IL-10 plays an important role as an immune-modulator in the pathogenesis of atopic diseases

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Abstract. Interleukin (IL)-10 has anti-inflammatory activities in various immune reactions and plays an important role in the regulation of immune diseases. In the present study, we examined the role of IL-10 in atopic diseases. Peripheral blood mononuclear cells (PBMCs) from healthy control subjects, patients with atopic dermatitis and patients with bronchial asthma were cultured with lipopolysaccharide (LPS). The production of IL-10, IL-12 or IFN-γ by PBMCs stimulated with LPS was measured. Next, we investigated whether the haplotype in the *IL-10* gene promoter region had an effect on the production of IL-10 by PBMCs. PBMCs from patients were cultured with phytohemagglutinin, to which recombinant human IL-10 had been added. IL-12, IFN-γ and IL-4 production by PBMCs was measured. ß-lactoglobulin (BLG)-specific T cell clones were cultured with BLG peptide (P-17), antigen-presenting cells and recombinant human IL-10. The antigen-induced proliferation of the T cell clones and cytokine production were assayed. Results demonstrated that IL-10 production by LPS-stimulated PBMCs was lower in atopic patients than in healthy control subjects. Three different haplotypes in the *IL-10* gene promoter region were detected. These haplotypes did not correlate with IL-10 production by PBMCs. IL-10 inhibited Th1 cytokine production by PBMCs, and also inhibited the antigen-induced proliferation of T cell clones and Th2 cytokine production. In conclusion, IL-10 inhibits both the production of Th1 and Th2 cytokines and the antigen-induced proliferation of T cell clones. Thus, IL-10 modulates other cytokines and plays an important role as an immune-modulator in the pathogenesis of atopic diseases.

Introduction

Interleukin (IL)-10, which is a homodimeric cytokine produced by activated monocytes, macrophages, mast cells and T cells, is deeply involved in the regulation of inflammatory responses and immune reactions. IL-10 was originally described as an inhibitory factor produced by murine Th2 cells that suppresses interferon-γ (IFN-γ) production by activated murine Th1 cells (1-3). Later, studies demonstrated IL-10 to be a potent inhibitor of monocyte and macrophage functions, suppressing the production of many pro-inflammatory cytokines and chemokines (4-7).

Several studies demonstrated that IL-10 has an important role in the pathogenesis of inflammatory bowel disease and autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis (8,9). These diseases are called Th1-mediated diseases, as Th1 cytokines play a central role in their inflammation.

Recently, studies have revealed that IL-10 is associated with the pathogenesis of Th2-mediated diseases, such as allergic diseases. Therefore, we investigated the involvement of IL-10 in allergic reactions.

Materials and methods

Atopic patients and control subjects. Twelve healthy control subjects and 31 patients with atopic disease were studied. The serum IgE levels and radioallergosorbent test (RAST) scores of 12 healthy control subjects, 12 patients with atopic dermatitis (AD) and 19 patients with bronchial asthma (BA) are listed in Table I. AD was diagnosed according to the criteria of Haniffin, and BA according to the criteria of The American Thoracic Society. The healthy control subjects had a negative history of atopic disease, and their serum IgE levels were within normal limits for their age. They were moreover healthy and free of any acute infections at blood sampling. The subjects were randomly selected through our hospital, and informed consent was obtained from all subjects or their parents.

Cell preparation. PBMCs were isolated from the heparinized blood samples of healthy control subjects and atopic patients by gradient centrifugation using Ficoll-Paque (Pharmacia,

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Abbreviations: AD, atopic dermatitis; BA, bronchial asthma; IL-10, interleukin-10; IL-12, interleukin-12; IFN-γ, interferon-γ; Th1, helper T cell type 1; Th2, helper T cell type 2; BLG, ß-lactoglobulin; PBMCs, peripheral blood mononuclear cells

Key words: interleukin-10, atopic dermatitis, bronchial asthma, peripheral blood mononuclear cells, T cell clone, *interleukin-10* gene

Uppsala, Sweden). PBMCs were suspended at a density of 10^6/ml in RPMI-1640 medium supplemented with 10% heat-inactive fetal calf serum, 2 mmol/l L-glutamine, 100 U/ml penicillin and 100 mg/μl streptomycin (10).

