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Soluble Low Affinity Fc Receptors for IgE in the Serum of Allergic and Nonallergic Children

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ABSTRACT. IgE-binding factors are thought to have regulatory activity in *in vitro* IgE synthesis. To obtain evidence of the participation of IgE-binding factors in *in vivo* IgE synthesis, the serum level of low affinity Fc receptors for IgE (sFcεRII) (IgE-BFs) was examined in 41 nonallergic children and in 37 allergic children whose serum IgE levels were significantly higher than those of nonallergic children. The serum level of sFcεRII showed a marked age-dependent variation. It was highest in infants and then decreased gradually with age. The serum level of sFcεRII in allergic children was significantly higher than that of nonallergic children in early childhood (1128.0 ± 323.8 vs 777.3 ± 227.0 pg/ml, $p < 0.01$ in infants (<1 y) and 851.8 ± 270.0 vs 579.4 ± 197.1 pg/ml, $p < 0.05$ in children aged 1–2 y) but not in older children (3–15 y). Three allergic infants (<1 y) with serum sFcεRII levels higher than the mean + 1 SD (1451.8 pg/ml) of all allergic infants (<1 y) had serum IgE levels (geometric mean 125.9 IU/ml) significantly higher than the other seven allergic infants (<1 y) (geometric mean 5.6 IU/ml, $p < 0.05$). A close positive correlation between the serum level of sFcεRII and the absolute number of FcεRII(+) peripheral blood lymphocytes was observed (Spearman's rank correlation coefficient = 0.79, $p < 0.001$ in 27 allergic and Spearman's rank correlation coefficient = 0.72, $p < 0.001$ in 19 nonallergic children). In conclusion, serum sFcεRII may be derived mainly from FcεRII(+) lymphocytes, and may have relationship to the increased production of IgE in early childhood (0–2 y). (*Pediatr Res* 26: 49–53, 1989)

Abbreviations

FcεRII, low affinity Fc receptors for IgE
IgE-BF, IgE-binding factor
MNC, mononuclear cells
RAST, radioallergosorbent test
rs, Spearman's rank correlation coefficient
sFcεRII, soluble form of FcεRII

It has been demonstrated in rodents that IgE production is regulated by IgE-BF (1–3). IgE-BF are glycoprotein molecules with affinity for IgE (4, 5) consisting of two functionally different components: one enhances IgE synthesis (IgE-potentiating factor) (2), and the other inhibits it (IgE-suppressive factor) (3). The former is produced by FcεRII(+) T lymphocytes, and the latter is produced by FcεRII(−) T lymphocytes (6). Human FcεRII(+) T lymphocytes can secrete IgE-potentiating factor (7–10). Recently, FcεRII(+) B lymphocytes, which are more numerous than FcεRII(+) T lymphocytes (11, 12), have also been shown to be capable of producing IgE-potentiating factor (13–15). Thus, FcεRII(+) B lymphocytes, as well as FcεRII(+) T lymphocytes, appear to be involved in the regulation of IgE synthesis.

With the use of FcεRII(+) human B lymphoblastoid cell lines (RPMI1788, RPMI8866), several anti-FcεRII mAb have been produced (16–19). It is now easy to detect not only FcεRII, but also IgE-BF because of their common antigenic determinants to FcεRII (20, 21). The production of the mAb was followed by the determination of the gene structure of FcεRII (22–24), which in turn enabled its more precise molecular analysis. FcεRII was demonstrated to be the same molecule as the CD23 Ag (19, 25). The IgE-BF obtained from the supernatants of FcεRII(+) T and B cell lines was demonstrated to be the soluble form of FcεRII (sFcεRII) released by cleavage of the polypeptide chain (15, 26, 27).

The serum IgE level is often increased in allergic individuals (28). The proportion of FcεRII(+) lymphocytes has been shown to be increased in allergic patients and in those with nonallergic hyper-IgE conditions (29–31). This suggests that FcεRII(+) lymphocytes participate in the regulation of *in vivo* IgE synthesis by the production of sFcεRII. If sFcεRII actually plays a role in the *in vivo* synthesis of IgE, its serum level should be significantly different between allergic and nonallergic individuals. With this assumption, we investigated the serum level of sFcεRII in allergic and nonallergic children because the elevation of the percentage of FcεRII(+) lymphocytes, which release sFcεRII, is detected much more easily in allergic children than in allergic adults (31).

