

Serum levels of IgE-binding factor (soluble CD23) in diseases associated with elevated IgE

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Summary

Several *in-vitro* experiments suggest that the low affinity receptor for IgE (FcεRII) and its soluble fragment (IgE-binding factor, IgE-BF) are multi-functional molecules and more particularly that they are capable of regulating the synthesis of human IgE. In an attempt to examine the *in-vivo* significance of these *in-vitro* observations, the serum level of IgE-BF was measured in individuals with allergic or parasitic diseases, both associated with an increased production of IgE. IgE-BF was measured by a radioimmunoassay employing two mAbs against FcεRII (mAbER). We first compared 257 allergic subjects to 172 non-allergic controls matched for age and sex. Statistical analysis of the data, after logarithmic transformation of IgE-BF and IgE values, revealed that despite a great overlap, the allergic subjects had significantly higher levels of IgE-BF. The correlation between IgE and IgE-BF was very weak but significant. Allergic or non-allergic children had significantly higher IgE-BF levels than the corresponding groups of adults; moreover, the inverse correlation between age and IgE-BF levels was significant only in the children and not in the adults. The IgE-BF levels were not influenced by gender, by hyposensitization therapy or by treatment with local steroids. Subjects receiving systemic steroids had lower IgE-BF levels than untreated subjects. To assess the effect of seasonal exposure to allergen, IgE-BF levels were monitored for 1 year in six rye grass-sensitive hay fever subjects known to display a seasonal increase of both total serum IgE and of specific anti-*Lolp*I and *Lolp*II IgE antibodies. The levels of IgE-BF remained stable in the hay fever subjects as well as in the non-allergic controls. Twenty subjects with filariasis and high serum IgE concentrations also displayed increased levels of serum IgE-BF when compared to control individuals. The serum IgE-BF detected by the RIA was not bound to IgE as shown by two independent observations: (1) they were not adsorbed on an anti-IgE immunoadsorbent column and no serum IgE was retained on an immunoadsorbent column coupled to mAb against IgE-BF; and (2) the serum molecules binding to mAbER-coated solid phase did not react with radiolabelled monoclonal or polyclonal anti-IgE, and reciprocally the serum molecules binding to anti-IgE-coated solid phase did not react with labelled mAbER. Taken collectively, the present data are compatible with, but do not add further support to, the hypothesis that IgE-BF may regulate the synthesis of human IgE.

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Introduction

The low affinity receptor for IgE (FcεRII or CD23 antigen) exists in two forms (named a and b) differing only

in the first few amino acids of the intracytoplasmic region [1]. FcεRII a and b are encoded by the same single copy gene [2] which may be activated by two different promoters, resulting in different initiation sites and alternative splicing. FcεRII a is expressed on freshly isolated normal B cells whereas FcεRII b is found on monocytes and eosinophils as well as on IL-4-induced B

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cells. On monocytes, eosinophils and platelets, FcεRII was clearly shown to mediate IgE-dependent cytotoxic reactions [3]. However, this low affinity IgE-binding molecule is thought to have several other functions that are not IgE-dependent. An increasing number of observations suggest that FcεRII/CD23 may be involved in B-cell activation, antigen presentations to T cells and cell adhesion [review in 4]. FcεRII is cleaved into soluble fragments, among which some retain the ability of binding to IgE (IgE-binding factors; IgE-BF). These IgE-BF may have a molecular weight of 37, 33 and 25 kD [5, 6]. Several functions have also been ascribed to soluble FcεRII fragments, including: (1) the regulation of B and T cell proliferation [7–11], (2) the inhibition of monocyte migration [12], and (3) the maturation of early thymocytes [13]. Studies from this laboratory [14–16] and from others [17, 18] have suggested further that IgE-BF may regulate the synthesis of human IgE. All these activities of IgE-BF have been observed *in vitro* and their physiological significance remains to be documented. One approach to address this issue is to measure the serum level of IgE-BF in selected clinical conditions where these molecules might play a role as suggested by the *in-vitro* observations. In the present study we have examined the relationship between the serum levels of IgE-BF and of IgE in allergic and in parasitic diseases known to be associated with an overproduction of IgE.

