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Association between a TGFβ1 promoter polymorphism and rhinosinusitis in aspirin-intolerant asthmatic patients ☆

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Summary
Background: Rhinosinusitis is highly associated with aspirin-intolerant asthma (AIA). The risk of aspirin intolerance is higher in people with rhinosinusitis than in those without it. Recently, the role of transforming growth factor β1 (TGFβ1) in the pathogenesis of chronic rhinosinusitis has come under investigation. The goal of this study was to evaluate the association of *TGFβ1* gene polymorphism with an AIA phenotype in the Korean population.
Methods: A promoter polymorphism of the *TGFβ1* gene, TGFβ1-509C>T, and a coding polymorphism (L10P), were genotyped in 203 patients with AIA, 324 patients with aspirin-tolerant asthma (ATA), and 456 normal controls (NC). Serum TGFβ1 levels were determined by ELISA.
Results: The TGFβ1-509C>T polymorphism was not significantly associated with the AIA phenotype; however, a significant association with the prevalence of rhinosinusitis in AIA ($P = 0.012$), but not in ATA ($P > 0.05$), was observed. When stratified by the presence of rhinosinusitis, the frequency of T allele carriers (CT or TT genotype) of TGFβ1-509C>T was significantly higher in AIA (87.1%) compared to ATA (52.9%, $P < 0.001$, OR = 6.0, 95% CI = 3.3–11.1). In addition, AIA patients carrying the TGFβ1-509T allele showed a lower serum TGFβ1 level compared to AIA patients carrying the TGFβ1-509 CC genotype, especially when stratified by the presence of rhinosinusitis ($P = 0.002$).

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Conclusion: Our results show that the TGFβ1 polymorphisms are not associated with the AIA phenotype in the Korean population, but may contribute to the development of the AIA phenotype with rhinosinusitis.

Introduction

Aspirin-intolerant asthma (AIA) is a clinical syndrome characterized by eosinophilic rhinosinusitis, nasal polyposis, aspirin sensitivity, and asthma.[1–3] AIA has been regarded as a distinct syndrome from allergic asthma. This condition is most commonly found in middle-aged female asthmatic patients with chronic rhinosinusitis and/or nasal polyps, and there is no relationship with atopy.[3–5] Up to 70% of patients with AIA also have nasal polyps, and the incidence of rhinosinusitis identified by radiography in AIA may be up to 90%. Recent studies examining the role of transforming growth factor β1 (TGFβ1) in chronic rhinosinusitis and nasal polyps have demonstrated increased transcription of TGFβ1 in nasal polyp or sinus tissue of patients with chronic rhinosinusitis.[6,7] We previously reported that eosinophils are more activated in nasal polyp tissue of AIA patients than in tissue of aspirin-tolerant asthma (ATA) patients[8] and that the degree of eosinophilic inflammation of nasal polyp tissue is related to the TGFβ1 level.[9]

The *TGFβ1* gene is located on chromosome 19q13.1–13.2,[10] a genomic region that was linked to asthma in a genome-wide scan, and plays an important role in airway inflammation and remodeling.[11] TGFβ1 is strongly expressed in response to inflammation of the nasal mucosa and in allergic rhinitis, but not in normal nasal mucosa.[12] TGFβ1 may also contribute to eosinophilic inflammation of nasal polyp tissue.[6–9] The mRNA levels of TGFβ1 in eosinophils are increased in patients with severe asthma compared to mild asthma,[13] increased in the bronchoalveolar lavage fluid of asthmatics compared to those of non-asthmatics, and further increased in response to allergen challenge.[14] Several polymorphisms in the *TGFβ1* gene are associated with the asthmatic phenotype.[15,16] However, there are no published data on genetic polymorphisms of *TGFβ1* in AIA. In this study, we present the first investigation on the effect of *TGFβ1* polymorphism on AIA and evaluate the possible role of *TGFβ1* polymorphism in the association between AIA and rhinosinusitis in the Korean population.