MATERIALS AND METHODS

Donors. Allergic disorders were diagnosed when children with typical symptoms showed positive results in RAST or skin tests and/or elevated serum IgE levels higher than the geometric mean + 1 SD of those of nonallergic children in this study. In actual practice these levels were set at 10 IU/ml in infants, 100 IU/ml in 1- to 2-y-old children and 400 IU/ml in older children (3–15 y).

The allergic group consisted of 37 children (25 males and 12 females); 15 had atopic dermatitis, 14 had bronchial asthma, and 8 had both. Among them, 33 (89.1%) had a positive family history of allergy, and 28 (75.7%) had both positive RAST scores and elevated serum IgE. Patients receiving continuous medication with systemic corticosteroids, which have been reported to inhibit FcεRII expression (29, 32, 33), were not included. The nonallergic group consisted of 41 children (23 males and 18 females); none had allergic, immunologic, or hematologic problems. Between March 1987 and January 1988, peripheral blood

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samples were obtained at the time of the child's routine blood examinations after informed consent had been obtained from their parents. Eleven cord blood samples were obtained at full-term, uneventful deliveries. Blood of normal and allergic adults was drawn from volunteers in our laboratory. Heparinized blood samples for the examination of the percentage of FcεRII(+) lymphocytes were used immediately, and serum samples for sFcεRII determination were stored at −40°C until the examination. Under this condition, the value of serum sFcεRII was stable for at least 1 y.

Measurement of serum IgE levels. Serum IgE levels were examined by Pharmacia IgE RIA kits (Pharmacia Fine Chemicals, Uppsala, Sweden), which were generously provided by Shionogi & Company Ltd., Osaka, Japan. The measurable range is 10–2,000 IU/ml with the standard procedure, and 1 to 40 IU/ml with the high sensitivity procedure.

Determination of serum sFcεRII. sFcεRII was measured by the solid phase sandwich ELISA method described previously (15). Two mouse anti-human FcεRII mAb, which recognized different epitopes, were applied to the assay. One was the H107 antibody (18) and the other was the mAb 176 antibody which was kindly provided by Dr. G. Delespesse of the University of Montreal, Quebec, Canada (16). Both the H107 and Mab176 antibodies are demonstrated to react with sFcεRII derived from FcεRII(+) T and B lymphocytes (15, 27). This assay system is also able to detect sFcεRII derived from a human monoblastic cell line U937 (15) and a human eosinoleukemic cell line EoL (M. Hosoda and J. Yodoi, unpublished data).

Briefly, 2 μg/ml of mAb176 antibody in $NaOH\text{-}NaHCO_3$ solution (pH 9.0) was delivered into a polystyrene microplate (Immuno plate I, Nunc, Roskilde, Denmark) in a volume of 50 μl/well and incubated overnight at 4°C. Residual binding sites of the solid phase were blocked by 150 μl of ELISA solution (10 mM PBS containing 2% BSA and 0.05% Tween 20) in each well. After incubation overnight at 4°C, a 50 μl sample was placed in each well in triplicate and incubated overnight at 4°C. Then, 50 μl of alkaline phosphatase VII-S (Sigma Chemical Co., St. Louis, MO) coupled H107 antibody in ELISA solution (0.4 μg/ml) was put into each well and incubated for 4 h at 4°C. Finally, 100 μl of enzyme substrate solution (1 tablet of phosphatase substrate (Sigma) per 5 ml substrate buffer) was placed in each well. Then 1 liter of substrate buffer, pH 9.8, contained 97 ml of diethanolamine, 100 mg of $MgCl_2 \cdot 6\ H_2O$ and 200 mg of NaN_3. Plates were washed vigorously five times with washing solution (PBS containing 0.05% Tween 20) after the completion of each incubation.

The enzyme activity bound to the solid phase was determined by reading the absorbance at a wave-length of 405 nm with an automated photometer (MTP12, Corona Electric Co Ltd, Ibaragi, Japan). Standard human sFcεRII was collected and purified from the supernatant of RPMI 8866 cells (23).

