

Soluble CD23 (sCD23) serum levels and lymphocyte subpopulations in peripheral blood in rhinitis and extrinsic and intrinsic asthma

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To determine serum levels of IgE and sCD23 and lymphocyte subpopulations, we studied 37 control subjects and 84 patients (27 with allergic rhinitis, 27 with extrinsic asthma, and 30 with intrinsic asthma). A rise in surface CD23 on B and monocyte cells and sCD23 serum levels was exhibited by patients with rhinitis and extrinsic asthma. Unexpectedly, in intrinsic asthmatic patients, high CD23 expression on monocytes and high sCD23 levels were seen that did not result in IgE production. It appears that CD23, in its soluble form, could be a good disease marker, especially in asthma. Atopic patients yielded a significantly lower proportion of CD4 + T cells than intrinsic asthmatic patients and normal persons. Otherwise, CD4 + CD29 + CD45RA – and CD4 + CD29 – CD45RA + T-cell subsets were significantly decreased in all patient groups.

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Asthma is a chronic inflammatory disorder of the airways in which many types of cells play a role (11, 21). Asthma has been traditionally subdivided into extrinsic (allergic) and intrinsic (nonallergic) forms (9). The cause of nonallergic asthma is not known, but allergic asthma (6) and allergic rhinitis (15) are caused by an IgE-mediated mechanism.

T cells control IgE antibody production by B cells and they activate nonspecific effector cells (42). Stimulation by both interleukin (IL)-4 and allergens results in IgE synthesis, CD23 expression, and sCD23 release from peripheral blood lymphocytes (PBL) (5, 32, 35). Primary *in vivo* IgE response has been shown to be completely IL-4 dependent (13). However, a part of the secondary IgE response is IL-4 independent, probably because B cells have previously switched to the expression of IgE (23). Additional signals are also needed for *in vitro* IgE synthesis by B cells. These signals could be provided by CD4 + T cells (30) after cognate interaction (34, 40). Cognate interaction would result in the induction of CD23 (Fc γ RII) expression and sCD23 release. Soluble CD23 plays a regulatory role in ongoing IgE

production. Recently, a model has been proposed by Gordon et al. to explain this regulation system (19, 20).

Mosmann et al. (26) have defined two subsets of mouse CD4 + Th cells with distinct effector functions (1, 14). CD4 + T cells from atopic patients resemble murine Th2 in lymphokine production and helper function (22, 28, 36). Recent studies suggest that these subsets of T helper cells correspond to different stages of maturation (10, 31, 41). Memory T cells are found within the CD4 + CD29 + CD45RA – subset, which shows helper/inducer activity (24), and naive T cells are found within the CD4 + CD29 – CD45RA + subset, which has suppressor/inducer activity (25). It has been reported that lymphocytes from allergic patients express the memory T helper-cell phenotype CD4 + CD29 + CD45RA – (43).

This report investigates the changes in serum levels of IgE and sCD23 and the relationship between these variables and the distribution of lymphocyte subpopulations in allergic rhinitis, allergic asthma, and nonallergic asthma.

Material and methods

Subjects

Four groups of persons have participated in this study: 37 normal volunteers, 27 allergic rhinitis patients, 27 extrinsic asthma patients, and 30 intrinsic asthma patients (Table 1). Rhinitis patients were defined as having rhinitis symptoms (nasal blockage, sneezing, and nasal discharge) but showing no evidence of bronchial hyperresponsiveness. All of them showed positive responses to skin prick test with a standard set of allergens. Asthmatic patients were defined by the criteria of the American Thoracic Society (2) on the basis of clinical symptoms, physical examination, and pulmonary function studies showing normal or reversible airway obstruction, as manifested by a postbronchodilator increase in FEV₁ > 15%. At the time of study, the patients were not in acute respiratory distress. Medications used by patients with asthma included oral theophylline and inhaled β-agonists on an as-needed basis. No patients had required treatment for exacerbation of asthma with oral or intravenous corticosteroids for at least 6 months before the study. Inhaled therapy (β-agonists) and theophylline were withheld for at least 12 h before blood sampling, and no patient had received immunotherapy in the last year.