Subjects and methods

Study participants

Allergic diseases. (a) *Cross-sectional study.* Serum was obtained from 257 Japanese allergic subjects (172 were attending the adult out-patient clinic at the National Sagamihara Hospital; they are referred to as 'adults'; 85 subjects were attending the paediatric allergy clinic and are referred to as 'children') and from 119 non-allergic Japanese controls. The age and sex distribution of the participants is shown in Table 1. All the asthmatics (120 adults and 78 children) were symptomatic and were being treated with bronchodilators; some were also treated by

corticosteroids and/or by immunotherapy. All of the asthmatic subjects had positive skin and RAST tests to either house dust mite and/or animal danders. The subjects with allergic rhinitis were all sensitive to Japanese red cedar pollen. Sera were collected from the beginning of March to the beginning of May (i.e. during or immediately after the red cedar pollen season). The controls comprised either volunteer staff members at the Sagamihara Hospital or of children suffering from either epilepsy, minor surgical disease or viral infection. All of the controls had negative RAST tests against house dust mite, grass pollen and red cedar pollen; none had a history of allergic disease. (b) *Longitudinal study.* Six rye grass-sensitive hay fever subjects and six normal controls all living in the Baltimore area were tested. Their IgE response to rye grass pollen antigens (*Lol p I* and *Lol p II*) have been reported previously [19]. Seven serum samples were collected from each participant over a 1-yr period.

Parasitic diseases. The subjects included in this section have been described previously [20]. Twenty North-American individuals with loiasis acquired in West Africa were studied along with 18 age-matched non-allergic controls.

Normal controls. Besides the controls mentioned above, 40 sera from healthy Canadian Caucasians, aged between 21 and 42 yr, were also tested. These participants had no history of allergic disease and they had a negative RAST test against house dust mite, grass pollen, ragweed and animal dander.

All the sera included in the present work were stored at -20°C and those received from foreign centres were shipped on dry ice.

Radioimmunoassay for the detection of IgE-BF

This method has been described in detail elsewhere [21]. Briefly, the wells of polyvinyl microtitre plates were coated with mAbER 176 (from the clone 208.25.D.2.1/176), blocked with Hanks' solution containing 10% foetal

Table 1. Participants

	Adults			Children		
	Asthma	Rhinitis	Controls	Asthma	Rhinitis	Controls
No. of cases	120	52	69	78	7	50
Age (yr) (mean $\pm$ 1 s.d.)	42 $\pm$ 11.7	31.7 $\pm$ 11.8	33.5 $\pm$ 7.5	10 $\pm$ 3.1	9.5 $\pm$ 2.8	10.4 $\pm$ 3.9
Females/males	60/60	26/26	30/39	40/38	5/2	25/25

calf serum and washed with phosphate-buffered saline (PBS). One hundred microlitres of test sample were added to the wells and, after 4 hr incubation at room temperature, the wells were washed and 100 μ l of ^{125} I-labelled mAbER 135 (from the clone 208.25.A.4.3/135; $2-3 \times 10^5$ c.p.m., in Hanks' solution containing 10% bovine serum and 2% normal mouse serum) was added. After an overnight incubation, the wells were washed and counted in a gamma counter. The assay was calibrated by reference to a standard preparation made from a culture supernatant of RPMI 8866 cells, prepared as previously described [21], to which all sera were compared. The interassay variation, determined on 38 sera tested on three occasions at 2 and 4 week intervals was $18.3 \pm 11.7\%$ [21]. It was recently determined that one unit of IgE-BF corresponds to 50 pg protein [E. Kilcherr; Ciba-Geigy, Switzerland; personal observation]; the sensitivity of the assay (two times the background c.p.m.) is less than 50 pg/ml.

