± 303	0.019
C3 (73–134 mg/dl)	43 ± 22	28.5 ± 17	0.044
C4 (18.2–45.5 mg/dl)	7.3 ± 3.2	5.6 ± 2	0.093
SLEDAI	15 ± 6.8	17 ± 6.2	0.375

ANA: antinuclear antibody, anti-dsDNA Ab: anti-double-stranded DNA antibody, SLEDAI: SLE Disease Activity Index.

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the frequency of the RANTES –28G allele was significantly higher in patients with SLE than in healthy controls (23.9% vs 11.7%; p = 0.006) and the distribution of genotype frequencies of –28(C/G) RANTES gene polymorphism was also significantly different between the 2 groups (p < 0.001). The mutation of RANTES –28 C to G increased the risk of SLE by 2.37 times. This mutation might therefore be strongly associated with susceptibility to SLE.

The promoter of the RANTES –28 (C/G) gene is close to the nuclear factor-κB (NF-κB) binding site, which is located at position –32 and plays a critical role in the upregulation of RANTES promoter activity[30]. The NF-κB induction may be the most important mechanism for RANTES expression in CD8+ T cells or CD4+ T cells and monocytes/macrophages[31]. In the functional analysis, it is shown that the RANTES –28G allele elevates promoter activity and increases RANTES expression[12]. The RANTES increases the expression of the other chemokine genes macrophage inflammatory protein-2 (MIP-2), interferon-induced protein-10 (IP-10), and MCP-1[32]. While the observations in this study may reflect the influence of the RANTES –28G allele, there are differences in initial clinical manifestations and laboratory findings between patients with RANTES –28G allele and –28C allele. The –28G allele was associated with decreased blood concentrations of C3 (p = 0.04) and C4 (p = 0.09), with an elevation of anti-dsDNA (p = 0.10), homogeneous ANA (p = 0.01), and speckled ANA (p = 0.02) in our SLE children. Decreasing complement and increasing anti-dsDNA have been associated with an increase in SLE activity[33,34]. SLE patients with RANTES –28G allele also have significant higher incidence of CNS lupus.

We also studied serum levels of RANTES in patients with SLE and tried to correlate RANTES levels and SLE disease activity. In the cross-sectional analysis, there was no significant difference in the serum levels of RANTES between the SLE patients with the RANTES –28C allele and patients with RANTES –28G allele (16.01 ± 12.74 vs 16.67 ± 10.57 ng/ml; p = 0.87). The serum RANTES levels were similar in these patients with various genotypes of RANTES –403. Liu, *et al*[12] also reported that there was no significant difference in serum RANTES levels between individuals with RANTES –28G and those without RANTES –28G. However, the activated CD4+ lymphocytes from individuals with RANTES –28G secreted significantly more RANTES than those without RANTES –28G.

Moreover, in the individuals infected with HIV-1 the RANTES –28G allele increases RANTES expression and thus delays the progression of HIV-1 disease. The chemokine receptor CCR5 is a coreceptor for the cellular entry of R5 strains of HIV-1[35]. The RANTES is one of the 3 natural CC5 ligands and it can suppress *in vitro* replication of R5 strains of HIV-1[36]. This means that the levels of RANTES were correlated inversely with the rates of HIV-1 disease progression. We speculate that the SLE patients with RANTES –28G allele also secreted more RANTES, and thus could be more resistant to HIV-1 disease progression. The serum RANTES levels in patients with active SLE were also not significantly higher than in those with inactive SLE (17.62 ± 13.83 vs 14.40 ± 9.43 ng/ml; p = 0.37). A precise association between serum RANTES levels and SLE disease activity was difficult to confirm in our study because SLE is a chronic disease characterized by exacerbations and remissions; thus, measures of disease activity and laboratory assays (e.g., serum RANTES) vary with time. Further investigation requires a longitudinal analysis.