Cell culture. PBMCs (10^6/ml) were cultured with 1 μg/ml lipopolysaccharide (LPS) (Sigma, St. Louis, MO, USA) for 24 h in a volume of 1 ml in a round-bottom tube (Falcon 2059, Becton Dickinson Labware, Lincoln Park, NJ, USA) at 37˚C in a humidified atmosphere containing 5% CO_2.

PBMCs (10^6/ml) from one randomly selected healthy control subject, one AD patient and three BA patients were cultured with 10 μg/ml phytohemagglutinin (PHA) (Gibco BRL, Grand Island, NY, USA) or 1 μg/ml LPS and recombinant human IL-10 (Genzyme, Minneapolis, MN, USA) at 0.1, 0.5, 1, 5, 10, 20 or 100 ng/ml for 24 h in a volume of 1 ml in a round-bottom tube.

Antigen-induced proliferative responses and cytokine production of BLG-specific T cell clones. ß-lactoglobulin (BLG)-specific T cell clones were used as described previously (11). The antigen-induced proliferation of the T cell clones was assayed by culturing T cells ($2x10^4$/well) in 96-well flat-bottomed culture plates with the BLG peptide (P-17) and 3000 cGy-irradiated autologous PBMCs ($1.5x10^5$/well) as antigen-presenting cells (APCs) and recombinant human IL-10, (0.1, 1, 10 or 100 ng/ml) or recombinant human TGF-ß, (0.001, 0.01, 0.1, 1 or 10 ng/ml). Cells were cultured for 72 h with 1 μCi/well of [^{3}H] TdR during the final 16-h period, and the incorporated radioactivity was measured by liquid scintillation counting. To assay cytokine production, culture supernatants in 96-well flat-bottomed tubes were spun to remove cells after the cultures and were stored at -80˚C until used for assay.

Cytokine assays. IL-10 concentration was measured with a human IL-10 enzyme-linked immunosorbent assay (ELISA) kit (BioSource International, CA, USA) with a detection limit of 15.6 pg/ml. IL-12 concentration was measured with a human IL-12 ELISA kit (BioSource International) with a detection limit of 7.81 pg/ml. IFN-γ concentration was measured with a human IFN-γ ELISA kit (Ohtsuka, Tokyo, Japan) with a detection limit of 15.6 pg/ml, and IL-4 concentration was measured with a human IL-4 ultrasensitive ELISA kit (BioSource International) with a detection limit of 0.39 pg/ml. Lastly, IL-5 concentration was measured with a human IL-5 ELISA kit (Bio Source International) with a detection limit of 11.7 pg/ml.

Detection of polymorphisms in the IL-10 gene. Genomic DNA was extracted from neutrophils with a Sepagene kit (Sanko Junyaku, Tokyo, Japan). The promoter region and five exons of the *IL-10* gene (Gene Bank accession no. U16720) were amplified and sequenced using an ABI PRISM 377 DNA sequencer.

Statistical analyses. The significance of the differences between groups was analyzed using the Mann-Whitney U test. Probability (p) values <0.05 were considered statistically significant.

Table I. Clinical features of the 43 subjects.