Radioimmunoassays for the detection of complexes containing IgE and IgE-BF

The presence of complexes made of IgE and IgE-BF was tested by two solid-phase radioimmunoassays (RIAs) performed exactly as above. In the first assay, the wells of a 96-well microtitre plate were coated with anti-IgE monoclonal antibody (10 μ g/ml; clone 4.15 received from Dr A. Saxon, UCLA, U.S.A. After overnight incubation with the test samples, the plates were washed and reacted with ^{125} I-labelled mAbER 135, as in the previous assay. The second series of RIAs were performed under identical conditions, except that ^{125} I-labelled anti-IgE was used as the second antibody, whereas one of the following mAbER was adsorbed on the solid-phase: 208.75.D.2/94; 208.25.A.4.2.64; 207.25.A.4.4/30; 208.25.A.4.3/135; 208.25.D.2.1/176 produced in our laboratory or mAb 3-5 kindly provided by Dr T. Kishimoto (Osaka, Japan). In some experiments, affinity-purified polyclonal anti-IgE was used as labelled second antibody. It must be noted that all the RIAs were performed in the presence of 2% normal mouse serum, to avoid false positive results caused by the presence of anti-mouse antibodies in some sera.

Immunoabsorption experiments

The adsorptions were carried out by passing 0.5 ml serum through a 0.3 ml immunoabsorbent column at a flow rate of 1-2 ml/hr. The two immunoabsorbents used in this study were prepared exactly as described earlier, by coupling mAbER 135 or anti-IgE mAb to Affi-gel [21]. After adsorption, the columns were washed successively

with 20 gel-volumes of PBS containing 0.5% Tween 20 and 20 volumes of PBS. The adsorbed material was eluted with 0.1 M glycine buffer, pH 2.6 and the eluate was collected in tubes containing 1 M Tris buffer (pH 9) and 5% foetal calf serum.

Statistical analyses

Mean values of serum IgE-BF levels in the different study groups were compared by Student's *t*-test after logarithmic transformation of the data. Two-way variance analysis was used in the longitudinal study. Correlations of IgE-BF levels versus IgE levels and age were examined by the non-parametric Spearman's rank-correlation test.

Results

Cross-sectional study of allergic subjects

The comparison of serum IgE-BF levels in the different study groups indicates that despite of a great overlap, the allergic subjects had significantly higher ($P < 0.001$) levels than their age-matched controls (Fig. 1). Moreover, allergic or non-allergic children had significantly higher ($P < 0.001$) levels of serum IgE-BF than the corresponding groups of adults. It is of interest to note that subjects treated with small doses of systemic corticosteroids (3-10 mg of prednisone/day) had significantly lower levels of serum IgE-BF than untreated subjects of similar age (Table 2). This finding must, however, be interpreted with caution because the number of subjects receiving oral steroids (19) is small compared to that of untreated patients (100). Inhaled steroid therapy (100-600 μ g/day of beclomethasone dipropionate) did not influence the serum IgE-BF levels (Table 2). Additionally, IgE-BF

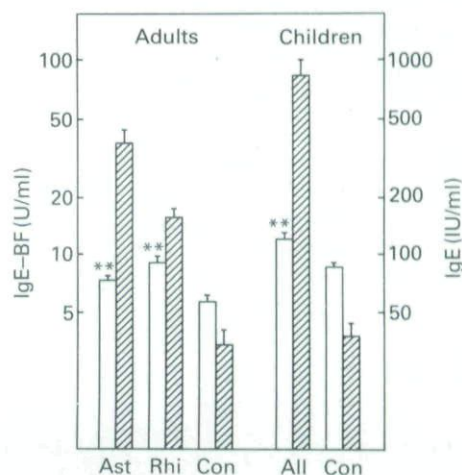


Fig. 1. Serum levels of IgE-BF (□) and of IgE (▨) in allergic subjects and non-allergic age-matched controls. Geometric mean values $\pm$ 1 s.e.m.; ** different from controls at $P < 0.001$. Ast: asthma; Rhi: rhinitis; Control; All: allergic.

