EXPERIMENTAL and MOLECULAR MEDICINE, Vol. 37, No. 6, 553-558, December 2005

The association of *eotaxin-2* and *eotaxin-3* gene polymorphisms in a Korean population with ulcerative colitis

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Accepted 6 October 2005

Abbreviations: AHR, airway hyperreactivity; LD, linkage disequilibrium; OR, odds ratios; PCR, polymerase chain reaction; SBE, single-base extension; SNP, single nucleotide polymorphism; UC, ulcerative colitis

Abstract

The eotaxin gene family (*eotaxin*, *eotaxin-2* and *eotaxin-3*) have been implicated in the recruitment of eosinophils, basophiles and helper T (Th) 2 lymphocytes that is a central aspect of allergic disease. We previously suggested that *Eo2* +*179T*> *C* and *Eo2* +*275C*> *T* of the *eotaxin-2*, and *Eo3* + *2497T*> *G* of the *eotaxin-3* were significantly associated with susceptibility to asthma. To determine whether the single nucleotide polymorphisms (SNPs) of *eotaxin-2* and *eotaxin-3* gene family are associated with the susceptibility of ulcerative colitis (UC), we analyzed the genotype of 119 patients with UC and 303 controls using single-base extension (SBE) method. We also calculated the haplotype frequencies among *Eo2* +*179T*> *C* and *Eo2* +*275C* > *T* of the *eotaxin-2 and Eo3* +*2497T*> *G* of the *eotaxin-3* in both control and UC patients. The genotype frequency of *Eo2* +*179T*> *C* and *Eo2* + *275C*> *T* between UC patients and controls were significantly different (*P* = 0.006 and 0.022, respectively). The genotype and allele frequencies of *EoA2497T*> *G* in UC patients were not significantly different from those in the controls without UC patients. Our results suggest that *Eo2* +*179T*> *C* and *Eo2* +*275C*> *T* of *eotaxin-2* might be associated with the susceptibility of UC.

Keywords: colitis ulcerative; inflammatory bowel diseases; polymorphism, single nucleotide

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two major forms of inflammatory bowel diseases (IBD) in humans (Blumberg *et al.*, 1999). The balance between pro- and anti-inflammatory cytokines secreted by T cells is responsible for both the initiation and perpetuation of IBD. Production of cytokines by lamina propria $CD4^+$ T lymphocytes differs between CD and UC. Whereas CD is associated with increased production of Th1 type cytokines, such as interferon-gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α), UC is associated with T cells producing large amounts of the Th2 type cytokine IL-5, but dose not affect IFN-γ production (Targan *et al.*, 1995; Fuss *et al.*, 1996; Plevy *et al.*, 1997).

Eotaxin gene family (*eotaxin*, *eotaxin-2* and *eotaxin-3*) is a CC chemokine that stimulates the migration of eosinophil from the small blood vessels in the lungs by acting on the CC chemokine receptor CCR3. Whereas the Eotaxin (CCL11) has been identified to be located on chromosome 17q21, Eotaxin-2 (CCL24) and Eotaxin-3 (CCL26) are located on chromosome 7q11.23. The homologues to the *eotaxin* gene, *eotaxin-2* (*CCL24*) and *eotaxin-3* (*CCL26*) have been identified (Patel *et al.*, 1997; Shinkai *et al.*, 1999) and have similar eosinophil-selective properties. While Eotaxin-3 has less potency than Eotaxin and Eotaxin-2 for binding to CCR3 (Kitaura *et al.*, 1999), the all *eotaxin* genes showed similar range in the chemotaxis efficacies of human eosinophils (Dulkys *et al.*, 2001). All three *eotaxin* genes have been shown to be associated with eosinophil recruitment in asthma patients. *Eotaxin-2* mRNA levels increased in bronchial biopsies taken from atopic and non-atopic asthmatics (Ying *et al.*, 1999). *Eotaxin* mRNA also contributes to the

early phase of allergen-induced recruitment of activated eosinophils into the airways of patients with allergic asthma (Brown *et al.*, 1998). In contrast, *eotaxin-3* mRNA was dramatically increased 24 h after allergen challenge (Berkman *et al.*, 2001). This result demonstrates that Eotaxin-3 may mainly act for the eosinophil recruitment in the later stage of asthmatic response. Eotaxin-2 production is differentially regulated in monocytes and macrophages (Watanabe *et al.*, 2002), and Eotaxin-2 and IL-5 cooperatively promoted eosinophil accumulation, IL-13 production, and airway hyper-reactivity (AHR) to methacholine (Yang *et al.*, 2003).