Asthmatic patients were divided into two different groups: allergic (extrinsic) and nonallergic (intrinsic). Extrinsic asthmatic patients had a positive history of a bronchoconstrictive response after allergen exposure and positive wheal and flare reaction to skin prick test. Intrinsic asthmatic patients had exacerbations of asthma during respiratory tract infections, no history of allergen-induced bronchospasm, and negative skin prick test reactions to a standard set of allergens. Healthy volunteers with no history of atopy were used as controls. None of them had taken any medication in the last 3 months. Appropriate informed consent was obtained from all the subjects.

Blood collection

Peripheral blood from both normal subjects and patients was collected between 08:00 and 08:30 under

Table 1. Patient characteristics

Subject	n	Age*	SPT	IgE**
Control	37	32	-	37
EA	27	28	+	209
IA	30	45	-	39
Rhinitis	27	27	+	214

* Age mean of group; ** serum IgE levels (U/ml) mean; SPT, skin prick test; EA, extrinsic asthma; IA, intrinsic asthma.

sterile conditions. EDTA (ethylenediaminetetraacetic acid) tubes for fluorometric analysis in whole blood and nonheparinized vacutainer tubes for serum determinations were used.

Flow microfluorometry analysis

Lymphocyte and monocyte differentiation antigens CD2, CD3, CD4, CD8, CD14, CD19, CD23, CD29, and CD45RA were quantified with murine monoclonal antibodies (mAb) conjugated to phycoerythrin (PE) or fluorescein (FITC). CD29 and CD45RA were supplied by Coulter Immunology and the rest by Becton Dickinson. Two-color fluorescence was performed to determine CD19 + CD23 +, CD14 + CD23 +, CD4 + CD29 +, and CD4 + CD45RA + cell subpopulations. FITC-conjugated rabbit antihuman IgE from Dakopatts was used to detect surface IgE on B cells. Before the surface IgE determination, venous blood was washed three times with phosphate-buffered saline (PBS) and incubated with 5% fetal calf serum PBS (PBS-FCS) for 30 min at 37°C, to eliminate serum immunoglobulins and citophilic nonspecific antibodies, respectively. This treatment was performed in both patients and controls. Samples were analyzed on a FACScan-Analyzer (Becton Dickinson). Data were expressed as percentage of total lymphocytes.

Soluble-CD23 assay

Serum sCD23 levels were measured by a sandwich enzyme-linked immunoassay (Cellfree CD23 Test-Kit, T-Cell Sciences, Cambridge, MA, USA). Standards and samples were performed in duplicate. Absorbance was measured at 492 nm in a Whittaker 2001 ELISA reader. The assay detection limit, established by the manufacturer, was 15 U/ml.

Serum IgE measurement

Serum IgE levels were determined by nephelometry with a Behring Nephelometer.

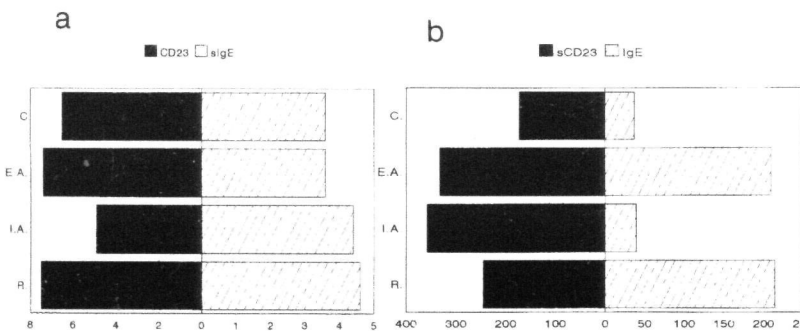


Fig. 1. a) CD23 and surface IgE expression on PBL, expressed as lymphocyte percentage; b) serum levels of sCD23 and IgE, expressed in U/ml, obtained from patients with extrinsic asthma (EA), intrinsic asthma (IA), rhinitis (R), and control subjects (C).

Table 2. Serum levels of IgE and sCD23 (U/ml)

	Control	EA	IA	Rhinitis
IgE	37±14	209±170*	39±16	214±97*
sCD23	172±120	332±200**	358±216**	245±170

EA, extrinsic asthma; IA, intrinsic asthma; * $P<0.05$; ** $P<0.02$.

Statistical analysis

Statistical analysis was performed with Student's *t*-test. Differences associated with probability values of $P<0.05$ were considered to be significant.