	Age (years)	Gender	Diagnosis	Serum IgE (IU/ml)	RAST scores	
					HD	Derf
Control subjects						
1	11	M	Healthy	5.7	0	0
2	1	M	Healthy	5.9	0	0
3	1	F	Healthy	11.0	0	0
4	1	M	Healthy	15.0	0	0
5	1	M	Healthy	25.0	0	0
6	1	F	Healthy	29.1	0	1
7	6	F	Healthy	58.0	0	0
8	5	F	Healthy	70.0	0	0
9	2	M	Healthy	72.0	0	0
10	4	F	Healthy	98.3	1	0
11	5	M	Healthy	100.0	0	0
12	1	F	Healthy	110.0	0	0
Atopic patients						
1	1	M	AD	16.8	2	3
2	0	M	AD	236.0	0	0
3	3	M	AD	1,123.1	5	6
4	3	F	AD	2,024.7	6	6
5	1	M	AD	2,586.5	3	1
6	13	M	AD	2,769.0	3	3
7	1	M	AD	3,476.0	5	4
8	4	F	AD	3,782.6	6	6
9	3	F	AD	4,514.1	6	6
10	6	F	AD	5,500.0	6	6
11	5	M	AD	6,729.9	6	6
12	1	F	AD	14,666.3	3	3
13	5	M	BA	114.6	4	5
14	2	F	BA	127.6	4	4
15	2	F	BA	148.0	4	4
16	3	F	BA	251.4	5	5
17	7	F	BA	267.7	3	4
18	4	M	BA	300.0	0	0
19	11	M	BA	451.0	5	5
20	14	F	BA	484.0	5	5
21	10	M	BA	516.5	5	5
22	9	M	BA	517.5	6	6
23	3	F	BA	545.2	6	6
24	6	M	BA	616.3	1	1
25	9	M	BA	669.9	3	3
26	14	M	BA	839.0	5	5
27	8	M	BA	907.0	6	6
28	12	F	BA	1,581.6	2	2
29	8	M	BA	1,700.0	6	5
30	13	M	BA	3,063.9	6	6
31	9	F	BA	3,860.6	3	4

AD, atopic dermatitis; BA, bronchial asthma. M, male; F, female. HD, house dust; Derf, *Dermatofagoides farinae*.

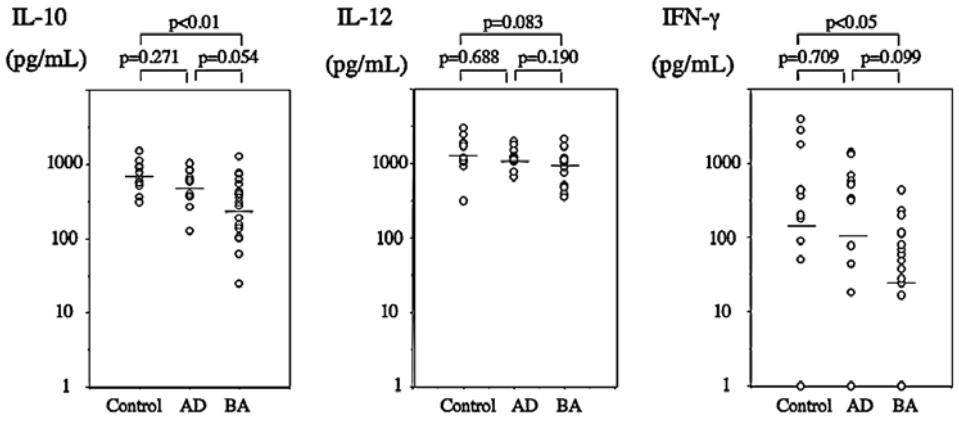

Figure 1. IL-10, IL-12 or IFN-γ production by LPS-stimulated PBMCs in healthy control subjects (n=12), AD (n=12) and BA patients (n=19).

Table II. The prevalence of haplotypes in the *IL-10* gene.

Haplotype	GCC	ACC	ATA
Control (n=10)	0 (0%)	4 (20.0%)	16 (80.0%)
AD (n=10)	0 (0%)	5 (25.0%)	15 (75.0%)
BA (n=13)	2 (7.7%)	7 (26.9%)	17 (65.4%)

AD, atopic dermatitis; BA, bronchial asthma.

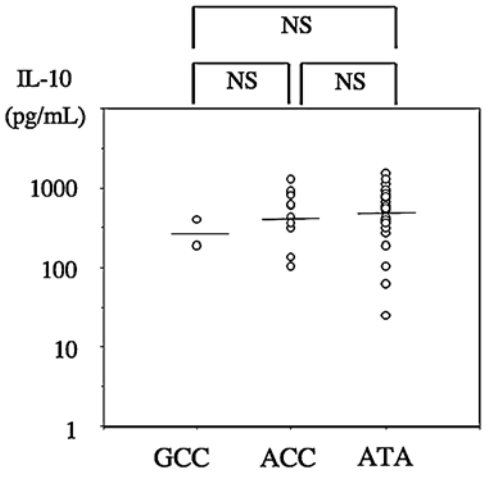

Figure 2. Relationship between the haplotype of the IL-10 gene promoter region and IL-10 production by LPS-stimulated PBMCs.

