

IgE Regulates Mouse Basophil FcεRI Expression In Vivo¹

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The binding of IgE to high-affinity IgE receptors (FcεRI) on the surface of mast cells and basophils primes these cells to secrete a panel of proinflammatory mediators upon subsequent exposure to specific Ag. We now find that the level of FcεRI expression on bone marrow basophils in mice infected with the nematode *Strongyloides venezuelensis* exhibits a strong positive correlation with the serum concentration of IgE, as was previously reported for human blood basophils. Moreover, the administration of IgE in vivo can significantly up-regulate FcεRI expression on mouse basophils, and genetically IgE-deficient (IgE ^{-/-}) mice exhibit a dramatic (~81%) reduction of basophil FcεRI expression compared with the corresponding normal (IgE ^{+/+}) mice. The finding that IgE can be a major regulator of mouse basophil FcεRI expression in vivo identifies a potentially important mechanism for enhancing the expression of effector cell function in IgE-dependent allergic reactions or immunologic responses to parasites. *The Journal of Immunology*, 1997, 158: 2517–2521.

Basophils are granulocytes that mature in the bone marrow, circulate in the blood, and can be recruited into the peripheral tissues, where they are thought to function as effector cells in IgE-dependent immune responses (1–8). Indeed, several lines of evidence indicate that IgE- and Ag-dependent activation of basophil mediator secretion significantly contributes to both the pathogenesis of allergic diseases and the expression of acquired immunity to infection with certain parasites (1–9).

While it is clear that human basophils and rat basophilic leukemia cells must display high affinity IgE receptors (FcεRI) on their

surface to express IgE- and Ag-specific function, the regulation of FcεRI expression on basophils is not fully understood (3, 4). Two groups reported that the level of FcεRI expression on the surface of circulating human basophils can exhibit a strong positive correlation with the serum concentration of IgE, but the basis for this association was not determined (10–12). Similarly, while IgE can enhance the expression of FcεRI by various mast cell populations in vitro (13–16) and on mouse peritoneal mast cells in vivo (16), the relevance of these observations to basophils is not yet clear. In this study, we used in vivo and genetic approaches to examine whether IgE can regulate FcεRI expression on the surface of mouse basophils in vivo. Some of these results have been submitted in abstract form (17).

Materials and Methods

Mice

BALB/c and C57BL/6J mice were purchased from Charles River Laboratory, Wilmington, MA, and The Jackson Laboratory, Bar Harbor, ME, respectively. FcεRI α-chain ^{-/-} mice (Ref. 18; fourth-generation backcross into BALB/c or C57BL/6 mice) and IgE ^{-/-} mice (Ref. 19; third generation backcross into BALB/c) were produced by targeted disruption of the FcεRI α-chain or IgE Cε genes, respectively. Some mice were infected s.c. with 800 *Nippostrongylus brasiliensis* (N.b.)³ third-stage infective larvae (L₃) (20) or 2,000 L₃ of *Strongyloides venezuelensis* (S.v.) (21). All animal care and experimentation was conducted in accord with current National Institutes of Health and Beth Israel Deaconess Medical Center Institutional Animal Care and Use Committee guidelines.

Flow cytometry of mouse bone marrow basophils

Freshly isolated mouse femoral bone marrow cells were depleted of RBCs by hypotonic lysis in water, incubated with rat anti-mouse B220 mAb (PharMingen, San Diego, CA; at 10 μg/ml) for 25 min at 4°C, washed, and stained with phycoerythrin-goat F(ab')₂ anti-rat IgG (Caltag, San Francisco, CA; at 2 μg/ml) for 25 min at 4°C. After washing, cells were incubated with B3B4 (22) and 2.4G2 (23, 24) mAbs for 15 min to block low affinity binding of IgE or other subsequent Abs to CD23 or FcγRII/III, respectively, and then incubated at 4°C with mouse IgE anti-DNP mAb (Sigma Chemical Co., St. Louis, MO; clone SPE-7, at 10 μg/ml) for 50 min, to saturate fully any FcεRI expressed by these cells (23). After washing once in DMEM (Life Technologies, Grand Island, NY) supplemented with 3% heat-inactivated FCS (Sigma Chemical Co.), cells were stained with FITC-rat anti-mouse IgE Ab (PharMingen, at 10 μg/ml) for 25 min at 4°C. For detection of c-kit, cells were incubated for 25 min at 4°C with biotinylated rat anti-mouse c-kit mAb (PharMingen, clone 2B8, at 15 μg/ml) followed by phycoerythrin-streptavidin (Sigma Chemical Co., at 14 μg/ml). Stained cells were analyzed using a FACSCalibur (Becton Dickinson, San Jose, CA). Twenty thousand bone marrow cells in each sample were analyzed, and at least 100 basophils were studied to calculate the median value of FITC fluorescence intensity. An instrument setting of the