Results

When total serum IgE levels were measured, no difference was found between intrinsic asthmatic patients and normal subjects, while significantly higher values were obtained in allergic patients ($P<0.05$). All the patient groups showed an increase in sCD23 serum levels, an increase which was not significant in the rhinitis group. However, both types of asthma revealed significantly increased sCD23 levels ($P<0.02$) (Fig. 1). These data are shown in Table 2.

The B-cell population was quantified by measuring CD19 expression. For detection of the presence of surface IgE and its low-affinity receptor ($Fc_\epsilon RII$) on B cells, anti-IgE and anti-CD23 were used. CD19 expression was increased in all patient groups, although significant differences were found only in rhinitis and intrinsic asthma ($P<0.05$). Similar surface IgE values were observed in both patients and normal subjects. Analysis of the CD19+CD23+ subpopulation showed significantly increased levels in allergic rhinitis and allergic asthma, without any modification in nonallergic asthma, as compared with control subjects (Table 3).

Table 3. Lymphocyte subpopulations in extrinsic asthma, intrinsic asthma, rhinitis, and controls

	Control	EA	IA	Rhinitis
CD2	84.3±6.5	81.6±5.6	81.7±7.6	81.5±5.5
CD3	75.9±10	71.5±10	71.6±13	71.8±8.7
CD4	49.2±9.6	43.0±7.2*	47.5±11.8	41.9±8.3***
CD8	30.6±6.3	31.6±6.4	28.3±11.4	32.8±8.6
CD29	96.3±4.1	75.0±22.3#	70.6±18.4#	82.6±3.0#
CD45RA	81.3±16.2	60.6±24.5**	46.0±14.4#	45.0±13***
CD19	6.6±3.5	7.5±2.1	10.2±8.5*	8.6±2.8*
sIgE	3.6±2.8	3.6±1.5	4.4±3.6	4.6±3.9
CD23	6.5±5.6	7.4±3.6	4.9±4.2	7.5±4.4
CD4CD29	53.1±10.6	39.4±14.6***	33.9±10.8#	40.6±6.6*
CD4CD45RA	49.8±18.8	31.3±18.2*	25.3±14.5*	20.1±14.3#
CD19CD23	3.0±2.2	4.5±2*	3.7±4.8	4.6±2.1*

* $P<0.05$, as compared with control; ** $P<0.01$; *** $P<0.005$; #, $P<0.001$; EA, extrinsic asthma; IA, intrinsic asthma. Data are expressed as mean values ± SEM (%).