Results

IL-10 production by PBMCs in atopic patients and healthy control subjects. We studied IL-10 production by PBMCs in atopic patients and healthy control subjects. Twelve healthy control subjects, 12 patients with AD and 19 patients with BA were studied. IL-10, IL-12 and IFN-γ production by LPS-stimulated PBMCs was measured with ELISA kits. The features of the patients are summarized in Table I.

IL-10 production by PBMCs stimulated with LPS is shown in Fig. 1. IL-10 production was lower in atopic patients than in healthy control subjects. In particular, IL-10 production was lower in patients with BA (average, 275.4 pg/ml; 1 SD range, 102.3-741.3 pg/ml) than in healthy control subjects (average, 691.8 pg/ml; 1 SD range, 446.7-1071.5 pg/ml) ($p<0.01$) (Fig. 1). IFN-γ production was also lower in patients with BA than in healthy control subjects. IL-10, IL-12 and IFN-γ production was lower in patients with AD than that in control subjects, but there was no statistically significant difference between the two groups when analyzed using the Mann-Whitney U test.

IL-10 gene polymorphisms and atopic diseases. The *IL-10* gene from allergic patients and healthy control subjects was sequenced. We detected three polymorphisms in the *IL-10* gene promoter region, -1082 (G/A), -819 (C/T) and -592 (C/A) as previously reported (12,13). These polymorphisms produced three different haplotypes, GCC, ACC and ATA.

We determined the prevalence of these haplotypes in the *IL-10* gene in both allergic patients and healthy control subjects by direct sequencing (Table II). None of the healthy control subjects or AD patients had the GCC haplotype. Two of the BA patients had the GCC haplotype. Most of the healthy control subjects and atopic patients had the ATA haplotype.

Next, we investigated whether these polymorphisms were associated with the production of IL-10 by LPS-stimulated PBMCs. As shown in Fig. 2, these polymorphisms did not have an effect on IL-10 production by PBMCs in this study.

Effect of IL-10 on Th1 and Th2 cytokine production by PBMCs. The effect of IL-10 on Th1 and Th2 cytokine production in atopic patients was examined. IFN-γ production by PBMCs stimulated with PHA was significantly inhibited by IL-10 in a dose-dependent manner (Fig. 3A). Similarly, IL-12 production by PBMCs stimulated with PHA was inhibited by IL-10 in a dose-dependent manner (Fig. 3B). IL-12 production by PBMCs stimulated with LPS was inhibited by IL-10 (data not shown). These data suggest that the production of Th1 cytokines such as IL-12 and IFN-γ by PBMCs are directly inhibited by IL-10.

Furthermore, we investigated the effect of IL-10 on the production of the Th2 cytokine IL-4. IL-4 production by

