

CD23 expression on B-lymphocytes and its modulation by cytokines in allergic patients

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Summary

The aim of this study was to assess the expression of CD23 on peripheral blood B-cells, and its *in vitro* modulation by recombinant human interferon- γ (IFN- γ) in phytohaemagglutinin- (PHA) or recombinant human interleukin-4 (IL-4)-stimulated cultures in atopic patients with *Dermatophagoides pteronyssinus* hypersensitivity and in healthy non-atopic subjects. Atopic patients with asthma not receiving allergen-specific immunotherapy ($n=21$) were studied and further compared with a group of atopic subjects with asthma under allergen-specific immunotherapy ($n=21$). They were age (± 5 yr) and sex-matched. The results were also compared with those obtained in the non-atopic group ($n=11$). CD23 expression on B-lymphocytes and its modulation were analysed by flow cytometry using conjugated monoclonal antibodies with a double immunofluorescence method. Atopic patients had an increase in the percentage of B-cells expressing CD23 in peripheral blood. Phytohaemagglutinin and IL-4 induced a rise in the percentage of CD23-positive B-cells in both atopic groups and non-atopic subjects. Phytohaemagglutinin provoked an increase in the intensity of CD23 expression on B-cells from stimulated cultures in all groups, while IL-4 only produced a significant increase in atopic patients. The presence of IFN- γ decreased the CD23 expression on B-cells in PHA-stimulated culture of atopic patients, whereas it caused an increase in CD23 expression in the non-atopic group. Furthermore, the presence of IFN- γ in IL-4-stimulated cultures induced a decrease in CD23 expression on B-cells in all cases. These results indicate a difference between atopic and non-atopic donors in their responses to IL-4 and IFN- γ . On the other hand, allergen-specific immunotherapy did not induce any shift in the expression and modulation of this receptor.

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Introduction

Immunoglobulin E (IgE) synthesis is regulated by T-cells and their soluble products. B-lymphocyte factors, identified as soluble fragments of the low-affinity IgE Fc epsilon receptor type II (Fc ϵ RII), have been involved as well [1,2]. Fc ϵ RII has shown to be identical to CD23 B-lymphocyte differentiation and activation antigen [3] and two molecular forms of CD23 differing at the N-terminal cytoplasmic region have been described [4]. The expression of CD23 is modulated by lymphokines which also regulate

IgE synthesis; recombinant human interleukin-4 (IL-4) up-regulates CD23 expression and this effect can be inhibited by recombinant human interferon- γ (IFN- γ) [5] or other substances (IFN- α , TGF- β , PGE-2, anti-CD19 monoclonal antibody, glucocorticoids) [6–8]. CD23 has also been involved in the IgE-dependent presentation of antigen to T-cells. In this way, antigen may be processed on CD23-bearing B-cells by means of the binding to IgE and later be presented to T-cells [9].

Atopic patients are characterized by IgE hyperproduction. Cross-linking of antigen-specific IgE bound to the cell surface of mast cells and basophils induces the release of substances by these cells, which produce the clinical symptoms. Allergen-specific immunotherapy is one of the

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Table 1. Expression of CD23 on peripheral blood B-lymphocytes

	NI	IM	NA
CD20+/CD23+ cells	2.35 ± 1.22	3.47 ± 2.31	1.18 ± 0.60*
% CD23+ B-cells	29.05 ± 12.69	36.89 ± 16.17	14.63 ± 8.23*

*NI vs NA; IM vs NA $P < 0.01$.

NI, Non-immunotherapy group; IM, immunotherapy group; NA, non-atopic group. CD20+/CD23+ cells, percentage of peripheral blood lymphocytes expressing both CD20+ and CD23+; % CD23+ B-cells, percentage of peripheral blood B-cells that expressed CD23.

treatments used in these diseases. Its clinical efficacy has been demonstrated in many trials [10,11] but the immunological changes produced by the administration of this treatment are not well known.