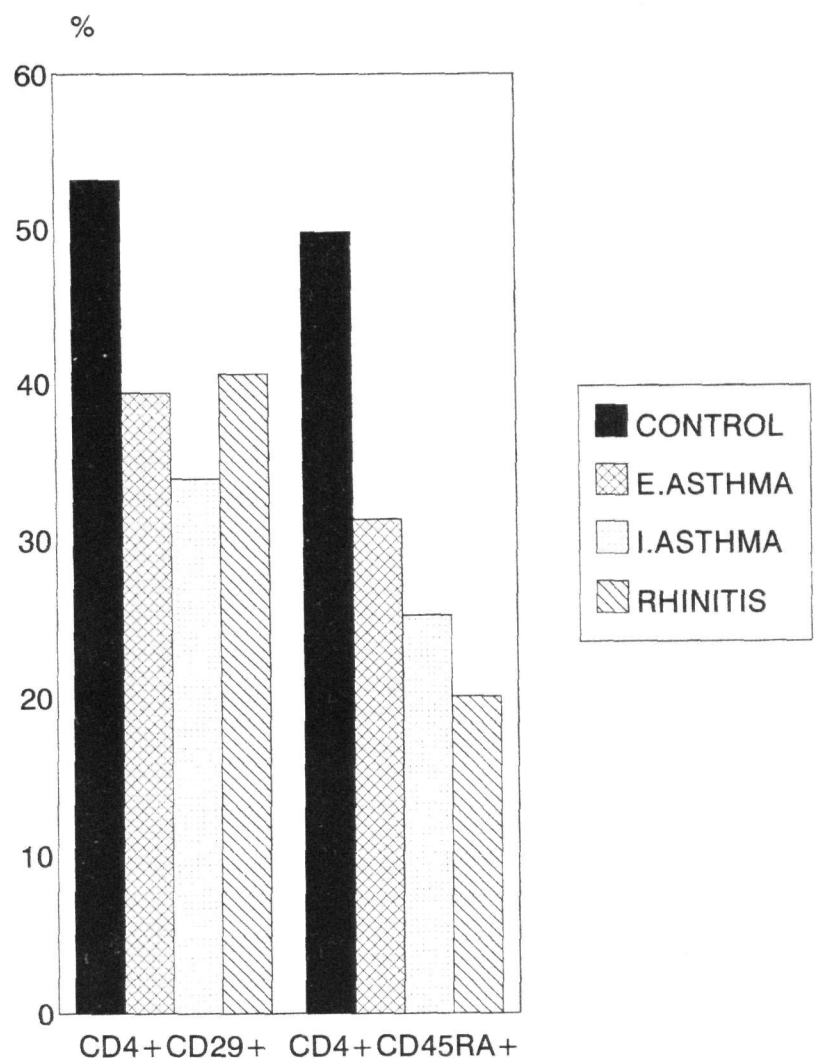


Fig. 2. CD4+CD29+ and CD4+CD45RA+ T-cell subpopulations in patients with rhinitis (R), extrinsic asthma (EA), intrinsic asthma (IA), and healthy subjects (C). Data are represented as lymphocyte percentage mean values.

CD14 has been considered to be a useful marker for monocyte characterization. It is known that CD23 is expressed on human blood monocytes. Therefore, we measured the CD14+CD23+ co-expression in every group. As shown in Table 4, CD14 expression was found to be similar in patients and normal subjects. However, determination of $Fc_\epsilon RII$ expression on monocytes revealed a significantly higher number of CD14+CD23+ in all groups of patients and especially in both types of asthma ($P<0.001$).

For characterization of the T-cell population and its subsets, expression of CD2, CD3, CD4, and CD8 was determined. CD2 and CD3 expression revealed no significant differences among the studied groups.

Table 4. Monocyte populations in extrinsic asthma, intrinsic asthma, rhinitis, and controls

	Control	EA	IA	Rhinitis
CD14	7.1±2.3	5.8±4.3	6.6±3.5	6.3±4.4
CD14CD23	22.6±7.4	95.1±16.2*	93.6±20.1*	87.4±7.2*

* $P<0.001$, as compared with control; EA, extrinsic asthma; IA, intrinsic asthma. Data are expressed as mean values ± SEM (%).

A decrease in CD4 T cells was found in all patient groups, as compared with controls. This fall was statistically significant in the allergic rhinitis ($P < 0.005$) and allergic asthma ($P < 0.05$) groups. In the nonallergic asthma group, the CD4 + T-cell decrease was not significant. The measurement of the CD8 subset showed an increase in both allergic groups and a decrease in intrinsic asthmatic patients, although these differences were not significant. To explain the CD4 fall, we analyzed CD4 + CD29 + and CD4 + CD45RA + subsets by double-fluorescence labeling (Fig. 2). A significant decrease in CD4 + CD29 + T cells was observed in all patient groups ($P < 0.01$). Moreover, CD4 + CD45RA + T cells also showed statistical diminution (rhinitis and extrinsic asthma $P < 0.05$ and intrinsic asthma $P < 0.001$). Data are summarized in Table 3.

Discussion

Allergic processes are complex disorders in which inflammatory and immunologic mechanisms are involved. In our work, differences in CD23 expression on B cells and monocytes, sCD23 levels, and T-cell subsets have been found in patients suffering from rhinitis, allergic asthma, and nonallergic asthma. CD23 is an activation marker expressed on B cells as they undergo isotype switching, and it acts as a low-affinity IgE receptor. Furthermore, soluble CD23 may act as an autocrine on IgE synthesis (5, 8). That is why it was important for us to analyze CD23 expression and serum sCD23 release.

We found CD19 + CD23 + cells to be significantly increased in rhinitis and extrinsic asthma, while normal levels were observed in intrinsic asthma, as compared with controls, in agreement with other authors (5, 41). In contrast, CD19 expression showed an increase in all patients. All the groups exhibited similar surface IgE expression, whereas serum IgE levels were clearly different, as classically established (Fig. 1). Consequently, a decrease in B cells seems unlikely to cause the low IgE level observed in nonallergic asthma, although its degree of lower B-cell activation could be involved in this.