Absolute number of FcεRII(+) lymphocytes. The procedure to determine the percentage of FcεRII(+) PBL was described previously (31). Briefly, heparinized blood was incubated with silica particles (KAC2, Japan Immunoresearch Laboratories, Takasaki, Japan) to remove monocytes/phagocytes. MNC were obtained by centrifugation over Ficoll-Paque (Pharmacia) (34). MNC were incubated with 20 μl of 20 μg/ml H107 antibody (first incubation), and then with 20 μl of 20 μg/ml FITC-conjugated anti-mouse IgG antibody (Tago Inc., Burlingame, CA) (second incubation) at 4°C for 30 min. A negative control for each sample was prepared by the same procedure except that 20 μl of 20 μg/ml non-related purified mouse myeloma IgG2b protein (Miles Scientific, Naperville, IL), which is the same class as the H107 antibody, was used at the first incubation instead of the H107 antibody. The percentage of fluorescence-positive cells in the lymphocyte population was determined by flow cytometry (FACS 440, Becton Dickinson Labware, Mountain View, CA). The difference in the percentage of fluorescence-positive cells between the sample and each negative control sample was recorded as the percentage of FcεRII(+) cells. The absolute number of FcεRII(+) peripheral blood lymphocytes was calculated by the equation

$$\text{Absolute number of Fc}\epsilon\text{RII(+) lymphocytes (1/mm}^3) = \text{Leukocyte count (1/mm}^3) \times \text{Percentage of lymphocytes}/100 \times \text{Percentage of Fc}\epsilon\text{RII(+) lymphocytes}/100$$

Analysis of data. Data on the serum sFcεRII were presented as the mean ± 1 SD. Data on the serum IgE were first transformed logarithmically, and then presented as the geometric mean and a range of 1 SD (28). The statistical significance of the difference in serum sFcεRII levels was evaluated by a *t*-test. The statistical significance of the difference in serum IgE levels and the absolute number of FcεRII(+) lymphocytes was evaluated by Wilcoxon's rank-sum test. The correlation of serum sFcεRII and serum IgE levels or the absolute number of FcεRII(+) lymphocytes was evaluated by rs. For convenience in calculation, serum IgE levels lower than 1 IU/ml were all approximated at 0.5 IU/ml.

RESULTS

Serum level of sFcεRII. The serum level of sFcεRII varies considerably with age in both allergic and nonallergic children. It was highest in infants and decreased gradually with age, reaching the adult level at about 8 y of age and then remaining constant. For statistical purposes, children were divided into four age groups, I, II, III, and IV, aged <1, 1–2, 3–7, and 8–15 y, respectively (Table 1). The mean ± 1 SD of age in allergic and nonallergic group I was 5.0 ± 2.3 and 4.5 ± 3.3 mo, respectively.

Allergic children in groups I and II had significantly higher

Table 1. *Serum sFcεRII in allergic and nonallergic individuals (mean ± 1 SD)*

Age group	Allergic (pg/ml) (*n*)	Nonallergic (pg/ml) (*n*)	*p*
Cord blood		479.1 ± 199.2 (11)	
I (<1 y)	1128.0 ± 323.8 (10)	777.3 ± 227.0 (13)	<0.01
II (1–2 y)	851.8 ± 270.0 (11)	579.4 ± 197.1 (9)	<0.05
III (3–7 y)	586.3 ± 194.6 (8)	510.6 ± 183.2 (9)	NS
IV (8–15 y)	337.5 ± 43.2 (8)	360.5 ± 122.2 (10)	NS
Adults	278.1 ± 69.0 (8)	313.9 ± 145.5 (9)	NS

Table 2. *Serum IgE in allergic and nonallergic individuals (geometric mean and range of 1 SD)*

Age group	Allergic (IU/ml) (*n*)	Nonallergic (IU/ml) (*n*)	*p*
I (<1 y)	14.1 (1.8–112.2) (10)	0.8 (0.4–1.7) (13)	<0.01
II (1–2 y)	120.2 (25.1–575.4) (11)	3.9 (0.9–17.0) (9)	<0.01
III (3–7 y)	776.2 (331.1–1819.7) (8)	26.9 (4.4–166.0) (9)	<0.01
IV (8–15 y)	446.7 (169.8–1174.9) (8)	38.9 (7.4–204.2) (9)	<0.01
Adults	371.5 (100.0–1380.4) (8)	85.1 (21.9–331.1) (9)	<0.05

Table 3. *Percentage and absolute number of FcεRII(+) peripheral blood lymphocytes in children (mean ± 1 SD)*