We also compared the polymorphisms of MCP-1 –2518 gene in SLE patients and healthy controls. There was no significant difference in the frequency of genotypes of the –2518(A/G) MCP-1 gene polymorphisms between SLE patients and controls. The results were similar to those reported by Aguilar, *et al*[37], and this polymorphism does not seem to be related to susceptibility to SLE. The prevalence of the MCP-1 –2518G allele in a Chinese population was higher than that in Spaniards (51.4% vs 42%, respectively). This discrepancy might be caused by racial heterogeneity, because there is a high frequency of the MCP-1 –2518 genotypes bearing G in the Asian population[38].

MCP-1 is also controlled at the transcriptional level by NF-κB[39]. MCP-1 expression is inducible by proinflammatory cytokines (TNF-α, IL-1ß) through NF-κB induction in various cell types[40]. Monocytes from individuals carrying a G allele at –2518 produce more MCP-1 after treatment with IL-1ß[15]. However, Kim, *et al*[41] reported that patients with SLE had significantly greater serum MCP-1 levels. The MCP-1 –2518A was associated with more production of MCP-1. But the MCP-1 polymorphism also does not relate to the susceptibility to SLE among Koreans. Aguilar, *et al*[37] reported that MCP-1 –2518G allele is associated with the presence of cutaneous vasculitis, but does not increase the susceptibility to SLE in Spaniards. Our study showed similar results, that the polymorphisms of –2518(A/G) MCP-1 were not associated with susceptibility to SLE.

The prevalence of RANTES –403A allele was almost significantly higher in our SLE group (35%) than in healthy controls (p = 0.07). The 2 polymorphisms of RANTES –28 (C/G) and –403 (G/A) genes were located on the same chromosome 17, and the –403A allele may be linked to the –28G allele, since the 2 are adjacent. We found that the frequency of RANTES –28G allele carriers in our cohort of SLE patients and controls that also bore the –403A allele were 100% and 91%, respectively. This strong linkage disequilibrium between the –28G and –403A was also reported by McDermott, *et al*[29]. Some reports describe a reduction in the rate of decline of CD4+ T cells in individuals who possessed a RANTES –403A, –28G-containing haplotype[12,29]. It means that the survival of CD4+ T cells becomes more prolonged by RANTES and the effect on polyclonal B

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cell activation is enhanced, which likely contributes to persistent inflammation.

Most patients with SLE have autoantibodies to components of the cell nucleus (ANA). These ANA arise in genetically susceptible individuals in whom immune abnormalities promote B and T autoreactivity. These autoantibodies can mediate inflammation and tissue destruction. In this study the carriers of both mutant alleles (–28G and –403A) and those bearing the –403A allele alone had comparably higher titers of mean ANA levels than those with no mutation (–28C and 403G) (1:1040, 1:788, 1:564, respectively). The higher elevated ANA concentration enhanced the chronic inflammation in SLE. This suggests that the RANTES –403A may also have some effect on progression of SLE. Generally speaking, the susceptibility to disorders usually results from the accumulated effect of many genetic loci and environmental influences.

Our results show that there is no association between the polymorphisms of –2518(A/G) MCP-1 and susceptibility to SLE, whereas there is a significant association of –28(C/G) RANTES polymorphisms with SLE and there are some effects of –403(G/A) RANTES polymorphisms on SLE. Moreover, patients with the C/G or G/G genotype at RANTES –28 have significantly higher initial levels of ANA, lower initial levels of C3, and higher incidences of CNS lupus than patients with the C/C genotype, although there is no significant difference in the initial levels of anti-dsDNA, C4, and SLEDAI score between the 2 groups. No significant differences were found in the distribution of the different genotypic frequencies of –2518 MCP-1, –28 RANTES, and –403 RANTES in SLE patients with or without hypertension, lupus nephritis, arthritis, and rashes.

In conclusion, RANTES –28C/G polymorphisms influence the severity of SLE disease activity and represent a genetic risk factor for susceptibility to SLE in Chinese children. The OR for the risk of susceptibility to SLE was 2.37 for children with the RANTES –28G allele compared to those with the RANTES –28C/C genotype. In children with SLE, the RANTES –28G allele was significantly associated with higher levels of ANA, lower levels of C3, and higher incidences of CNS lupus. Inhibition of RANTES expression may be therapeutic in this disease, although the precise role of the polymorphism in the RANTES –28 in SLE is still unclear.

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