The results of some reports suggest that $Fc_\epsilon RII$ participates in the allergic response [2,12], so that atopic patients may show a different CD23 induction and modulation on B-cells with respect to healthy non-atopic subjects. In the same way, immunotherapy may induce changes in CD23 regulation. The aim of this study was to assess the expression of CD23 on peripheral blood B-lymphocytes and its *in vitro* modulation by IFN- γ in phytohaemagglutinin- (PHA) or IL-4-stimulated cultures in atopic patients and non-atopic subjects. Moreover, the effect of immunotherapy on both CD23 expression and modulation was also studied.

Materials and methods

Forty-two asthmatic patients with *Dermatophagoides pteronyssinus* hypersensitivity were studied, according to a case-control methodology. They were age- (± 5 yr) and sex-matched. The 'non-immunotherapy group' (NI; case group) was composed of 21 patients who had never received allergen immunotherapy and had not been treated with systemic or topical glucocorticoids during the last 6 months: 10 males and 11 females, mean age 22 ± 10.93 yr (9–48 yr old). The 'immunotherapy group' (IM; control group) with 21 patients, mean age 21.10 ± 11.19 yr (10–49 yr old), received *D. pteronyssinus* immunotherapy for more than 2 yr and remained without symptoms for more than 1 yr.

Eleven non-atopic subjects were also studied: six males and five females, age 25.00 ± 7.01 yr (13–36 yr old) (non-atopic group (NA)). Atopy was excluded in this group by clinical history, prick test and concentration of IgE.

Cell cultures

Peripheral blood mononuclear cells (MNC) were collected from heparinized blood by a density gradient

method [13]. The optimal concentration of PHA, IL-4 and IFN- γ was chosen from preliminary studies in which a range of concentrations was tested (PHA: 1.25, 2.5, 6.25, 12.5 $\mu\text{g/ml}$; IL-4, 25, 50, 100, 200, 400 U/ml; IFN- γ : 10, 20, 40, 80, 160, 320, 500, 1000 U/ml). Thus, MNC (1×10^6 cells/ml) were incubated in RPMI-1640 medium, supplemented with 2 mM glutamine, 100 U/ml penicillin, 100 $\mu\text{g/ml}$ streptomycin and 10% heat-inactivated fetal calf serum, with PHA (2.5 $\mu\text{g/ml}$) (Polysciences, Warrington, U.S.A.) or IL-4 (100 $\mu\text{g/ml}$) (Genzyme Corporation, Boston, U.S.A.) and PHA (2.5 $\mu\text{g/ml}$) + IFN- γ (500 U/ml) (Genzyme Corporation, Boston, U.S.A.) or IL-4 (100 $\mu\text{g/ml}$) + IFN- γ (500 U/ml) for 72 hr at 37°C in a water-saturated atmosphere containing 5% CO_2 .

Flow cytometry analysis

Cultured cells were harvested and washed after 72 hr of stimulation. Both fresh and cultured mononuclear cells were stained with fluorescein isothiocyanate-conjugated anti-CD20 (Leu16) monoclonal antibody as B-cell marker (log green fluorescence measured as FL1) and phycoerythrin-conjugated anti-CD23 (Leu20) monoclonal antibody (log red fluorescence measured as FL2) (Becton Dickinson, Mountain View, U.S.A.) using a double immunofluorescence method. Both CD23-bearing B-lymphocyte percentage and CD23 expression were analysed by flow cytometry (FACScan) with the Consort 30 program. An electronic gate of unstimulated cells that showed FL1 fluorescence (CD20+ B-lymphocytes) was drawn based on side light scatter (which measures the granularity of cells) and FL1 parameter dot plots. In order to eliminate the interference of autofluorescence due to the presence of dead cells, we used control samples consisting of PHA-cultured cells only stained with anti-CD20 (FL1). In this way, any gate presenting non-specific fluorescence in FL2 was systematically discarded. Using the same gate, the percentage of CD23-bearing B-lymphocytes was analysed in all cultures from the same

Table 2. Percentage of B-lymphocytes that expressed CD23 in cell cultures

	NI	IM	NA
Unstimulated	2.85 ± 2.08	2.71 ± 2.17	3.45 ± 1.91
PHA	64.14 ± 17.01	68.47 ± 17.11	70.90 ± 15.85
IL-4	41.61 ± 14.83	35.00 ± 12.86	41.09 ± 17.75
PHA + IFN- γ	49.28 ± 13.58	50.85 ± 19.75	53.00 ± 19.48
IL-4 + IFN- γ	25.04 ± 12.97	23.00 ± 10.87	25.45 ± 13.06

P values. Unstimulated vs phytohaemagglutinin (PHA) and unstimulated vs recombinant human interleukin-4 (IL-4): *P* < 0.01 in each group. PHA vs PHA + recombinant human interferon- γ (IFN- γ) and IL-4 vs IL-4 + IFN- γ : *P* < 0.01 in each group. PHA vs IL-4: *P* < 0.01 in each group.

