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ORIGINAL ARTICLE

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Association between genetic variation in the gene for death-associated protein-3 (DAP3) and adult asthma

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Abstract Lung epithelium plays a central role in modulation of the lung inflammatory response, and lung repair and airway epithelial cells are targets in asthma and viral infection. Activated T lymphocytes release cytokines such as interferon-gamma (IFN-γ) that induce apoptosis, or programmed cell death, of damaged epithelial cells. Death-associated protein-3 (DAP3) is involved in mediating IFN-γ-induced cell death. To assess the possible involvement of genetic variants of *DAP3* with asthma, we searched for single-nucleotide polymorphisms (SNPs) in the gene and conducted a case-control study with 1,341 subjects. We found a strong association between bronchial asthma (BA) in adults ($P = 0.0051$, odds ratio = 1.87, 95% CI = 1.20–2.92), whereas no association was found with childhood asthma. The tendency was more prominent in patients with higher serum total immunoglobulin E (IgE) (> 250 IU/ml) ($P = 0.00061$, odds ratio = 2.40, 95% CI = 1.44–4.00). *DAP3* was expressed in normal bronchial epithelial cells, and the expression was induced by IFN-γ. These results indicated that specific variants of the *DAP3* gene might be associated with the mechanisms responsible for adult BA and contribute to airway inflammation and remodeling.

Keywords Bronchial asthma · Single-nucleotide polymorphism · DAP3 · Association study · Immunoglobulin E

Introduction

Bronchial asthma (BA) is a complex disorder caused by a combination of genetic and environmental factors (Busse and Lemanske 2001). In recent years, a growing body of clinical and experimental evidence has

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highlighted the importance of respiratory infections in acute asthma exacerbation (Gern and Busse 2002; Message and Johnston 2001). Most infections induce asthma exacerbation and a T helper (Th) 1 inflammatory response. Some studies have shown that some Th1 cells are present in asthmatic patients, which could be related to bronchial hyperreactivity (Krug et al. 1996; Magnan et al. 2000; Cho et al. 2002). Interferon-γ (IFN-γ), produced by Th1 cells, exerts an inhibitory effect on Th2 cells and has extensive and diverse immunoregulatory effects on various cells (Chung and Barnes 1999). A recent study showed that IFN-γ alone and in combination with activation of the Fas pathway induced apoptosis, or programmed cell death, in A549 lung epithelial cells (Wen et al. 1997). Disruption of the bronchial epithelium is frequently observed in mucosal biopsies obtained from asthmatic airways (Laitinen et al. 1985; Jeffery et al. 1989; Montefort et al. 1992).

Apoptosis plays crucial roles in numerous biological processes ranging from growth and development to combating viral infections. Human *DAP3* was originally isolated as a novel mediator of IFN-γ-induced cell death by performing functional selection by gene cloning. The gene codes for a 46 kDa protein with a potential nucleotide-binding motif (Kissil et al. 1995). Functional analyses of the protein indicate that the intact full-length protein is required for its ability to induce apoptosis when overexpressed, and DAP3 is implicated as a positive mediator of tumor necrosis factor α (TNF-α) and Fas (Kissil et al. 1999). Furthermore, genome screens for asthma and related phenotypes have been completed in 11 study populations. The human *DAP3* gene lies on chromosome 1q21–q22 (Kissil and Kimchi 1997), a locus linked to atopy susceptibility (Ober et al. 1999). To investigate the possible involvement of variants of *DAP3* with asthma in humans, we searched for single-nucleotide polymorphisms (SNPs) in the gene and conducted a genetic association study in Japanese.

Materials and methods

Subjects

We recruited 305 patients with child atopic asthma [mean age 9.6, range 1–15 years; male/female ratio = 1.54:1.0; mean serum immunoglobulin E (IgE) level, 1,083 U/ml], 322 with adult atopic asthma (mean age 49, range 20–91 years; male/female ratio = 1.0:1.18; mean serum IgE level, 762.8 U/ml), and 95 with adult nonatopic asthma (mean age 60, range 42–80 years; male/female ratio = 1.0:1.71; mean serum IgE level, 152.5 U/ml) from Osaka Prefectural Habikino Hospital and the Miyatake Asthma Clinic.. All subjects with asthma were diagnosed according to the criteria of the National Institutes of Health, with minor modifications (National Heart, Lung, and Blood Institute, National Institutes of Health, 1997). The diagnosis of atopic asthma was based on a positive immunoassay test to one or more allergens or total serum IgE level of ≥400 kU/l. The criteria for a diagnosis of nonatopic asthma were a total serum IgE level of $<$400kU/l and all allergen-specific IgE level of $\leq$ 0.35 kU/l (Mao et al. 2001). As controls, we analyzed 571 randomly selected population-based individuals who did not have atopy-related diseases (mean age 36, range 18–83 years; male/female ratio = 2.42:1.0). All individuals were Japanese and gave written informed consent to participate in the study (or, for individuals younger than 16 years old, their parents gave consent) in accord with the rules of the process committee at the SNP Research Center, The Institute of Physical and Chemical Research (RIKEN).