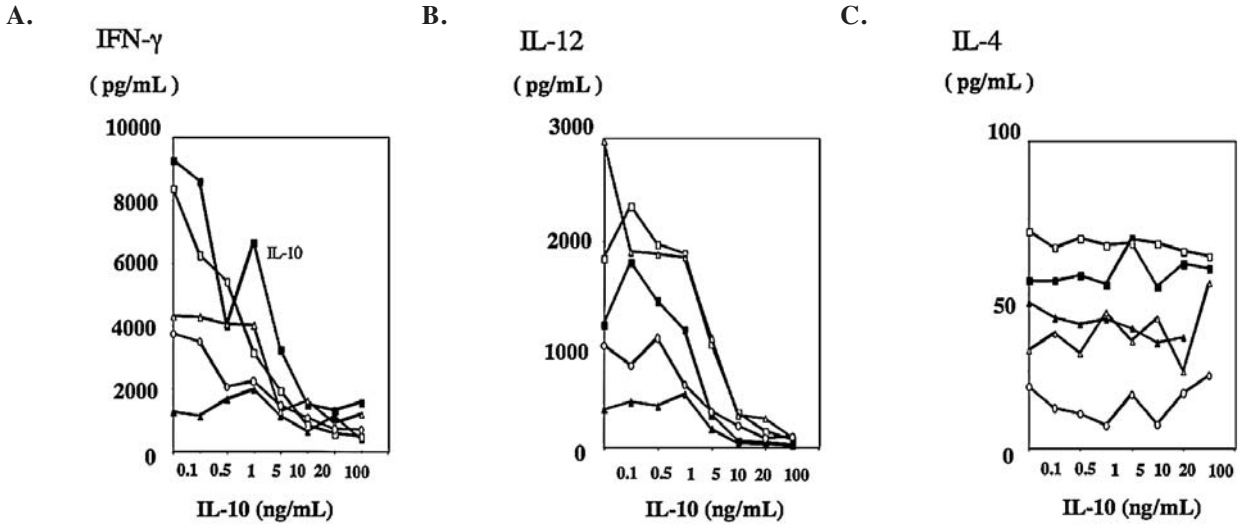

Figure 3. Effect of IL-10 on IL-12, IFN-γ or IL-4 production by PHA-stimulated PBMCs in one randomly selected healthy control subject, one AD patient and three BA patients (control subject -■-, AD patient -▲-, BA patient 1 -□-, BA patient 2 -△-, BA patient 3 -○-). (A) IFN-γ production by PHA-stimulated PBMCs was inhibited by IL-10 dose-dependently in one healthy control subject and three BA patients. In one AD patient, IFN-γ production by PHA-stimulated PBMCs was low and was not evaluated. (B) IL-12 production by PHA-stimulated PBMCs was inhibited by IL-10 dose-dependently in all patients. (C) IL-4 production by PHA-stimulated PBMCs was not affected by IL-10.

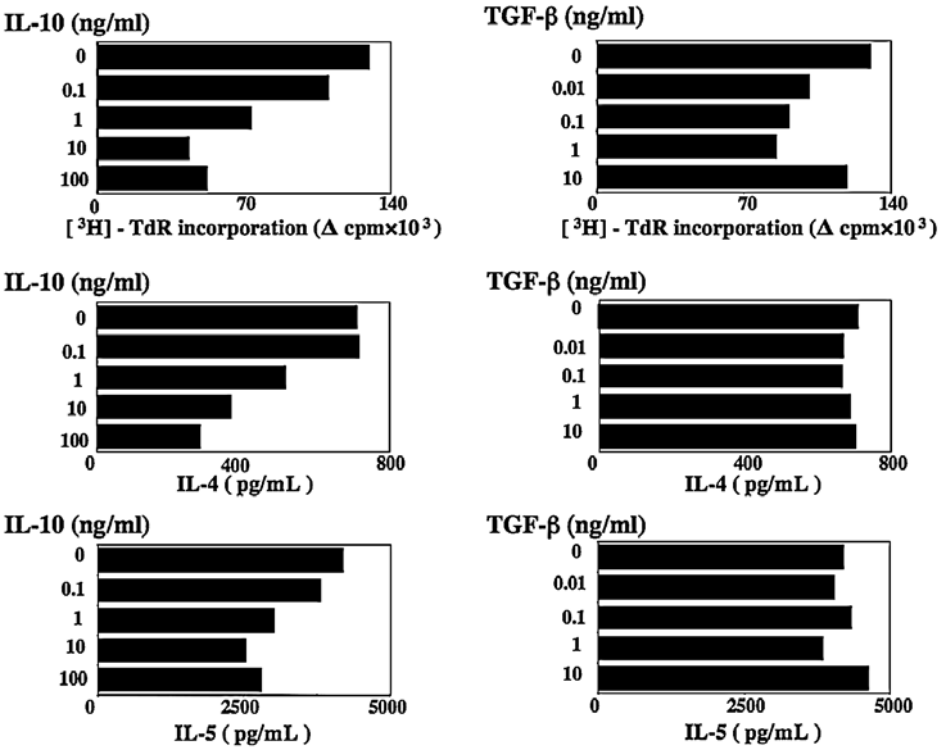

Figure 4. Antigen-induced proliferative responses and cytokine production of ß-lactoglobulin (BLG)-specific T cell clones. IL-10 inhibited the BLG-specific antigen-induced proliferation of T cell clones. IL-10 also inhibited the production of IL-4 and IL-5 by T cell clones.

PBMCs stimulated with PHA did not change with the addition of IL-10 (Fig. 3C).