Materials and methods

Subjects

Three subject groups (203 patients with AIA, 324 patients with ATA, and 456 normal controls (NC)) were enrolled from Ajou University Hospital and Soonchunhyang University Hospital in Korea. The diagnosis of AIA was based on a positive response to a lysine–aspirin (L–ASA) bronchoprovocation test, which was performed with increasing doses of ASA (75–300 mg/ml Althargyl; Arthromedica, Switzerland) according to a previously described modified method.[17] A change in the forced expiratory volume in 1 s (FEV_1) was followed for up to 5 h after the last dose of the aspirin challenge. The ASA-induced change (%) in FEV_1 was calculated as the percentage of post-challenge FEV_1 to pre-challenge FEV_1. Methacholine bronchial challenge tests were performed as previously described.[17] NC were recruited from the general population answering negatively to a screening questionnaire for respiratory symptoms; had no past history of aspirin hypersensitivity and had a FEV_1 greater than 80% predicted; PC_{20} methacholine greater than 25 mg/ml; and normal findings on simple chest radiograms. Atopy was defined as one or more positive reactions to a skin prick test using 12 common aeroallergens (Bencard, Brentford, UK) with histamine and saline controls. Total IgE was measured using the UniCAP system (Pharmacia Diagnostics, Uppsala, Sweden). The presence of rhinosinusitis and nasal polyps were evaluated using a paranasal sinus (PNS) X-ray and rhinoscopy. All subjects gave informed consent, and the study was approved by the institutional review board of Ajou University Hospital, Suwon, Korea. The clinical characteristics of the study subjects are summarized in Table 1. There were significant differences in mean age, atopic status, and total serum IgE level between the AIA and NC groups (all $P<0.001$). Between the AIA and ATA groups, there were significant differences in PC_{20} methacholine and the presence of rhinosinusitis and a nasal polyp ($P = 0.032$, <0.001, and <0.001, respectively).

Genotyping of TGFβ1 polymorphism

Two SNPs in the TGFβ1 gene (-509C>T and L10P) were genotyped using a single base extension method. Sequences of amplifying and extension primers for TGFβ1-509C>T and TGFβ1 L10P polymorphisms were used for genotyping of SNPs according to previously described methodology.[18] Primer extension reactions were performed with the SNaPshot ddNTP primer extension kit (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions.

ELISA for TGFβ1

The measurement of TGFβ1 in serum samples was performed by ELISA (R&D Systems, Inc., Minneapolis, MN, USA). Before measuring the level of TGFβ1, the serum samples were treated with acid to convert the inactive form of TGFβ1 into the active form. After neutralizing the sample with sodium hydroxide, TGFβ1 was measured according to the manufacturer's instructions.

Statistical analysis

A significant departure of genotype frequency from the Hardy–Weinberg equilibrium (HWE) at each SNP was tested by χ^2 analysis. A difference in genotype frequency between

Table 1 Clinical characteristics of the study subjects.

	AIA*	ATA*	NC*	*P*-value	
	($n = 203$)	($n = 324$)	($n = 456$)	AIA vs. ATA	AIA vs. NC
Age (year)†	42.7±14.1	41.8±14.4	33.4±14.7	0.504	<0.001
Sex (male)	83 (40.9%)	126 (38.9%)	210 (46.1%)	0.649	0.126
Atopy	103/183 (56.3%)	161/262 (61.5%)	38/292 (13.0%)	0.282	<0.001
Asthma duration (year)†	6.2±5.8	4.9±5.9	NA	0.037	NA
FEV_1 (%)†	80.1±28.3	84.6±21.8	NA	0.058	NA
PC_{20} methacholine (mg/ml)†	5.0±8.1	6.9±9.1	NA	0.032	NA
Log serum total IgE (IU/ml)†	2.2±0.5	2.2±0.6	1.6±0.6	0.916	<0.001
Rhinosinusitis (presence/total)	131/161 (81.4%)	189/313 (60.4%)	NA	<0.001	NA
Nasal polyp (presence/total)	72/147 (49.0%)	10/193 (5.2%)	NA	<0.001	NA

n, number of patients; NA, not applicable.
*AIA, ASA-intolerant asthma; ATA, ASA-tolerant asthma; NC, normal controls.
†This value was presented as mean±SD.

Table 2 Allele and genotype frequencies of the TGFβ1-509C>T.

Genotype	AIA*	ATA*	NC*	*P*-value†	
	($n = 203$)	($n = 324$)	($n = 456$)	AIA vs. ATA	AIA vs. NC
CC	50 (24.6%)	87 (26.9%)	130 (28.5%)	0.324	0.428
CT	98 (48.3%)	162 (50.0%)	215 (47.1%)	0.299	0.695
TT	55 (27.1%)	75 (23.1%)	111 (24.3%)	0.566	0.364
q	0.512	0.481	0.479	0.323	0.417

n, number of patients; *q*, minor allele frequency.
*AIA, aspirin-intolerant asthma; ATA, aspirin-tolerant asthma; NC, normal controls.
†Each *P*-value was calculated with co-dominant, dominant and recessive models. Logistic regression analysis was used to control for age and sex as covariables.

the case and control was assessed by a χ^2-test and the calculation of odds ratios (OR) with 95% confidence intervals (CI). Contingency tables (2×2) and χ^2-tests were used to assess differences in TGFβ1 polymorphism and the prevalence of rhinosinusitis. Logistic regression models were used for analyzing SNPs and haplotypes controlling for age and sex as covariates with three alternative models (codominant, dominant, and recessive). Differences in the mean value of the phenotypic characteristics within AIA patients were compared using ANOVA and a *t*-test. Statistical analyses were performed using SPSS v.11 (SPSS Inc., Chicago, IL, USA). The significance level was set at $P<0.05$.