Table 2. Corticosteroid treatment and serum IgE-BF

	Treated		Untreated
Oral steroids*			
No. of cases	19		100
IgE-BF (U/ml)	6.3 ± 5.9	$P < 0.01$	9.3 ± 5.6
IgE (IU/ml)	525 ± 743		710 ± 719
Age (yr)	43		41
Range	18-78		17-76
Local treatment†			
No. of cases	36		16
IgE-BF (U/ml)	10.1 ± 4.8		10.3 ± 3.5
IgE (IU/ml)	294.2 ± 395		300 ± 278
Age (yr)	30.1		35.3
Range	16-53		17-54

* Adult subjects with bronchial asthma.

† Adult subjects with allergic rhinitis.

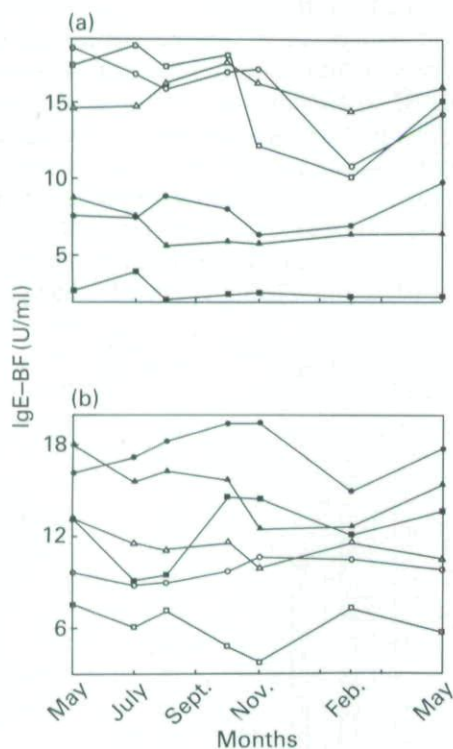


Fig. 2. Influence of pollen exposure on serum IgE-BF levels. Rye-grass-sensitive hay fever subjects (a) and normal controls (b) were tested, as indicated, for their serum IgE-BF levels; the pollen season extends from the second week of May to the end of June. Note that the IgE-BF levels remained stable and that there was no difference between allergic and non-allergic individuals.

Table 3. IgE-BF in parasitic (filarial) diseases

	Loa loa*	Normals
No. of cases	20	18
Age (yr)		
Mean	24 ± 6.5	23 ± 7.3
Range	21-49	22-49
IgE (IU/ml)		
	1080	137
	3607-180	24-560
IgE-BF (U/ml)		
	17.9 ± 7.6	9.9 ± 4.72

* North Americans acquiring *Loa loa* infection.

levels were not influenced by sex (data not shown) or by immunotherapy (the IgE-BF level in 111 treated cases was 9.5 ± 5.7 U/ml, as compared to 8.5 ± 4.6 U/ml in 61 age-matched untreated subjects).

The relationship between age and the presence of IgE-BF was examined next. Age was inversely correlated with IgE-BF levels only in the children ($r = -0.26$, $P = 0.006$) but not in the adults; the influence of age was the same for allergic and non-allergic children. As expected, age was also inversely associated with serum IgE levels; again, this association was significant only in the children. The relationship between IgE and IgE-BF levels was examined in the adult group (where age did not influence either IgE or IgE-BF levels). In these individuals, the two variables were weakly but significantly associated ($r = 0.16$, $P = 0.008$). Finally, it is of note that the Japanese controls had significantly lower IgE-BF levels (6.5 ± 3.2 U/ml; $n = 69$) than the Caucasian controls tested in the same assay (9.7 ± 4.2 , $n = 40$; $P < 0.01$).