Age group		Allergic	Nonallergic	
I (<1 y)	N*	429.8 ± 256.0	256.2 ± 47.0	$p < 0.05$
	%†	7.3 ± 1.5	4.9 ± 1.3	$p < 0.05$
	n	8	6	
II (1–2 y)	N	369.2 ± 119.4	181.4 ± 70.1	$p < 0.01$
	%	8.9 ± 2.7	4.3 ± 1.4	$p < 0.01$
	n	10	7	
III (3–7 y)	N	139.5 ± 111.9	127.5 ± 65.9	NS
	%	5.9 ± 2.1	4.2 ± 1.6	NS
	n	6	6	
IV (8–15 y)	N	89.4 ± 52.7	90.8 ± 40.7	NS
	%	4.4 ± 1.8	4.8 ± 1.3	NS
	n	9	12	

* Absolute number of FcεRII(+) lymphocytes ($1/mm^3$).
† Percentage of FcεRII(+) lymphocytes (%).

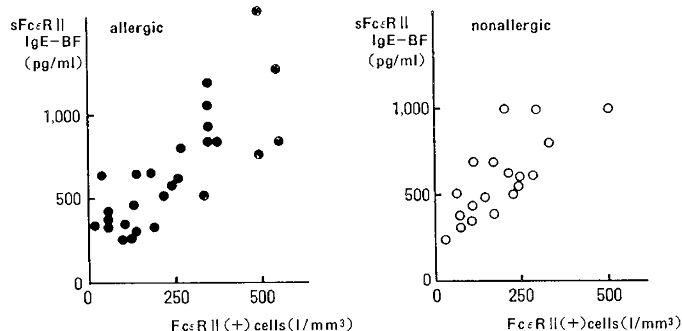

Fig. 1. Correlation of serum sFcεRII and absolute number of FcεRII(+) lymphocytes. The serum sFcεRII showed a close correlation with the absolute number of FcεRII(+) lymphocytes in both allergic (*left*)(rs = 0.79, $p < 0.001$) and nonallergic children (*right*)(rs = 0.72, $p < 0.001$).

levels of serum sFcεRII than their nonallergic counterparts ($p < 0.01$ and 0.05, respectively) (Table 1). However, significant differences in the serum levels of sFcεRII between allergic and nonallergic individuals were no longer observed in groups III and IV or in adults.

The serum sFcεRII was not affected by sex, medication with anti-allergic or anti-asthmatic agents, or type or severity of diseases (data not shown).

Correlation of sFcεRII with serum IgE. The serum level of IgE in allergic children was significantly higher than in nonallergic children in all age groups (Table 2).

Generally, the correlation between the serum levels of sFcεRII and of IgE was poor. The serum level of sFcεRII tended to correlate negatively rather than positively with the serum level of IgE in both allergic and nonallergic individuals.

However, in allergic group I, three children, who had serum sFcεRII levels higher than the mean + 1 SD (1451.8 pg/ml), also had significantly higher serum IgE (mean 125.9 IU/ml; 1 SD range 31.6–501.2 IU/ml) than the other seven children (5.6 IU/ml; 1.2–26.3 IU/ml: $p < 0.05$).

Correlation of serum sFcεRII with absolute number of FcεRII(+) PBL. In nonallergic children, although the percentage of FcεRII(+) PBL was constant in all age groups, their absolute number showed a marked age-dependent variation similar to that of serum sFcεRII (Table 3). It was highest in infants, and thereafter decreased with age. Both the absolute number of FcεRII(+) lymphocytes and the percentage of FcεRII(+) lymphocytes were significantly higher in allergic children of groups I and II than in their nonallergic counterparts ($p < 0.05$ and <0.01, respectively), whereas there was no significant difference between allergic and nonallergic children of groups III and IV (Table 3). The absolute lymphocyte count did not differ significantly between allergic and nonallergic children in each age-group (data not shown).

The relationship between the serum level of sFcεRII and the absolute number off FcεRII(+) lymphocytes was analyzed in 27 allergic and 19 nonallergic children. As shown in Figure 1, a significant positive correlation was demonstrated in both allergic and nonallergic individuals (rs = 0.79, $p < 0.001$ in the allergic and rs = 0.72, $p < 0.001$ in the nonallergic).