Screening for polymorphisms and genotyping

The *DAP3* genomic region targeted for SNP discovery included a 0.5 kb continuous region 5′ to the gene and 13 exons, each with a minimum of 200 bases of a flanking intronic sequence. Twelve primer sets (Table 1) were designed on the basis of the *DAP3* genomic sequence available from GenBank (accession number NT_079484). Each polymerase chain reaction (PCR) was performed with 5 ng of genomic DNA from 24 individuals. The PCR product was reacted with BigDye Terminator v3.1 (Applied Biosystems, Foster City, CA, USA). Sequences were assembled, and polymorphisms were identified using the Sequencher program (Gene Codes Corporation, Ann Arbor, MI, USA).

Genotyping

For the −20632 G/T polymorphism, genotyping was performed by PCR-restriction fragment-length

Table 1 Primers used in screening for single-nucleotide polymorphisms (SNPs)

F1	5′-AAGCCTTCTCCACCTCCTCT	R1	5′-CCATCACCAGGCTGTCTAAC
F2	5′-TGTCATGCCAGATGTAATAGC	R2	5′-AAGTAAACCAGCAGAATGGTC
F3	5′-CATGGCTCACCTTCTCAGTG	R3	5′-ATGGGAACTGATACAGACCG
F4	5′-GTCACTTTGTCACCATTATACC	R4	5′-CTATTTAGCTCAGGAGTGTAC
F5	5′-AGTGGCCCTAAGTGGTATAC	R5	5′-ACTGGAAGGATCACTTGTATG
F6	5′-CTCATGAACCAATGCTTTCTC	R6	5′-AGGATAACTAAACCTAACAGAC
F7	5′-TGACTTACCTTTCAAACCTGC	R7	5′-TCAAGTTATGAGTCCACTGTG
F8	5′-GAGGTCTCTTACAGAACCTG	R8	5′-ATATTGCATGGTCTACAAGGC
F9	5′-TTCTAGGGCCAGAGGCTACG	R9	5′-TCTTTTCCAAAGACGGTAAGG
F10	5′-GTATCTCCTTACCGTCTTTGG	R10	5′-GACCTACAAAATAGCTGGCATG
F11	5′-TGTGGAGTCCATATGTGGAG	R11	5′-CTCAAATGTGAGGTCAAGGG
F12	5′-TGGGGTGAGGGTCTAGAAG	R12	5′-GCCTCAACAGAACCACTGG

polymorphism (PCR-RFLP) analysis using *EcoT14*I (Takara, Shiga, Japan). The primers for the SNP were 5′TCAGGACGGGCGCTTTGTG and 5′GGTCTACCGGCCTCACT.

Statistical analysis

Allele frequencies for each SNP were calculated. A χ^2goodness-of-fit test was used to assess deviation from Hardy–Weinberg equilibrium for genotype frequencies at each locus. Associations of genotypes or alleles with patient groups versus nonatopic control subjects were determined by using χ^2 analysis with appropriate df.

Quantitative real-time PCR

Human bronchial epithelial cells (NHBE) were purchased from BioWhittaker, and human recombinant IFN-γ was purchased from Genzyme/Techne. Total RNA (5 μg) extracted from each sample was treated with DNaseI (Roche), and cDNA was synthesized with Thermoscript reverse transcriptase (Life Technologies) by dT_{15} priming. TaqMan probes and primers for *DAP3* and *GAPDH* were Assay-on-Demand gene expression products (Applied Biosystems). TaqMan PCR was done with an ABI PRISM 7900 Sequence Detection System (Applied Biosystems) according to the manufacturer's instructions. The relative expression of *DAP3* mRNA was normalized to the amount of *GAPDH* in the same cDNA by using the standard curve method described by the manufacturer.