NI, Non-immunotherapy group; IM, immunotherapy group; NA, non-atopic group.

patient by double immunofluorescence cytograms. Furthermore, the mean channel of fluorescence intensity due to CD23 expression was analysed with FL2 single histograms.

Statistical methods

The Wilcoxon test for paired samples and the Mann-Whitney test for independent samples were used. A correlation study was also performed between the percentage of CD23-bearing B-lymphocytes in peripheral blood and IgE values.

Results

Compared with the non-atopic group, significant increases were observed in atopic patients in the percentage of peripheral blood lymphocytes expressing both CD20+ and CD23+, and in the percentage of peripheral blood B-cells that expressed CD23 (Table 1). Moreover, there was a significant correlation between IgE levels and the percentage of B-cells expressing CD23 in atopic patients only (*P* < 0.05). The percentages of B-cells expressing CD23 after culture with IL-4 or PHA, in the presence or absence of IFN- γ , are shown in Table 2. Significant differences were observed when the cultures within the same group were compared. However, we did not observe significant differences between NI, IM and NA groups.

When the mean channel of fluorescence intensity due to the expression of CD23 on B-cells was calculated we observed that PHA induced an increase in the mean expression of CD23 in all groups, as compared with unstimulated cells (Table 3). However, the degree of CD23 expression induced by PHA was similar in all

Table 3. Mean fluorescence intensity due to CD23 expression on B-lymphocytes in cell cultures

	NI	IM	NA
Unstimulated	245.2 ± 65.4	254.0 ± 87.0	166.5 ± 78.3
PHA	1060.9 ± 85.6	1044.0 ± 84.4	852.6 ± 154.3
IL-4	627.2 ± 63.1	596.8 ± 94.4	600.0 ± 14.4
PHA + IFN- γ	835.4 ± 98.1	822.0 ± 78.5	728.5 ± 66.3
IL-4 + IFN- γ	351.6 ± 33.3	351.1 ± 39.8	274.2 ± 38.8

The values are expressed in 'fluorescence units'.

P values. Unstimulated vs phytohaemagglutinin (PHA): NI, IM, *P* < 0.01; NA, *P* < 0.05. Unstimulated vs recombinant human interleukin-4 (IL-4): NI, IM, *P* < 0.01; NA, *P* = 0.06. PHA vs PHA + recombinant human interferon- γ (IFN- γ): NI, *P* = 0.01; IM, *P* = 0.05; NA, *P* = 0.40. IL-4 vs IL-4 + IFN- γ : NI, IM, *P* < 0.01; NA, *P* = 0.02. PHA vs IL-4: NI, *P* < 0.01; IM, *P* = 0.02; NA, *P* = 0.08.

NI, Non-immunotherapy group; IM, immunotherapy group; NA, non-atopic group.