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Received for publication December 23, 1996. Accepted for publication January 21, 1997.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

¹ This work was supported by National Institutes of Health Grants AI/CA-23990 and CA/AI-72074 (S.J.G.), GM-53950 (J.-P.K.), K08 AI-01253 (H.C.O.), and AI-26150 (I.M.K.), and Uniformed Services University of the Health Sciences Protocol RO 86AB (to I.M.K.).

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³ Abbreviations used in this paper: N.b., *Nippostrongylus brasiliensis*; S.v., *Strongyloides venezuelensis*; MESF, molecules of equivalent soluble fluorochrome units.

flow cytometer that was appropriate for analysis of bone marrow cells was determined in the first experiment and was used for all such analyses throughout this study. The median values of FITC (FcεRI) fluorescence intensity of basophils were converted to the numbers of molecules of equivalent soluble fluorochrome units (MESF) using Quantum 26 fluorescein microbead standards (Flow Cytometry Standards Co., San Juan, PR) on each day an experiment was performed, as per the manufacturer's specifications.

Assessment of the effect of administration of IgE *in vivo* on basophil FcεRI expression

Twelve- to twenty-two-week-old mice were used in four independent *in vivo* experiments, two with BALB/c mice (data combined in Fig. 3A), one with untreated IgE $-/-$ and corresponding IgE $+/+$ mice (see Fig. 3B), and one with Ab-treated IgE $-/-$ mice (Fig. 3C). Purified mouse monoclonal IgG2a mAb (Sigma Chemical Co., clone UPC 10) and mouse anti-DNP IgE mAb (Sigma Chemical Co.) were dialyzed to remove NaN_3 , centrifuged at $100,000 \times g$ for 1 h at 4°C , and filtered before use. For *i.v.* treatment, IgG2a or IgE ($100 \mu\text{g}$ in 0.24 ml PBS) or 0.24 ml of PBS alone was administered to each mouse daily in the tail vein. Blood was obtained at time of sacrifice ($\sim 18 \text{ h}$ after the last *i.v.* injection) for measurement of total serum IgE concentration by ELISA (25).

Statistics

Unless otherwise specified, all data are expressed as mean $\pm$ SEM, and all differences between values were compared using the two-tailed Student's *t* test.

Results and Discussion

Mouse basophil surface binding of IgE requires the FcεRI α -chain and is increased in N.b.- or S.v.-infected mice

We first confirmed that a c-kit $^+$, B220 $^-$ population of cells capable of binding IgE (i.e., basophils (26–28)) was identifiable by flow cytometry in the femoral bone marrow cells of normal BALB/c mice (representing $\sim 0.73 \pm 0.05\%$ of the total bone marrow cells) (Fig. 1, A and B). By contrast, no such population was detectable in the femoral bone marrow cells derived from FcεRI α -chain $-/-$ mice (Fig. 1C). This finding indicates that the IgE that is detected on the basophil surface in our assay largely or solely reflects the binding of the Ab to the FcεRI α -chain. This result also represents direct evidence that mouse basophils (like human basophils (3, 4)) express the FcεRI.

We then examined basophils from 6- to 8-wk-old female BALB/c mice that had been infected (or not) with N.b. larvae 20 days before sacrifice ($n = 4$ per group). The percentage of bone marrow basophils (as assessed on day 20 after infection, after egg expulsion was complete; Ref. 20), was $0.63 \pm 0.04\%$ in N.b.-infected mice vs $0.73 \pm 0.05\%$ in control mice ($p = 0.174$). However, basophil FcεRI expression was markedly (~ 3.6 -fold) higher in N.b.-infected mice than in the uninfected animals ($464,939 \pm 14,085$ vs $100,539 \pm 9,725$ MESF, respectively; $p < 0.0001$); serum concentrations of total IgE were also much higher in the N.b.-infected than in the uninfected mice (35.5 ± 5.1 vs $0.09 \pm 0.01 \mu\text{g/ml}$, respectively; $p < 0.002$).