Results

We performed a genetic association study of the *TGFβ1* gene (TGFβ1-509C>T) polymorphism in three groups of study subjects classified as AIA, ATA, and NC. No significant differences in the allele and genotype frequencies of TGFβ1-509C>T polymorphism were observed among the three study groups (Table 2). The frequency of the non-synonymous polymorphism of *TGFβ1* gene at codon 10 (TGFβ1 L10P) was also not significantly different among the groups (data not shown). Asthma-associated quantitative phenotypes such as atopy, serum total IgE level, initial baseline FEV_1, and PC_{20} methacholine values were evaluated for any association with the promoter polymorphism of the *TGFβ1* gene (Table 3). Although no significant associations of TGFβ1-509C>T polymorphism with clinical parameters were observed, the TGFβ1-509C>T polymorphism was significantly associated with the prevalence of rhinosinusitis within the AIA group ($P = 0.012$). No significant associations were noted for the TGFβ L10P polymorphism for any phenotype ($P>0.05$; data not shown). Further analysis revealed that the distribution of the TGFβ1-509C>T polymorphism in AIA patients and ATA controls stratified by the presence of rhinosinusitis was significantly different ($P<0.001$, OR = 6.000, 95% CI = 3.253–11.067; Table 4); individuals carrying the TGFβ1-509T allele with rhinosinusitis were found significantly more often in AIA (87.1%) than in ATA (52.9%). Furthermore, a significant association between the serum TGFβ1 level and the TGFβ1-509C>T polymorphism was also noted ($P = 0.002$; Table 3 and Fig. 1). Within AIA patients, serum TGFβ1 levels were significantly different according to the TGFβ1-509C>T polymorphism (Fig. 1A). The level of serum TGFβ1 in AIA patients carrying the TGFβ1-509 CT or TT genotype was lower compared to the

Table 3 Clinical characteristics within AIA patients stratified by TGFβ1-509C > T genotype.

Genotype	Sex (F, %)	Age (year)	Rhinosinusitis (%)	Nasal polyp (%)	Log serum total IgE (1 U/ml)	Asthma duration (year)	FEV_1 (%)	Atopy (%)	PC_{20} methacholine (mg/ml)	Serum TGFβ1
CC	25/50 (50.0)	41.5 ± 13.7	30/44 (68.2%)	15/38 (39.5)	2.1 ± 0.5	7.0 ± 6.8	78.8 ± 29.9	24/48 (50.0)	6.5 ± 8.9	52.7 ± 15.3
CT or TT	95/153 (62.1)	43.1 ± 14.2	101/117 (87.1%)	57/109 (52.3)	2.3 ± 0.5	5.9 ± 5.4	80.5 ± 27.7	79/135 (58.5)	6.2 ± 8.8	37.6 ± 10.4
P-value	0.139	0.492	0.012	0.192	0.089	0.326	0.714	0.307	0.693	0.002

Table 4 Distribution of TGFβ1-509C > T polymorphism in AIA patients and ATA controls stratified by the presence of rhinosinusitis.

	Rhinosinusitis	AIA*	ATA*	*P*-value AIA vs. ATA
CC	Presence	30 (68.2%)	44 (60.3%)	0.433
	Absent	14 (31.8%)	29 (39.7%)	
	N	44	73	
CT or TT	Presence	101 (87.1%)	101 (52.9%)	$<0.001^{\dagger}$
	Absent	15 (12.9%)	90 (47.1%)	
	N	116	191	

*AIA; aspirin-intolerant asthma, ATA; aspirin-tolerant asthma.

†OR = 6.000 (95% CI = 3.253–11.067).

AIA patients carrying the TGFβ1-509 CC genotype. The effect was more clearly evident in the AIA patients with rhinosinusitis (Fig. 1B).

Discussion

TGFβ1 is a multifunctional cytokine with both immunosuppressive and pro-inflammatory effects.[19–21] TGFβ1 contributes to the pathogenesis of asthma and is associated with disease severity by enhancing the deposition of the extracellular matrix.[13,22] Additionally, mRNA levels of TGFβ1 are up-regulated in bronchial asthma.[22,23] Thus, TGFβ1 is likely to promote airway remodeling and irreversible airway obstruction.[24–26]

The -509C > T promoter polymorphism of TGFβ1 has been reported to influence the expression of the TGFβ1 gene.[28–30] This effect is thought to occur through an enhancement of the binding affinity of the YY1 transcription factor, leading to increased TGFβ1 transcription and higher circulating concentrations of TGFβ1 in the plasma. This polymorphism has been associated with asthma[27] and asthma severity.[31] However, the role of this polymorphism in the pathogenesis of AIA has not been addressed.