Longitudinal studies

To examine the relationship of allergen exposure to the presence of IgE-BF, serum from six rye grass-sensitive subjects and six non-allergic controls were tested during a 1-yr period. As illustrated in Fig 2, the levels of IgE-BF remained stable in both groups. The significance of these observations stems from a previous study [19], when the same allergic subjects were shown to display a seasonal increase of both total serum IgE and of specific IgE antibodies to *Lol p I* and *Lol p II*.

Parasitic diseases

The level of IgE-BF in a filarial parasitic disease associated with markedly elevated serum IgE levels was then studied (Table 3). In subjects with the immunologically hyperresponsive form of *Loa loa* infection, the levels of IgE-BF were significantly elevated compared to normal North American age-matched controls ($P < 0.05$).

Table 4. Adsorption experiments

Serum no.	Before adsorption		Effluent		Eluate IgE-BF
	IgE (IU/ml)	IgE-BF (U/ml)			
			IgE	IgE-BF	
Adsorption on anti-IgE					
1	2500	28	20	26	0.1
2	23 000	22	650	19	0.1
3	266	19	0	17	0
4	48	10	0	8.5	0
Adsorption on mAbER					
1	145	12	120	0	0
2	48	8	48	0	0
3	65	9	45	0	0
4	3300	27	3100	0	0
5	2500	24	2500	0	0

Detection of IgE-BF bound to IgE

Two approaches were used to define if the serum IgE-BF detected by the RIA were bound to IgE; (1) immuno-adsorption of the sera on mAbER or on anti-IgE affinity columns; and (2) sandwich RIAs. Removal of serum IgE by adsorption on an anti-IgE column did not affect the level of IgE-BR measured (Table 4) and, moreover, the IgE-BF could not be recovered in the glycine eluate. Conversely, the depletion of IgE-BF by adsorption on mAbER column did not influence the level of IgE (Table 4).

Finally, sera from allergic ($n=20$) and non-allergic ($n=20$) individuals were tested in parallel by sandwich solid-phase RIAs employing six different mAbER to coat the wells and radiolabelled anti-IgE as the second antibody. The same sera were also tested by a similar RIA employing anti-IgE-coated wells and labelled mAbER. In none of these assay was the bound radioactivity greater than control wells containing buffer (data not shown). The same results were obtained when polyclonal anti-IgE antibody was used instead of monoclonal IgE antibody.

Discussion

The present studies were initiated following the *in-vitro* observations [14-17] that IgE-BF (soluble CD23) may play a role in the regulation of human IgE synthesis. The results indicate that subjects with an increased serum IgE due to allergic or parasitic diseases have significantly higher levels of serum IgE-BF than control individuals of the same age and of the same ethnic group. However, the

data do not provide a good case for a causal relationship between the increased production of IgE-BF and that of IgE. First, there is a great overlap between the IgE-BF levels in the subject and the control groups. Secondly, the correlation between IgE and IgE-BF levels is very weak, although statistically significant. Finally, in the grass-sensitive subjects with hay fever, the level of serum IgE-BF was not influenced by the pollen season which is known to increase their IgE antibody production [19].

The poor correlation between IgE and IgE-BF levels cannot be accounted for by an inhibiting effect of IgE on the detection of IgE-BF; indeed the latter is not affected by the addition of up to 100 $\mu\text{g/ml}$ of IgE [21]. Moreover, the possibility that IgE-BF might be bound to IgE and form complexes that would not be detected by the RIA analysis (because of 'hidden' antigenic determinant(s)) has been excluded by two series of independent observations. First, the serum IgE-BF are not retained on anti-IgE immunoadsorbents, and no detectable IgE is retained on mAbER-columns. Secondly, the serum molecules binding to immobilized mAbER do not react with labelled monoclonal or polyclonal anti-IgE and, reciprocally, the material bound to immobilized anti-IgE does not react with labelled mAbER.