We next assessed the level of basophil FcεRI surface expression (measured as MESF; Fig. 2) and numbers of bone marrow basophils (expressed as the percentage of total femoral bone marrow cells) in S.v.-infected C57BL/6J mice ($n = 12$) or the corresponding uninfected mice ($n = 4$). Infection with S.v. resulted in an increase in the percentage of bone marrow basophils, with the highest levels detected on day 12 after infection, coinciding with the virtual cessation of parasite egg production (Fig. 2). Basophil FcεRI expression increased markedly during the course of S.v. infection, to levels on day 16 that were ~ 15 -fold those in uninfected mice (Fig. 2). S.v. infection was also associated with a striking increase in the serum concentration of total IgE (Fig. 2).

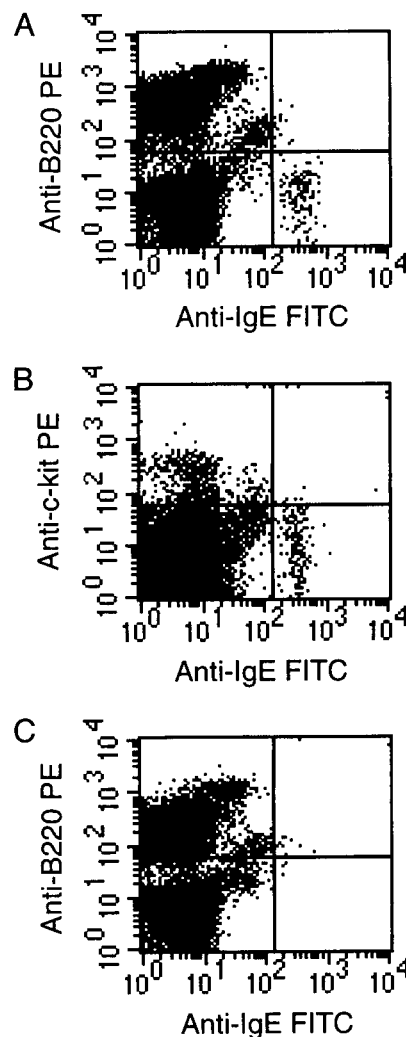


FIGURE 1. Identification of mouse bone marrow basophils by flow cytometry. Freshly isolated femoral bone marrow cells of BALB/c mice (A, B), or FcεRI α -chain $-/-$ mice (C) were stained for the expression of surface IgE receptor and B220 Ag (A, C) or c-kit (B). The IgE $^+$, B220 $^-$ cells (e.g., in A) were sorted and confirmed microscopically as highly enriched in basophils (recognized as cells with cytoplasmic granules that stained with alcian blue; see Ref. 27). Note that no cells strongly positive for IgE staining were detected in bone marrow cells from FcεRI α -chain $-/-$ mice (C). The results shown in C (from a mouse on the C57BL/6 background) are representative of those obtained in 14 different FcεRI α -chain $-/-$ mice, 3 on the C57BL/6 and 11 on the BALB/c background.

IgE regulates the expression of basophil FcεRI *in vivo*

Infection with either N.b. (20, 26) or S.v. results in increased levels of serum IgE. However, in either of these contexts, one would expect many other changes as well, such as alterations in levels of immunoregulatory and/or hemopoietic cytokines (6, 29). In complex settings such as these, it may be difficult to ascertain the roles of the individual factors that can potentially influence basophil FcεRI expression. We therefore performed four experiments to investigate directly whether IgE Ab alone could increase basophil surface expression of FcεRI. In two experiments, affinity-purified mouse IgE mAb ($100 \mu\text{g/day}$), or either IgG2a mAb Ab ($100 \mu\text{g/day}$) or vehicle (PBS) alone, were administered *i.v.* to BALB/c mice daily for 4 days, and bone marrow basophils were analyzed for FcεRI by flow cytometry $\sim 18 \text{ h}$ after the last injection. Administration of IgE,