Recently, the single nucleotide polymorphisms (SNPs) in the *eotaxin* gene family were identified (Shin *et al.*, 2003; Chae *et al.*, 2004). We previously reported that the *Eo2 +179T> C*, *Eo2 +275C> T* of *eotaxin-2* and the *Eo3 +2497T> G* of *eotaxin-3* are significantly associated with susceptibility to asthma, and also demonstrated that the *Eo3 +2497T> G* is related to serum total IgE level, and to the peripheral blood eosinophil counts in asthma patients (Chae *et al.*, 2004). We also suggested that the SNPs of *eotaxin-3* might be associated with susceptibility to allergic rhinitis (Chae *et al.*, 2005). UC as well as asthma is generally associated with a disease with strong Th2 type cytokine expression. We analyzed the genomic DNA isolated from 119 UC patients and 303 controls to determine whether polymorphisms of the *eotaxin-2* and *eotaxin-3* are associated with the susceptibility of UC.

Materials and Methods

Subjects and DNA samples

Blood samples and records were obtained from 119 UC (70 males, 49 females) patients and 303 (196 males, 107 females) controls without UC. The mean age of UC patients and controls were 40.7 yrs and 49.7 yrs, respectively. Genomic DNA was extracted from leukocytes in peripheral blood, by a standard phenol-chloroform method, or by using the Puregene® DNA Purification kit (Gentra) according to the manufacturer's instruction. The UC patients were recruited from the outpatient clinic at Wonkwang University Hospital and Chonbuk National University Hospital. Patients were classified into the UC group according to clinical features, endoscopic findings, and histopathologic examinations. The controls without UC were recruited from the general population, and had received comprehensive medical testing at the Wonkwang University Hospital. All subjects in this study were Korean, who lived in the same area.

Polymerase chain reaction (PCR)

Two primer pairs were used for amplification of the full length of *eotaxin-2 and eotaxin-3* genes (Chae *et al.*, 2005). PCR reactions were performed using EX *Taq* polymerase (TaKaRa, Japan) and using 50 ng total genomic DNA per reaction. Amplification was carried out in a GeneAmp PCR system 9700 thermocycler (Applied Biosystem) at 92°C for 1 min, followed by 10 cycles at 92°C for 10 s, 68°C for 45 s, and 68°C for 10 min. Then 20 cycles at 92°C for 10 s, 68°C for 45 s and 68°C for 10 min (with 10 s incremental increases per cycle) were followed by a final extension at 68°C for 7 min. The PCR products purified by PCR purification kit (Millipore) were used as the template DNA for cycle sequencing (Chae *et al.*, 2004).

Genotyping

Genotyping was performed by single-base extension (SBE) using the ABI Prism® SNaPshot™ Multiplex kit (Applied Biosystems). The previously used seven SBE primers (Chae *et al*., 2005) were used in this study for genotyping of *eotaxin-2* and *eotaxin-3* SNPs in UC patients and controls. The SBE reaction mixture was prepared according to the manufacturer's instructions. The primer extension reaction was performed at 96°C for 1 min, followed by 25 cycles at 96°C for 10 s, 55°C for 40 s, and 60°C for 30 s. To clean up the primer extension reaction, 1.5 U of CIP (New England BioLabs) was added to the reaction mixture, and the mixture was incubated at 37°C for 90 min, followed by 15 min at 72°C, to inactivate enzyme The purified extension products were added to Hi-Di formamide (Applied Biosystems) according to the recommendations of the manufacturer. The mixture was incubated at 95°C for 5 min, followed by 5 min on ice, and then electrophoresis was performed, using the ABI Prism 3100 Genetic Analyzer. The results were analyzed using the ABI Prism GeneScan and Genotyper software (Applied Biosystems).