The serum level of IgE-BF is determined by several factors: (1) the pool of Fc ϵ R2-bearing cells and the density of Fc ϵ R2 on these cells; (2) the rate of cleavage of Fc ϵ R2 into IgE-BF, which is inhibited by IgE [22,23]; and (3) the clearance of serum IgE-BF.

An augmentation of the number of Fc ϵ R2-bearing cells and of the cellular density of Fc ϵ R2 has been documented in patients with allergic [24,25] and parasitic [26] diseases as well as in other hyper-IgE states [27]. The inhibiting effect of IgE on the cleavage of Fc ϵ R2 may explain why subjects with very high IgE levels, like those with filariasis, have relatively low levels of serum IgE-BF. This interpretation is also supported by the finding of reduced serum IgE-BF levels in patients with the hyper-IgE syndrome [D. Leung and G. Delespesse, personal observations]. Little is known about the clearance of IgE-BF from the serum except that these molecules may be found in the urine [M. Sarfati, personal observation].

Allergic and non-allergic children have significantly higher levels of serum IgE-BF and the inverse relationship between age and serum IgE-BF levels is significant in children only. While this manuscript was in preparation, similar observations were reported by Kim *et al.* [28]. These authors further observed that in normal children the proportion of Fc ϵ R2-bearing lymphocytes was not influenced by age. They concluded therefore that the age-dependent variation of serum IgE-BF levels was due to the physiological reduction of the lymphocyte pool during infancy. As in the present study, they found that

allergic children had significantly higher levels of serum IgE-BF than the non-allergic age-matched controls; the correlation between the serum levels of IgE and of IgE-BF was also very weak.

The present observation that the non-allergic Japanese participants have significantly lower serum IgE-BF levels than the Caucasian age-matched controls is intriguing. As trivial explanations have been excluded (e.g. all sera were kept frozen until tested and they were tested in the same RIA) it is possible that serum IgE-BF is regulated by ethnic and perhaps by genetic factors.

Taken collectively, the present study and that by Kim *et al.* [28] are compatible with the hypothesis that IgE-BF regulate the *in-vivo* production of IgE although they add no further support to this possibility. More suggestive is the recent report by Bengtsson *et al.* [29], showing that the transient increase of serum IgE levels after autologous bone marrow transplantation is preceded, by a few days only, by an increase of serum IgE-BF levels. This study does not, however, provide any further evidence for a causal relationship between the changes of IgE-BF levels and those of IgE. Interestingly, the levels of IgE-BF may return to basal values at the time when the IgE peak is observed. This might explain why we have not observed any change of the IgE-BF levels in the longitudinal study on the hay fever subjects. Indeed, IgE and IgE-BF levels were measured in the same serum samples which had been collected in order to observe a maximum effect of the pollen season on the serum levels of IgE antibodies [19]. It is possible that the increased levels of serum IgE-BF might be unrelated to the abnormal production of IgE by atopic subjects and that it reflects another abnormality of their immune response. Indeed, as already mentioned, FcεRII and its soluble fragments are thought to be multi-functional molecules that regulate B-cell activation. In this regard it is relevant to note that the serum of patients with B cell chronic lymphocytic leukaemia contains markedly elevated levels of IgE-BF contrasting very low levels of IgE [30].

Independent of the possible function of IgE-BF, the present results may also be interpreted in the light of our current knowledge of the mechanisms regulating the expression of FcεRII and thus the production of IgE-BF. To date, the only agent capable of inducing the expression of FcεRII is IL-4, which was shown *in vivo* and *in vitro* to be required for the induction of an IgE response [31,32]. On the other hand, the expression of FcεRII as well as the synthesis of IgE may be suppressed by IFN-α, IFN-γ and PGE₂ [18]. It is therefore likely that the over-expression of FcεRII observed in diseases associated with an increased production of IgE reflects an imbalance between the production of IL-4 and that of its antagonists.

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