Tissue expression

We used human multiple tissue, human immune system, and human blood fractions multiple tissues cDNA panels from CLONTECH for expression analysis by PCR amplification of target sequences. The primers for *DAP3* were 5′GCACTTGTTCACAACTTGAG and 5′TCTGTAGGAGCTTTCTCATG. The primers for *GAPDH* were 5′CCCCATGTTCGTCATGGGT and 5′GTGATGGCATGGACTGTGG. Southern blotting was done with DIG reagents and kits for nonradioactive nucleic acid labeling and detection (Roche) according to the manufacturer's instructions. The probes for *DAP3* and *GAPDH* were 5′AAATGATTGGCATGGAGGCG and 5′CCATGAGAAGTATGACAACAG, respectively.

Results

An extensive search identified four SNPs by PCR-directed sequencing using genomic DNA from 24 individuals on the basis of the *DAP3* genomic sequence. Position one was the adenine of the initiation codon.

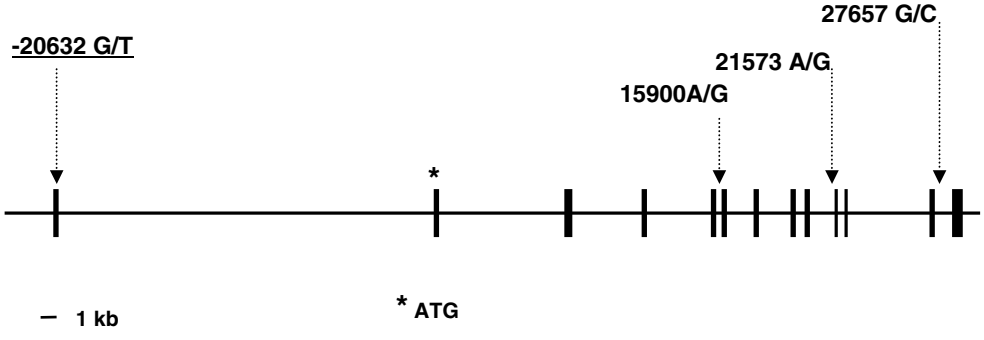

Fig. 1 Genomic structure and polymorphism map of *DAP3*. Thirteen exons are indicated by *closed squares*. ATG represents the translational start codon. The *underlined* single-nucleotide polymorphism (SNP), −20632 G/T, was genotyped in this study

Table 2 Locations and allele frequencies of single-nucleotide polymorphisms (SNPs). *JSNP* Japanese Single Nucleotide Polymorphisms Database, *NCBI* National Center for Biotechnology Information

SNP[a]	Location	Gene sequence	Allele frequency (%)[b]	Primers	JSNP ID[c]	NCBI dbSNP[d]
−20632 G/T	Exon 1	GGTCGCCTAG(G/T)CTGGAGAACT	27	F1R1	–	rs1058207
15900 A/G	Intron 5	CCTGGCCAAC(A/G)TGGCGAAACC	2	F6R6	IMS-JST084352	–
21573 A/G	Intron 9	TGTCCGATAT(G/A)CAGATTGCCC	4	F9R9	IMS-JST070763	rs2274787
27657 G/C	Intron 12	GTGCAAGGGC(T/C)ACTCCAGCAC	2	F11R11	–	–

[a]Positions are numbered according to their position relative to the published DAP3 gene (GenBank NT_079484). Position 1 is the A of the initiation codon
[b]Frequency of minor allele
[c]JSNP ID, number from the Japanese SNP database (http://snp.ims.u-tokyo.ac.jp/index_ja.html)
[d]dbSNP ID, Number from the dbSNP database of NCBI (http://www.ncbi.nlm.nih.gov/SNP/)

These were −20632 G/T, 15900 A/G, 21573 A/G, and 27657 G/C (Fig. 1, Table 2). The 15900 A/G (IMS-JST084352) and 21573 A/G (IMS-JST070763) are contained in the J-SNPs that are available from the Web site (http://snp.ims.u-tokyo.ac.jp). Since three of the SNPs were quite rare, further case-control analysis focused on −20632 G/T, which was located in the 5′ noncoding region of *DAP3*. We found a strong association between −20632 G/T and BA in adults ($P = 0.0051$, odds ratio = 1.87, 95% CI = 1.20–2.92), whereas no association was found with childhood asthma (Table 3). The tendency was more prominent in patients with higher serum total IgE (> 250 IU/ml) ($P = 0.00061$, odds ratio = 2.40, 95% CI = 1.44–4.00) (Table 4).

We investigated *DAP3*expression of cultured NHBE by RT-PCR, and *DAP3* was expressed in NHBE (data not shown). Next we compared relative expression of *DAP3* in NHBE that were either unstimulated or stimulated with 10 ng/ml IFN-γ for 3 h. Levels of *DAP3* mRNA were increased 10.6 fold by stimulation with IFN-γ (Fig. 2).