DISCUSSION

The serum level of sFcεRII showed a marked age-dependent variation in both allergic and nonallergic children and had a close positive correlation with the absolute number of FcεRII(+) lymphocytes. Because the percentage of FcεRII(+) cells in PBL is constant irrespective of age, except in allergic younger children (Table 3), the age-dependent variation of the absolute number of FcεRII(+) lymphocytes is likely to reflect the total lymphocyte count. Therefore, the age-dependent variation of serum sFcεRII of nonallergic children as well as of allergic older children may be due mainly to the physiologic age-dependent variation of the absolute number of lymphocytes. However, the increase in the serum level of sFcεRII and in the absolute number of FcεRII(+) lymphocytes in allergic younger children is due not to an increase in the total number of lymphocytes but to the increased percentage of FcεRII(+) lymphocytes (Table 3).

FcεRII are expressed not only on lymphocytes, but also on monocytes/macrophages, eosinophils, and platelets (35–37). Inasmuch as most sFcεRII, if not all, is a degradation product of cell surface FcεRII (15, 26, 27), blood cells other than lymphocytes may also release sFcεRII into the serum. However, because the pattern of the age-dependent variation of lymphocytes is unique to them and different from that of the other blood cells (38), it appears that FcεRII(+) blood cells other than lymphocytes do not influence significantly the serum level of sFcεRII; *i.e.*, most of the serum sFcεRII is probably derived from FcεRII(+) lymphocytes.

Although two functionally different IgE-BF, IgE-potentiating and IgE-suppressive factor, were noted in a rodent model for IgE synthesis (2, 3), only IgE-potentiating activity is described for human IgE-BF derived from FcεRII(+) B cells (13, 14). Because most FcεRII(+) PBL are B cells (31), the majority of serum sFcεRII may be a product of FcεRII(+) B cells. Therefore, serum sFcεRII is assumed to be an IgE-potentiating factor. Generally speaking, however, serum sFcεRII did not correlate with the serum IgE level. Although one of the most remarkable features of the serum level of sFcεRII is its age-dependent variation, it did not resemble that of the serum IgE level. Moreover, no significant difference of serum sFcεRII between allergic and nonallergic individuals of older age-groups was observed despite the significant difference of the serum IgE level. These results indicate that all serum sFcεRII cannot be an IgE-potentiating factor. sFcεRII may consist of multiple components with different functions, as has been shown in rodents (2, 3).

However, the biologic significance of sFcεRII cannot be denied entirely because the serum levels of sFcεRII and of IgE in allergic younger children (age groups I and II) were significantly higher than in nonallergic younger children. Moreover, in allergic group I, children with very high levels of serum sFcεRII also had significantly higher serum IgE levels than the other children. These findings suggest that sFcεRII is related in some way to increased IgE synthesis, at least in younger allergic children.

The reason for the elevation of serum sFcεRII in allergic younger children only is unknown. However, it is not disease-related because in group II (1–2 y) seven children had atopic dermatitis, two had bronchial asthma and two had both; their

serum levels of sFcϵRII were 861.4 ± 272.5, 885.0 ± 365.0, and 785.0 ± 45.0 pg/ml, respectively.

Recently, some lymphokines, such as IL-4 and IFN-γ have attracted attention as regulatory factors not only of the expression of FcϵRII or the release of sFcϵRII but also of the IgE synthesis itself (22, 39–42); IL-4 enhances and IFN-γ suppresses these reactions. The serum level of sFcϵRII as well as that of IgE might be affected by these lymphokines. However, we have little knowledge about the behavior of these lymphokines in allergic and nonallergic children, although the inability of T cells to produce IFN-γ has been noted in neonates (43, 44). Advances in the study of these lymphokines, as well as of sFcϵRII, may provide a solution to this problem.

The elevation of serum sFcϵRII in allergic younger children seems to be determined congenitally to some extent. In a study which aims to pinpoint neonates at high risk for developing atopic diseases by the serum level of sFcϵRII in cord blood, our preliminary data show that infants who later develop atopic symptoms have a significantly higher cord serum sFcϵRII than those who remain free of atopic symptoms (593.7 ± 334.4 *vs* 393.8 ± 174.8, $p < 0.01$ at 7 mo of age) (Kim KM, *et al.* unpublished data).

The measurement of serum IgE is an important laboratory test in the diagnosis of allergic disorders. However, in younger children the serum IgE level is often too low to be detected by routine assay systems. On the contrary, sFcϵRII is easily measured even in cord blood. For clinical purposes, serum sFcϵRII, along with other tests, may prove to be of value in diagnosing allergic disorders in early childhood.

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