Statistic analysis

The UC patients and controls were compared using case-control association analyses. The χ^2 tests were used to estimate the Hardy-Weinberg equilibrium (HWE). Logistic regression analyses were used to calculate odds ratios (OR) (95% confidence interval) for SNP sites (Shin *et al.*, 2005). Linkage disequilibrium (LD) analyses by pair-wise comparison of biallelic loci and haplotype, and their frequencies, were constructed with an EM algorithm or Permutation test, with genotyped SNPs. Fisher's exact test or χ^2 test from 2 $\times$ 2 contingency table was applied to

analyze the comparison of the frequency of discrete variables between unrelated UC patients and unrelated controls. A *P*-value of less than 0.05 was considered to indicate statistical significance.

Results

We previously identified a total of eight SNPs in the coding and boundary intron region of *eotaxin-2* and *eotaxin-3* gene; six SNPs in *eotaxin-2* gene, and two SNPs in *eotaxin-3* gene, and suggested that *Eo2 +179T> C* and *Eo2 +275C> T* of the *eotaxin-2* gene and *Eo3 +497T> G* of the *eotaxin-3* gene were significantly associated with the susceptibility of asthma (Chae *et al.*, 2004). We also analyzed the association between allergic rhinitis patients and controls, and suggested that the *Eo2 +179T> C* and *Eo2 +275C> T* of the *eotaxin-2* gene and *Eo3 +1577G> A* and *Eo3 +2497T> G* of the *eotaxin-3* gene may be associated with susceptibility to allergic rhinitis (Chae *et al.*, 2005). To precisely determine whether these polymorphisms were associated with susceptibility of another allergic disease such as UC in a Korean, we analyzed the genotype and allele frequencies in SNPs of the *eotaxin-2* and *eotaxin-3* gene by SBE method on genomic DNA samples isolated from 119 unrelated UC patients and 303 unrelated controls without UC. All genotype frequencies were in Hardy-Weinberg equilibrium (HWE), except *Eo2 +304A> C* in UC patients (data not shown). We analyzed LDs among these SNPs of *eotaxin-2* and *eotaxin-3* gene, and found that an absolute LDs (|D'| = 1 and d^2 = 1) was observed between the *Eo3 +77C> T* and *Eo3 +1577G> A* of *eotaxin-3* gene. The strong LDs (|D'| = 0.926) between the *Eo2 +179T> C* and *Eo2 +275C> T* of *eotaxin-2* was also observed. Interestingly, the strong LDs between the *Eo2 +179T> C* of *eotaxin-2* gene and *Eo3 +1577G> A* of *eotaxin-3* gene as well as between the *Eo2 +275C> T* of *eotaxin-2* gene and *Eo3 +2497T> G* of *eotaxin-3* gene were observed (|D'| = 0.994 and 0.999, respectively). These results prove our previous suggestion that *eotaxin-2* and *eotaxin-3* might be same block because these genes are closely located on the same chromosome at distance of about 40 kb (Chae *et al.*, 2004).

The *P* values of each polymorphism were analyzed between the UC patients and the controls (Table 1 and 2). Although the allele frequency of *Eo2 +179T> C* and *Eo2 +275C > T* between UC patients and controls was not significantly different (*P* = 1.000 and 0.679, respectively), the both genotype frequencies of *Eo2 +179T> C* and *Eo2 +275C> T* between UC patients and controls were significantly associated (*P* = 0.006 and 0.022, respectively). The genotype frequencies of *Eo2 +179T> C* and *Eo2 +275C> T* in UC patients were significantly different from those in non-UC controls, however all the odds ratios (OR) (95% CI) between UC patients and

Table 1. Genotype and allele frequencies of the *eotaxin-2* SNPs between UC patients and controls.