Effect of IL-10 on specific antigen-induced proliferation of T cell clones. The effect of IL-10 on specific antigen-induced proliferation of T cell clones and Th2 cytokine production by T cell clones was examined. The BLG-specific antigen-induced proliferation of T cell clones was significantly inhibited by IL-10 in a dose-dependent manner (Fig. 4). In contrast, TGF-ß did not inhibit the proliferation of T cell clones.

Furthermore, IL-10 inhibited the production of the Th2 cytokines IL-4 and IL-5 by T cell clones in a dose-dependent manner (Fig. 4).

Discussion

Immune responses generated by cytokines are essential to the development of allergic disease (14). IL-4, IL-5 and IL-13 produced by Th2 cells induce, prolong and amplify allergic responses by enhancing the production of IgE and the recruitment, growth and differentiation of eosinophils and mast cells. They also directly cause airway hyperreactivity in and of themselves. It has been suggested that Th2-mediated allergic diseases result from inadequate Th1 cytokine production. Our previous studies demonstrated that IL-12 and IFN-γ play important roles in the regulation of IgE synthesis by B cells (15,16).

IL-10 is an anti-inflammatory cytokine. Human IL-10, in contrast to murine IL-10 (which is primarily a Th2 product), is produced by both the Th1 and Th2 cells (17) as well as by mononuclear phagocytes, which may be its most important source (18). A role for IL-10 in the regulation of immune responses to allergens was first suggested by studies revealing that IL-10 inhibited cytokine production by eosinophils stimulated with LPS (19). Later, it was demonstrated that IL-10 might also inhibit the production of cytokines, such as TNF and IL-6, by stimulated mast cells (20,21). IL-10 inhibits monocyte major histocompatibility complex-class (MHC-class II), B7.1 (CD80), B7.2 (CD88), intercellular adhesion molecule-1, and CD23 expression and accessory cell function (22). Monocytes pre-treated with IL-10 fail to induce specific antigen T cell proliferation.

In this study, IL-10 production by PBMCs in atopic patients, particularly BA patients, was significantly lower than in healthy control subjects. This might be explained by reduced IL-10 production, which was noted in the lungs of asthmatic patients as a result of a decreased gene expression level (23,24).

Next, we investigated whether the difference in IL-10 production between healthy control subjects and atopic patients was due to a difference in the distribution of the haplotype in the *IL-10* gene promoter region. In a previous study, the GCC/GCC genotype was associated with higher production and the ATA haplotype with lower production of IL-10 by PBMCs compared with other genotypes. However, none of our subjects had the GCC/GCC genotype. Most of the healthy control subjects and atopic patients had the ATA haplotype. Two of the BA patients had the GCC haplotype. IL-10 production by PBMCs was not affected by these haplotypes of the *IL-10* gene promoter region. Lim *et al* reported that the IL-10 haplotype has a role in determining disease severity, but does not seem to be important to disease susceptibility (12). More studies are required to clarify these points.

Lastly, we investigated the effect of IL-10 on the Th1 or Th2 cytokines. In this study, IFN-γ and IL-12 production by PBMCs stimulated with PHA were inhibited by IL-10. IL-12 production by PBMCs stimulated with LPS was also inhibited by IL-10. These data suggest that IL-10 is an inhibitor of Th1 cytokines. Moreover, IL-10 inhibited the antigen-induced proliferation of T cell clones and Th2 cytokine production by T cell clones. Previous studies have demonstrated that IL-10 inhibits cytokine production and the proliferation of $CD4^+$ T cells and T cell clones via down-regulatory effects on APC function (2,25). In addition, IL-10 directly affects the function of T cells and inhibits IL-4 and IL-5 production depending on activation conditions (26). It is reported that IL-10 production by regulatory T cells ($CD4^+$/$CD25^+$ T cells) plays an important role in the regulation of allergies by inhibiting Th0, Th1 and Th2 cells (27,28). Recently, it was reported that IL-10 and IL-13Rα2 coordinatedly suppressed Th2-mediated inflammation and pathology, respectively (29).

IL-10 could play a critical role in the pathogenesis of atopic diseases and is a modulator of Th1 and Th2 cytokines. However, further research into the function of IL-10 is required.

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