Monocytes may also be considered to be potentially involved in the initiation and maintenance of allergic inflammation and to express CD23 on their surface (33). No difference was found in either the monocyte number or CD23 expression on this cell type between both types of asthma (Table 4). In agreement with previously reported studies (12, 16), our data showed that monocytes expressing CD23 were enhanced in allergic patients. To our surprise, we had found evidence that this subset was similarly augmented in intrinsic asthma. In fact, these results suggest that in the pathogenesis of intrinsic asthma this cell type could also play a role. In the same way,

serum sCD23 release in nonallergic asthmatic patients was as high as in allergic patients (Fig. 1). The intrinsic asthma group, whose CD23 expression on B cells was normal, exhibited high levels of sCD23 which did not result in IgE production. As noted above, sCD23 plays a crucial role in regulation of IgE synthesis (7, 18, 20, 29, 32, 41), increasing IL-4-induced IgE synthesis (8, 37). In another way, CD23 cleavage generates several soluble fragments, one of which, the 37-kDa fragment, retains the capacity to bind IgE, a capacity which is reduced in the 25-kDa form, as Gordon and Gordon et al. have recently reported (17, 20). Therefore, we argue that the IL-4 decrease reported in intrinsic asthma (41) could prevent a sCD23 effect on IgE synthesis regulation, but, on the other hand, the soluble CD23 fragments detected in intrinsic asthma could correspond to 12- and 25-kDa molecular forms, which were unable to promote IgE synthesis (20). Further studies including sCD23 fragments may resolve this issue.

It has been reported that β -adrenoceptor agonists induce sCD23 release (27). However, the increase of sCD23 observed in both groups of asthma seems to be independent of the β -adrenoceptor agonists, because, to avoid interference, this therapy was suspended at least 12 h before blood collection. In addition, this effect is IL-4 dependent, a fact which could explain the sCD23 increase in allergic but not in nonallergic asthma, in which this cytokine is reduced.

Fc ϵ R2/CD23 can be considered to be an accessory molecule in the interaction between T cells and antigen-presenting cells (APC), and it is physically related to the MHC class II molecules on B-cell and monocyte surfaces (3). The engagement of CD23 to a membrane counterpart, a subtype of CD21, previously described as the complement receptor 2 (4), would mediate a heterotypic adhesion and potentiate IgE production (39). In consequence, T cells release a combination of cytokines, among them IL-4, which can induce CD23 expression on B cells, and which may provide a costimulatory signal to amplify the T cell/B cell interaction, triggering IgE production in the presence of IL-4 (8). Thus, T cells through the network cytokine released could represent a factor linking IgE production and cells involved in the pathogenesis of allergic inflammation, such as eosinophils, mast cells, basophils, and macrophages (33).

Consistent with the proposed upregulator role of CD23 in IgE synthesis and the costimulator role of sCD23 for CD4 + T cells, it would be reasonable to expect changes in the distribution of CD4 + T-cell subpopulations in the patient included in this study. Our results, conflicting with data recently reported by Walker et al. and Schauer et al. (38, 41, 42),

showed no variation in this cell subset in intrinsic asthmatic patients, while a fall was observed only in allergic patients. Therefore, this CD4⁺ T-cell decrease suggests a selective mobilization of this subset into the airways, where it might exert its own influence. Another possible interpretation is that, although the total CD4⁺ population was decreased, high serum IgE levels in atopic patients are caused by an imbalance in the two functionally different CD4⁺ T-cell subsets, CD4⁺CD29⁺CD45RA⁻ and CD4⁺CD29⁻CD45RA⁺, with an increase of the helper/inducer subset (CD4⁺CD29⁺CD45RA⁻). However, our findings were unexpected, since both CD4⁺CD29⁺CD45RA⁻ and CD4⁺CD29⁻CD45RA⁺ subsets were decreased in all patient groups, even in the intrinsic asthmatic group, in which the total of CD4⁺ T cells was not decreased (Fig. 2).

Taken together, our results clearly indicate differences in CD19⁺CD23⁺ and CD4⁺ T cells between allergic and intrinsic asthmatic patients, although equally high CD14⁺CD23⁺ and sCD23 levels were found in both. In this respect, it appears that CD23, in its soluble form, may be a good disease marker, especially in asthma. On the basis of the findings summarized here, we think that sCD23, the pair CD23-CD21, and CD45 isoforms may have a potential function, which remains to be determined, in the immunoregulation of intrinsic asthma. Its determination will lead to better understanding of the pathogenesis of this disease and to new treatment for it.

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