Position[a]	Genotype/ Allele	Control *n* (%)	UC *n* (%)	OR[b] (95% CI)[b]	*P*[c]
Eo2 +179T > C (rs2302004)	CC	105 (44.5)	43 (36.1)	1.00	0.006
	TC	94 (39.8)	67 (56.3)	1.74 (1.08-2.79)	
	TT	37 (15.7)	9 (7.6)	0.59 (0.24-1.34)	
	C	304 (64.4)	153 (64.3)	1.00	1.000
	T	168 (35.6)	85 (35.7)	1.01 (0.73-1.39)	
Eo2 +275C > T (rs2302005)	TT	103 (44.4)	47 (39.5)	1.00	0.022
	CT	90 (38.8)	62 (52.1)	1.51 (0.94-2.42)	
	CC	39 (16.8)	10 (8.4)	0.56 (0.26-1.22)	
	T	296 (63.8)	156 (65.6)	1.00	0.679
	C	168 (36.2)	82 (34.4)	0.93 (0.67-1.29)	
Eo2 +304A > C (rs2302006)	CC	61 (26.1)	23 (19.3)	1.00	0.063
	AC	129 (55.1)	81 (68.1)	1.67 (0.96-2.90)	
	AA	44 (18.8)	15 (12.6)	0.90 (0.42-1.93)	
	C	251 (53.6)	127 (53.4)	1.00	1.000
	A	217 (46.4)	111 (46.6)	1.01 (0.74-1.38)	

[a]Calculated from the translation start site, [b]Logistic regression analyses were used for calculating OR (95% CI; confidence interval), [c]Value was determined by Fisher's exact test or χ^2 test from 2 × 2 contingency table.

controls were not significant except the TC genotype (OR = 1.74 (1.08-2.79)) in *Eo2 +179T > C* (Table 1). The genotype and allele frequencies of *Eo3 +2497T > G* in UC patients were not significantly different from those in the controls (P = 0.190 and P = 0.096, respectively). Our present results suggest that *eotaxin-2* might be associated with susceptibility to UC. We previously reported that *Eo2 +179T > C* and *Eo2 +275C > T* of the *eotaxin-2* were significantly associated with the susceptibility of asthma as well as allergic rhinitis (Chae *et al*., 2004; Chae *et al*., 2005). These results led us to think that the polymorphism of *eotaxin-2* was associated with allergic diseases such as asthma, allergic rhinitis and UC.

We calculated the haplotype frequencies between the *Eo2 + 179T > C* and *Eo2 +275C > T* of *eotaxin-2* in controls and UC patients. Four haplotypes were identified with two major haplotypes explaining more than 92% of distribution, and there was no significant difference in haplotype frequencies in both group (data not shown). We also calculated the haplotype frequencies among the *Eo2 +179T > C* and *Eo2 +275C > T* of *eotaxin-2* gene and the *Eo3*

Table 2. Genotype and allele frequencies in the *eotaxin-3* SNPs between UC patients and controls.

Position[a]	Genotype	Control *n* (%)	UC *n* (%)	OR[b] (95% CI)[b]	P[c]
Eo3 +77C > T (rs2240478)	CC	111 (37.8)	44 (37.0)	1.00	0.803
	CT	148 (50.3)	58 (48.7)	0.99 (0.62-1.57)	
	TT	35 (11.9)	17 (14.3)	1.23 (0.62-2.41)	
	C	370 (62.9)	146 (61.3)	1.00	0.692
	T	218 (37.1)	92 (38.7)	1.07 (0.78-1.46)	
Eo3 +1577G > A	GG	266 (87.8)	102 (85.7)	1.00	0.848
	GA	37 (12.2)	17 (14.3)	1.20 (0.65-2.22)	
	AA	0 (0.0)	0 (0.0)	-	
	G	569 (93.9)	221 (92.9)	1.00	0.639
	A	37 (6.1)	17 (7.1)	1.18 (0.65-2.14)	
Eo3 +2497T > G (rs23020009)	TT	254 (90.4)	100 (84.0)	1.00	0.190
	TG	27 (9.6)	19 (16.0)	1.79 (0.95-3.36)	
	GG	0 (0.0)	0 (0.0)	-	
	T	535 (95.2)	219 (92.0)	1.00	0.096
	G	27 (4.8)	19 (8.0)	1.72 (0.94-3.16)	

[a]Calculated from the translation start site, [b]Logistic regression analyses were used for calculating OR (95% CI; confidence interval), [c]Value was determined by Fisher's exact test or χ^2 test from 2 × 2 contingency table.