We performed RT-PCR using multiple tissue cDNA panels. Transcripts were expressed in lung and tissues and cells associated with immune function. The bands were present in both cDNAs from activated and inactivated lymphocytes (Fig. 3).

Discussion

Asthma is an inflammatory airway disease associated with infiltration of T cells and eosinophils, increased levels of proinflammatory cytokines, and shedding of bronchial cells (Busse and Lemanske 2001), which is an important histologic feature observed in bronchial biopsy specimens from asthmatic patients (Laitinen et al. 1985; Jeffery et al. 1989; Montefort et al. 1992). A recent study demonstrated that both T cells and eosinophils contribute to the induction of bronchial epithelial cell apoptosis by secretion of IFN-γ and TNF-α (Trautmann et al. 2002). Although we could not show functional data on this SNP in this study, we found that *DAP3* was expressed in NHBE, and the transcript was induced by IFN-γ. DAP3, a positive mediator of cell death induced by IFN-γ, may play an important role in the epithelial cell shedding frequently observed in asthma.

In our study, adult BA showed a stronger association with variant −20632 G/T than did childhood BA, especially in patients with high levels of serum IgE. Asthma in adults is often a slowly progressive, irreversible disease (Reed 1999). The majority of older

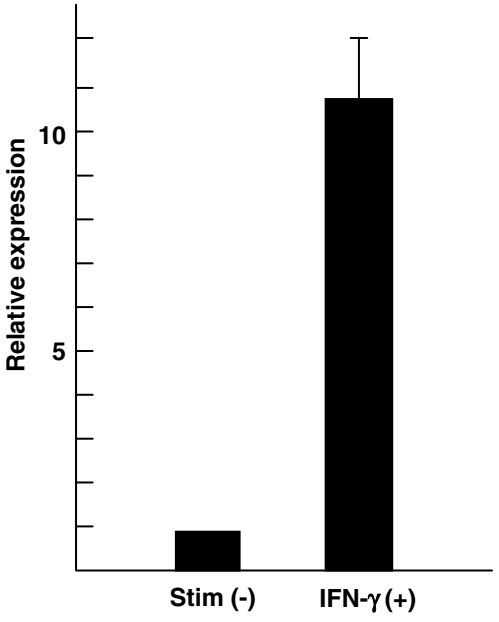

Fig. 2 Expression pattern of *DAP3* in NHBE cells. Results displayed are the averages of these measurements normalized to 1.0 for the nonstimulated control. Data are from three separate experiments

Table 3 Association between asthma and single-nucleotide polymorphisms (SNPs) in *DAP3*. *BA* bronchial asthma

−20632 G/T	Controls ($n = 571$)	Childhood BA ($n = 305$)	Adult BA ($n = 465$)	TT vs GG + GT			
				χ^2 (*P*-value)		Odds ratio (95% CI)	
				vs childhood BA	vs adult BA	vs childhood BA	vs adult BA
GG	301 (53%)	170 (56%)	238 (51%)	0.48	7.85	1.21	1.87
GT	234 (41%)	112 (37%)	175 (38%)	(0.49)	(0.0051)	(0.70–2.09)	(1.20–2.92)
TT	36 (6%)	23 (7%)	52 (11%)				

Table 4 Association between −20632 G/T substitution of *DAP3* and adult asthmatics with high serum total immunoglobulin E (IgE) (> 250 IU/ml). *BA* bronchial asthma

Genotype −20632 G/T	Control (%) $n = 571$	Adult BA with total IgE > 250 IU/ml (%) $n = 216$	OR (95% CI)	*P*
GG and GT	535 (94%)	186 (86%)	2.40	0.00061
TT	36 (6%)	30 (14%)	(1.44–4.00)	