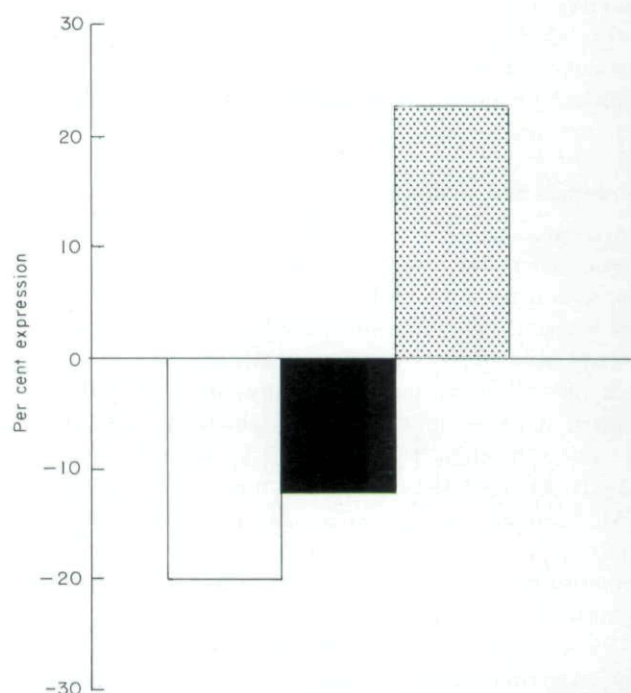


Fig. 1. The effect of recombinant human interferon- γ (IFN- γ) on B-lymphocyte CD23 expression in phytohaemagglutinin-stimulated cultures. The results are represented as the ratio between CD23 expression in cultures with IFN- γ by CD23 expression in cultures free of IFN- γ . □, Non-immunotherapy group. ■, immunotherapy group. ▨, Non-atopic group.

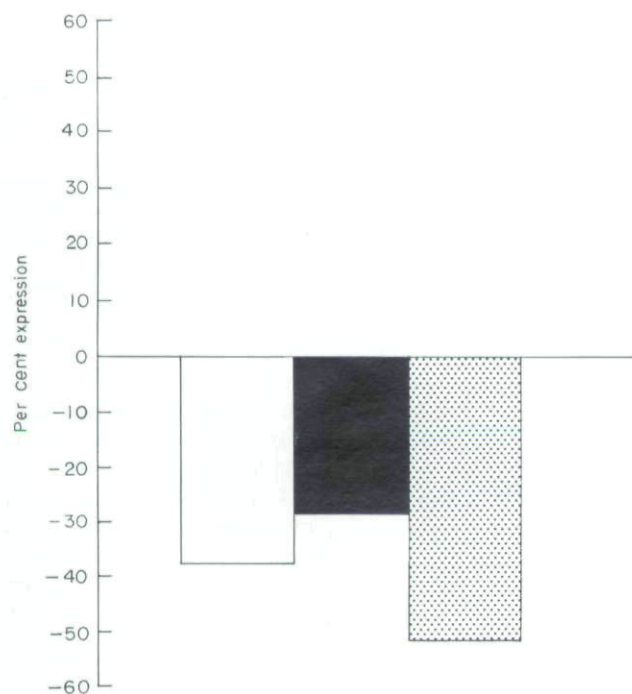


Fig. 2. The inhibitory effect of recombinant human interferon- γ (IFN- γ) on B-lymphocyte CD23 expression in recombinant human interleukin-4-stimulated cultures. The results are represented as the ratio between CD23 expression in cultures with IFN- γ by CD23 expression in cultures free of IFN- γ . □, Non-immunotherapy group. ■, Immunotherapy group. ▨, Non-atopic group.

groups. In IL-4-stimulated cultures, only atopic patients showed significant increases in mean CD23 expression. The presence of IFN- γ in the cultures blunted the response to PHA and IL-4 in the atopic groups. In contrast, IFN- γ did not affect the response of non-atopic B-cells to PHA, but did attenuate the response to IL-4 (Table 3).

When the mean fluorescence intensity of CD23+ B-cells induced by PHA was compared with those induced by IL-4, we observed that PHA consistently induced a higher level of CD23 expression. These differences were statistically significant in the atopic (NI, IM) groups, but not in the NA group.

The inhibitory effect of IFN- γ on PHA induction of increased B-cell CD23+ expression was greater in the NI group (20%) than in the IM group (12%) while, in the NA group, IFN- γ increased mean fluorescence intensity by 23% (Fig. 1). In contrast, in IL-4-stimulated cultures, IFN- γ inhibited CD23+ expression to a greater extent in the NA group (52%) than in the NI (38%) or IM (29%) groups (Fig. 2). However, there was wide variation in the magnitude of inhibition and none of these differences reached statistical significance.

Discussion

One of the main results of this work is an increase in the percentage of peripheral blood B-lymphocytes expressing CD23 in atopic patients with respect to the non-atopic subjects, which appears independent of the influence of immunotherapy. This increase may be attributed to a lower receptor proteolysis as a consequence of its stabilization by IgE, but it is more likely to result from increased synthesis as it has been shown that atopic patients have higher plasma concentrations of soluble CD23 [14,15].