In this study, we failed to demonstrate any relationship between TGFβ1 polymorphism and clinical characteristics of asthma such as the total serum IgE level, PC_{20} methacholine, and basal FEV_1 values. However, we did observe a significant association between the TGFβ1-509C > T polymorphism and the prevalence of rhinosinusitis, a typical characteristic of AIA, with patients carrying the T allele having a higher prevalence of rhinosinusitis. When stratified by the presence of rhinosinusitis, the genotypic distribution of the promoter polymorphism was significantly different between the AIA and ATA groups; the frequencies of the -509 CT or TT genotype were higher in the AIA (87.1%) than in the ATA patients (52.9%) with rhinosinusitis. We previously demonstrated a close correlation between eosinophil cationic protein (ECP) levels and the TGFβ1 level in nasal polyp tissue of AIA patients, suggesting that TGFβ1 may contribute to the eosinophilic inflammation of the nasal polyp.[7,9] The current findings suggest that there is a contribution of the TGFβ1-509C > T polymorphism to the susceptibility to AIA with

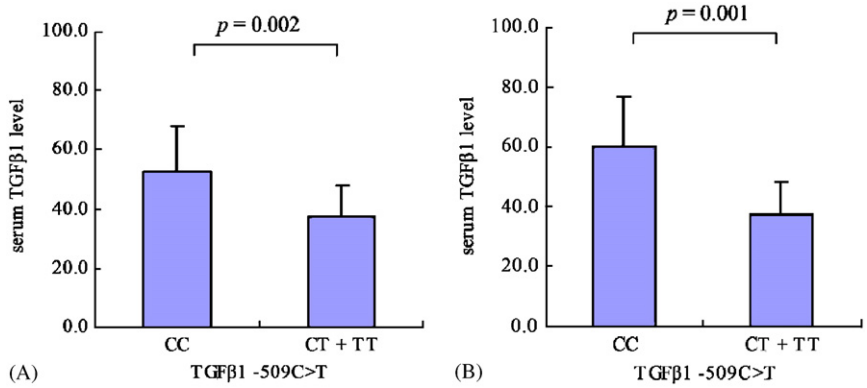

Figure 1 Association of serum TGFβ1 level with the promoter polymorphism: (A) serum TGFβ1 level within AIA patients; and (B) serum TGFβ1 level within AIA patients having rhinosinusitis.

rhinosinusitis and that the comorbidity of AIA and rhinosinusitis may result from a common genetic factor, i.e., the polymorphism of TGFβ1. In accord with previous studies,[28,30] the promoter polymorphism also showed a significant association with serum TGFβ1 levels; AIA patients carrying the TGFβ1-509 CT or TT genotype showed a lower serum level of TGFβ1 compared to AIA patients carrying the TGFβ1-509 CC genotype; this difference was highly significant when stratified by the presence of rhinosinusitis.

Studies have recently suggested that TGFβ1 plays a major role in chronic rhinosinusitis[32,33] due to increased expression of TGFβ1 in patients with rhinosinusitis and a nasal polyp[32] and the abundant expression of TGFβ1 at both the mRNA and protein levels in the nasal mucosa of patients with chronic rhinosinusitis[33] correlating with the ECP level.[9] These findings suggest that TGFβ1 production in AIA patients may be localized and compartmentalized within the nasal mucosa and/or polyp tissues with strong eosinophilic inflammatory responses. The local production and release of TGFβ1 in nasal mucosa and polyp tissues may serve either to localize the inflammatory response to nasal mucosa or as a local tissue response to eosinophilic inflammation.

In this study, we observed that the T allele was associated with lower plasma levels of TGFβ1. This finding contradicts a previous study of this polymorphism in which TGFβ1 concentrations in plasma were observed to be approximately twice higher in TT compared to CC homozygotes.[30] There are several factors that may account for the discrepancy. In the present study, we recruited patients with AIA, and TGFβ1 was only detected in its active form. In contrast, the study of Grainger et al. consisted of postmenopausal women and both the active and latent forms of TGFβ1 were studied. In addition, there was no difference in clinical severity according to this polymorphism in our study, so a possibility of glucocorticoid systemic effect seems to be very low. We speculated that these findings might be derived from that TGFB1 is localized and compartmentalized within the nasal mucosa of AIA patients with rhinosinusitis. However, the exact mechanism responsible for the decreased production of TGFβ1 in the sera of AIA patients with rhinosinusitis and/or a nasal polyp needs further investigation.

In conclusion, TGFβ1 promoter polymorphism is not associated with an AIA phenotype in the Korean population; however, the TGFβ1-509C$>$T polymorphism may contribute to the development of the AIA phenotype with rhinosinusitis.

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