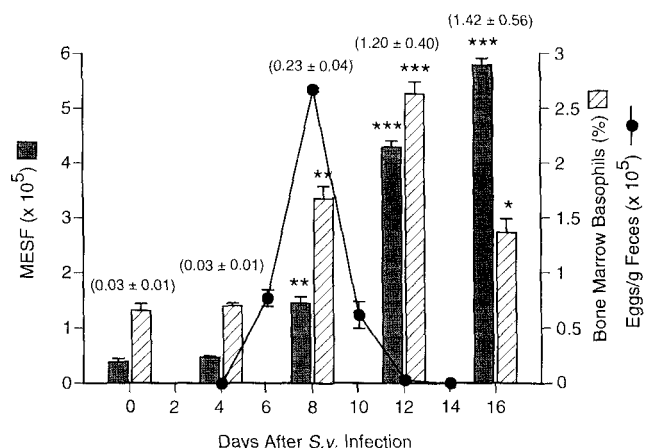


FIGURE 2. Surface FcεRI expression in mouse bone marrow basophils (and percentage of bone marrow basophils) derived from 7-wk-old C57BL/6 mice that had been infected with S.v. larvae (or not infected) up to 16 day before sacrifice (see *Materials and Methods*). Values in parentheses above the bars are serum IgE concentrations (μg/ml) for mice in that group. Parasite egg production is shown as number per gram of faeces. All data are mean ± SEM ($n = 3-4$ per group); * Indicates $p < 0.05$; **, $p < 0.001$; ***, $p < 0.0001$ vs values for uninfected mice.

but not IgG2a or PBS, resulted in a greater than threefold enhancement of basophil expression of FcεRI (Fig. 3A). By contrast, the percentage of bone marrow basophils in all three groups was very similar (IgE-treated = $0.79 \pm 0.04\%$, IgG2a-treated = $0.71 \pm 0.02\%$, and PBS-treated = $0.63 \pm 0.05\%$).

We next assessed the baseline levels of FcεRI expression in basophils of untreated IgE $-/-$ vs IgE $+/+$ mice, and found that FcεRI expression was reduced by ~81% in basophils from IgE $-/-$ mice as compared with those from wild-type mice (Fig. 3B). By contrast, IgE $-/-$ and IgE $+/+$ mice had similar percentages of bone marrow basophils (0.65 ± 0.06 vs $0.73 \pm 0.05\%$, respectively, $p = 0.341$).

Finally, we found that i.v. administration of IgE (but not IgG2a) mAb resulted in a marked increase in FcεRI expression by IgE $-/-$ mouse basophils (compare Fig. 3, B and C). The apparent percentage of bone marrow basophils in IgG2a-treated IgE $-/-$ mice (0.57 ± 0.045) was somewhat lower than that in IgE-treated IgE $-/-$ mice (0.79 ± 0.06 , $p < 0.016$) and probably reflects, at

least in part, the difficulty in resolving the basophil population in IgE $-/-$ mice, due to the cells' low level of IgE staining.

When we analyzed data from the C57BL/6 mice that had or had not been infected with S.v. (Fig. 4A), or the IgE-treated IgE $-/-$ mice and the BALB/c mice that had been treated with IgE, IgG2a, or PBS (Fig. 4B), we found in both cases a strong positive correlation between the $\log_{10}$ of the serum IgE concentration at sacrifice and the $\log_{10}$ of the level of basophil FcεRI expression, as assessed by MESF ($R^2 = 0.946$, $p < 0.0001$, or $R^2 = 0.950$, $p < 0.0001$, in Fig. 4, A or B, respectively).

Conclusions

Almost 20 years ago, two groups reported a strong positive correlation between the serum IgE concentration and the level of surface expression of FcεRI on circulating human basophils (10–12), and Malveaux et al. (12) suggested that one explanation for this finding might be IgE-dependent regulation of basophil FcεRI expression.