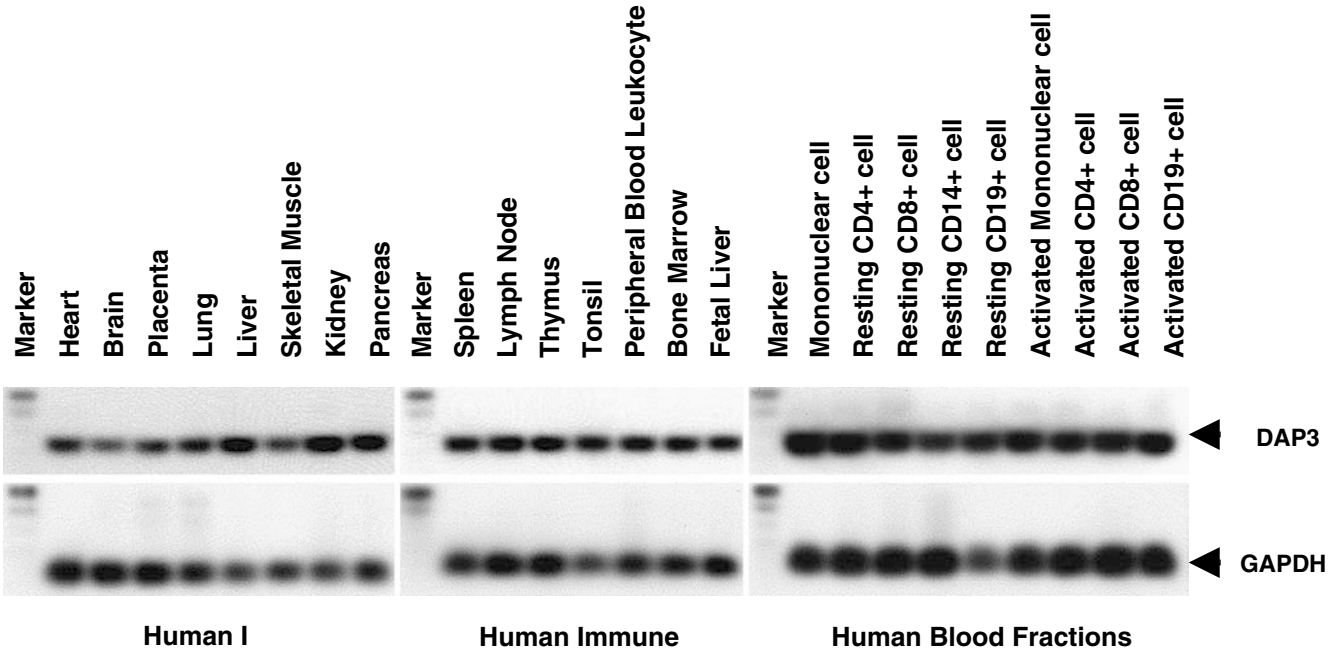

Fig. 3 Expression pattern of *DAP3* in multiple tissue cDNA panels

patients have a substantial degree of irreversible impairment of lung function that results from a combination of pathologic changes. These changes include airway remodeling from chronic lymphocytic-eosinophilic inflammation and bronchiectasis from repeated infections. DAP3 mediating IFN-γ-induced cell death might be involved in the development of chronic progressive irreversible inflammation, which is more frequently observed in adult asthma than childhood asthma. A recent report showed that influenza A viral infection, which induces a large amount of intrapulmonary IFN-γ production, enhanced later allergen-specific asthma and promoted dual allergen-specific Th1 and Th2 responses (Dahl et al. 2004). Several studies reported that some Th1 cells were present in asthmatic patients, which could be related to bronchial hyperreactivity (Krug et al. 1996; Magnan et al. 2000; Cho et al. 2002). The epithelial injuries might induce inflammatory reactions and change the mucosal permeability to allow allergens easier access to dendritic cells and enhance subsequent allergen sensitization.

Apoptosis provides a mechanism for removal of antigen-activated T cells and eosinophils, thereby leading to the resolution of the inflammatory response (Haslett 1992; Lenardo et al. 1995; Woolley et al. 1996). The accumulation of eosinophils in the asthmatic airway significantly contributes to the persistence of airway inflammation in these patients (Kroegel et al. 1994). Decreased numbers of eosinophils undergoing apoptosis have been observed in asthmatic subjects when compared with a nonasthmatic control group (Vignola et al. 1999). Although we found that *DAP3* was expressed in lung, tissue, and cells associated with immune function and NHBE, the expression profile of *DAP3* in eosinophils and antigen-activated T cells remains unclear. Thus, further study is required to clarify the physiological role of DAP3 in these cells.

Apoptosis is an essential process for functions such as the immune response, and glucocorticoids, the most effective treatments for asthma, are one of the important regulators of the cellular functions underlying these events (Walsh et al. 2003). It has been suggested that DAP3 directly interacts with the glucocorticoid receptor (GR), and DAP3 is needed to efficiently increase the GR level and enhance the transcriptional activity of GR (Hulkko et al. 2000; Hulkko and Zilliacus 2002). Dexamethasone has been reported to inhibit lung epithelial cell apoptosis induced by IFN-γ (Wen et al. 1997). Further analyses of genetic predisposition for expression of *DAP3*contributing to the pathogenesis of asthma might lead to improved diagnosis, treatment, and prevention.

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