Table 3. The haplotype frequencies of UC patients and controls in the *eotaxin-2* and *eotaxin-3*.

Haplotype			Frequency[a]		P[b]
Eo2 +179T > C	*Eo2 +275C > T*	*Eo3 +2497T > G*	Control	UC	
C	T	T	0.606	0.550	0.214
T	C	T	0.286	0.329	0.299
C	T	G	0.028	0.074	0.024
C	C	T	0.042	0.017	0.134
T	T	T	0.027	0.025	0.845
T	C	G	0.011	3.7E-07	0.447
T	T	G	6.0E-21	5.3E-03	0.139
C	C	G	2.6E-23	0.000	-

[a]Values were calculated by EM algorithm with genotyped SNPs, [b]Values were analyzed by permutation test.

+2497T> G of *eotaxin-3* gene in controls and UC patients because these genes are located on the same chromosome without any other interception. While eight haplotypes were identified with two major haplotypes, explaining more than 89% of distribution in controls, seven haplotypes in UC patients were identified out of eight possible haplotypes (Table 3). Although the haplotype frequencies by *Eo2 +179T> C* and *Eo2 +275C> T* of *eotaxin-2* gene between UC patients and controls were not significantly associated, the haplotype frequency of CTG between controls and UC patients was significantly different (P = 0.024).

Discussion

Generally, activated Th cells can differentiate to the development of at least two phenotypically and functionally distinct cell types, Th1 and Th2 cells (Mosmann *et al.*, 1989; Abbas *et al.*, 1996; Ho *et al.*, 2002). Th1 cells produce the cytokines interferon-gamma (IFN-γ), interleukin-2 (IL-2) and lymphotoxin, which are commonly associated with cell-mediated immune responses against intracellular pathogens and induction of organ-specific autoimmune diseases (Kuchroo *et al.*, 1995; Abbas *et al.*, 1996). The cytokines produced by Th2 cells, such as IL-4, IL-5 and IL-10, are known to be associated with atopic and allergic diseases and are usually accompanied by increased production of IgG1 and IgE, and by activation of eosinophil and mast cells (Sher *et al.*, 1992; Abbas *et al.*, 1996; Hofstra *et al.*, 1998). The balance between Th1 and Th2 cells is critical in immune response to pathogens, tumor antigens and allergens. Th1 and Th2 cells cross-regulate the differentiation of one another. In IBD, CD is associated with increased production of Th1 type cytokines, such as IFN-γ and TNF-α, whereas UC is associated with T cells producing large amounts of Th2-type cytokine and eosinophil (Plevy et al., 1997; Farrell et al., 2002).

We previously identified a total of eight SNPs in *eotaxin-2* and *eotaxin-3* gene considered as the Th2 cell type cytokine, and suggested that *Eo2 +179T> C* and *Eo2 +275C> T* of the *eotaxin-2* and *Eo3 +2497T> G* of the *eotaxin-3* were significantly associated with the susceptibility of allergic disease, such as asthma as well as allergic rhinitis (Chae *et al.*, 2004; Chae *et al.*, 2005). We analyzed the association of *eotaxin-2* and *eotaxin-3* gene in another allergic disease, UC, in this study and showed that the SNPs of eotaxin-2 and eotaxin-3 gene are associated with susceptibility to UC (Table 1). These results suggest that the SNPs of *eotaxin* gene family are extensively associated with susceptibility to allergic disease. The strong LDs among the SNPs of eotaxin-2 and eotaxin-3 gene suggested that *eotaxin-2* and *eotaxin-3* might work as a same block. It is very likely, considering that these genes are located on the same chromosome (7q11.23) at distance of about 40 kb without any other interception.

In this study, our results suggest that the *eotaxin-2* might be associated with susceptibility to UC. Although it is not clear that how *eotaxin-2* can act in the susceptibility of allergic disease, our results demonstrate that *eotaxin-2* is associated with susceptibility to various allergic disease.

Acknowledgement

This work was supported by a grant from the Korea Health 21 R&D Project by Ministry of Health & Welfare (01-PJ3-PG6-01GN09-003).

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