However, given the nature of these clinical studies, other explanations for the findings (such as genetic linkage between factors that regulate IgE production and/or levels of basophil FcεRI expression) could not be dismissed. We found that inbred mice infected with S.v. exhibited a strong positive correlation between levels of basophil FcεRI expression and serum concentrations of IgE. Moreover, administration of IgE to normal BALB/c mice in vivo markedly up-regulated surface expression of FcεRI on bone marrow basophils. Finally, IgE $-/-$ mice exhibited baseline levels of basophil FcεRI expression that were 81% lower than those in the corresponding IgE $+/+$ mice, and the i.v. administration of purified IgE to IgE $-/-$ mice resulted in a marked increase in basophil FcεRI expression. These findings provide compelling evidence that IgE is a major regulator of basophil FcεRI expression in vivo in mice.

Nevertheless, basophils from IgE $-/-$ mice exhibited detectable, albeit greatly reduced, levels of FcεRI on their surface (Fig. 3B), indicating that factors other than IgE must also contribute to the regulation of basophil FcεRI expression. We have no data regarding the factor(s) that may regulate basophil FcεRI surface expression independently of IgE. However, cytokines represent likely suspects. For example, IL-4 has multiple effects that augment IgE-dependent immune responses in mice; it is required for normal IgE responses (29, 30) and can promote the expansion of certain mast cell populations (31, 32), and the peritoneal mast cells of IL-4 $-/-$ mice exhibit fewer FcεRI than do those of IL-4 $+/+$

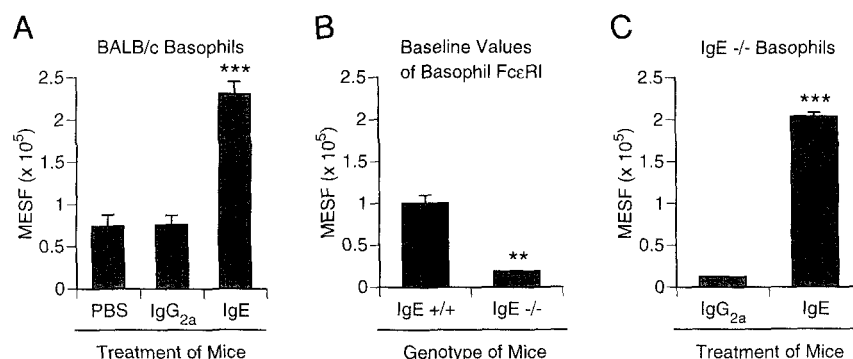


FIGURE 3. IgE-induced changes in mouse basophil FcεRI expression in vivo. All values are mean ± SEM. A, FcεRI expression in basophils from retired breeder BALB/c mice that had been treated for 4 days with a daily i.v. injection of 100 μg of purified IgE ($n = 7$) or IgG2a ($n = 5$), or vehicle (PBS) ($n = 4$). *** Indicates $p < 0.0001$ or < 0.005 vs values for PBS- or IgG2a-treated mice, respectively. B, Baseline levels of FcεRI expression on basophils from 6- to 12 wk-old BALB/c IgE $+/+$ ($n = 4$) and IgE $-/-$ ($n = 3$) mice. ** Indicates $p < 0.001$ vs values for IgE $+/+$ cells. C, FcεRI expression in basophils from 18- to 22-wk-old IgE $-/-$ mice treated with purified IgE ($n = 5$) or purified IgG2a ($n = 5$) as in A. *** Indicates $p < 0.0001$ vs values for cells from IgG2a-treated mice. The data are from the same groups of mice depicted in Figure 7 in Reference 16.