Since IL-4 up-regulates CD23 expression on B-cells, as has been found in the present and other studies [5,16], the increase in the percentage of CD23-bearing B-lymphocytes may be due to the fact that atopic subjects present a higher plasma concentration of IL-4 than non-atopic individuals [17]. This increase of CD23-positive B-cells may have important implications in the regulation of IgE synthesis in atopic patients. In this regard, it has been suggested that soluble forms of this receptor are enhancing factors in IgE synthesis [1,2]. On the other hand, the CD23 molecule has been implicated in antigenic presentation mediated by IgE [9] and in T/B-cell interaction, where it acts as an adhesion molecule [18].

The induction of CD23 expression by IL-4 on B-cells, and its inhibition by IFN- γ , were reported by Defrance *et al.* in 1987 [5]. Other substances such as PHA [19], Concanavalin A [16], leukotriene B₄ [20] and Epstein-Barr virus [21] have also been shown to induce CD23 expression.

In our system, PHA and IL-4 up-regulated both the percentage of CD23-bearing B-cells and the level of CD23 expression in atopic and non-atopic subjects. These effects were more pronounced in PHA-stimulated cultures, because this mitogen induces the synthesis of several cytokines such as IL-2, IL-4 and IL-5, which in turn can induce or enhance CD23 expression [22,23]. These data were discordant with the results obtained by Kicza *et al.* [16] who did not find any increase in CD23 expression on B-cells from PHA-stimulated mononuclear cells.

In the present study, the lack of significant differences in CD23 expression induced by PHA or IL-4 between atopic and non-atopic subjects could account for the great inter-individual variability observed. However, when we analysed the increase in CD23 expression on B-lymphocytes due to IL-4 induction in each group, we found a significant increase only in atopic patients. These results could suggest that B-lymphocytes from atopic patients have a higher susceptibility to the action of this cytokine than B-lymphocytes from non-atopic subjects, but it must be pointed out that the small number of non-atopic subjects prevents a definite conclusion.

Other authors have shown that both PHA and IL-4 induced a higher increase of CD23 expression in MNC from the atopic patients [24,25], but the methodology employed in these studies did not allow an assessment of whether this effect was actually due to an elevation in the percentage of CD23-bearing B-cells or to the increase in the number of receptors per cell.

In evaluating other reports, it is also important to take into account the concentration of lymphokines used. The results of several works have been obtained using diverse IL-4 concentrations; although Conrad *et al* [26] did not find differences in CD23 expression when concentrations of IL-4 between 10 and 1000 U/ml were used, we observed in a preliminary assay a relationship between the expression of CD23 on B-cells and the concentration of IL-4 used.

In the present work IFN- γ decreased the percentage of CD23-bearing B-cells in both the PHA- and IL-4-stimulated cultures in all three groups. Nevertheless, the inhibition of the expression of CD23 in PHA-stimulated cultures was only significant in atopic patients not receiving allergen-specific immunotherapy.

The mechanism by which IFN- γ provokes such a decrease is not well known, although the effect of IFN- γ on CD23 expression is dependent on both cell type and state of cellular activation [27]. The inhibition of IL-4-induced CD23 gene transcription by IFN- γ has been demonstrated in B-lymphocytes [28]. Furthermore, it has also been suggested that IFN- γ may enhance the CD23 breakdown at the B cell membrane, because IFN- γ induces a decrease in receptor expression and a simultaneous increase in soluble CD23 in culture supernatants [26].

The failure of IFN- γ to down-regulate CD23 expression in the PHA-stimulated cultures from non-atopic subjects suggests that the expression of CD23 is not preferentially induced by IL-4 in these individuals, provided that IFN- γ only could inhibit CD23 expression when induced by IL-4. This hypothesis is supported by the fact that IFN- γ was more effective in inhibiting CD23 expression on B-cells in IL-4-stimulated cultures from the non-atopic group.

In conclusion, these results indicate that B-lymphocytes of atopic subjects have a distinct modulation of CD23 expression with respect to non-atopic individuals. Moreover, allergen-specific immunotherapy does not induce important alterations in the CD23 expression.

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