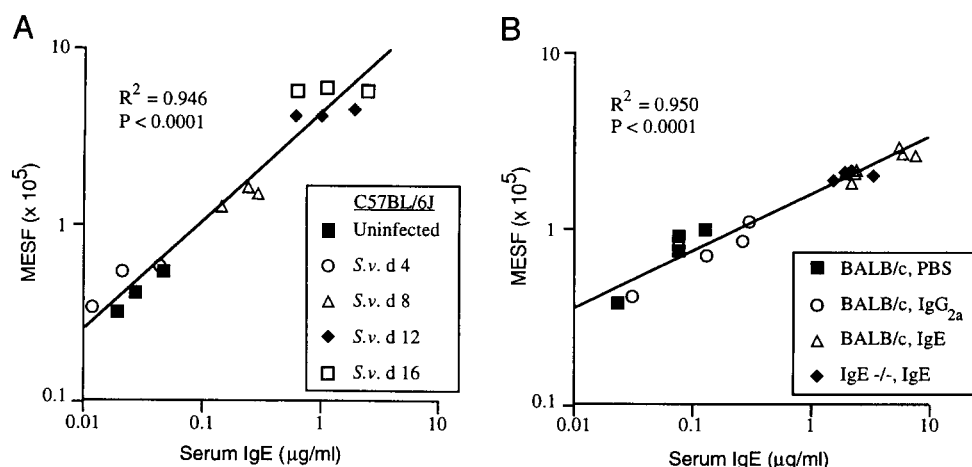


FIGURE 4. Correlation of serum IgE concentration at sacrifice and surface FcεRI expression of bone marrow basophils in the mice from the S.v. experiment (A) and the mice depicted in Figure 3A and the IgE-treated IgE $-/-$ mice in Figure 3C (B). The genotypes of the mice, and the treatment they received (A, without, or at various intervals after, infection with S.v.; B, PBS, IgE, or IgG2a, i.v. daily for 4 days) are depicted in the symbol keys in the figure. Note that the correlation coefficient in B was calculated based on all data from mice in Figure 3, A and C, except those from IgG2a-treated IgE $-/-$ mice, which were devoid of serum IgE; as a result, $n = 21$.

mice (33). IL-4 can also up-regulate levels of mRNA for the FcεRI α -chain in human eosinophils (34) or human mast cells (35), and can up-regulate expression of FcεRI on the surface of human mast cells (35). Accordingly, it will be of interest to investigate whether IL-4 and/or other cytokines can influence basophil FcεRI expression by mechanisms that are distinct from the effects of such cytokines on IgE production.

While the regulation of IgE production is complex, potentially involving multiple genetic and environmental factors, serum levels of IgE are typically greatly increased during parasite infections and are also elevated in most patients with allergic diseases (36–40). Our findings strongly suggest that any mechanism that results in the substantial elevation of IgE levels may also result in significantly enhanced surface expression of FcεRI by basophils.

IgE-dependent enhancement of basophil FcεRI surface expression would have at least two potential consequences for basophil effector function. It has been shown that the activation of mast cell (41) or basophil (42, 43) mediator release requires a certain minimum number of dimers or aggregates of the cells' FcεRI, which are produced when bi- or multivalent Ags are recognized by IgE bound to FcεRI on the cell surface. An increase in the number of FcεRI per basophil would therefore both equip the cell to be sensitized adequately and simultaneously by a greater number of IgE species of distinct Ag specificity and might also better prepare the cell to give a secretory response at fixed concentrations of specific IgE and Ag. Although it is difficult to purify sufficient mouse basophils to test these predictions experimentally, both Hsu and MacGlashan (15) and we (16) have recently determined that IgE can also enhance surface expression of FcεRI on mouse mast cells and that, in mast cells, such IgE-dependent enhancement of FcεRI expression is associated with significantly enhanced IgE- and Ag-specific mediator secretion.

In the context of acquired immune responses to parasites, IgE-dependent enhancement of basophil FcεRI expression would be expected to benefit the host. Unfortunately, IgE-dependent enhancement of basophil FcεRI expression would also be expected to increase the severity of allergic diseases. Accordingly, it will be of interest to assess to what extent IgE-dependent up-regulation of FcεRI surface expression, as is here identified in mouse basophils, also occurs in human basophils (or other FcεRI $^{+}$ effector cells, such as mast cells (1–7, 16), monocytes (44), or eosinophils (34,

45)) and, if so, to determine whether the ability of IgE to regulate the surface expression of FcεRI on effector cells can be exploited therapeutically in the management of allergic disorders.

Acknowledgments

We thank S. Fish and H.-Y. Park for technical assistance, Thomas F. Huff for *N. brasiliensis* larvae, Yukifumi Nawa for *S. venezuelensis* larvae, D. H. Conrad for B3B4 Ab, and J. J. Costa, M. Tsai, and B. K. Wershil for a critical reading of the manuscript.

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