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The High Affinity IgE Receptor (FcεRI) Mediates IgE-Dependent Allergen Presentation[1]

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The discovery that the high affinity IgE receptor (FcεRI) is expressed on APCs of patients with atopic diseases raised the possibility that the functional importance of FcεRI in the pathogenesis of atopy may extend beyond its role in type I allergic reactions. Here we show that, following removal of in vivo-bound IgE by lactic acid treatment, targeting of allergens to monocytes by Ag-specific IgE critically depends on FcεRI expression. Even more importantly, lactic acid-treated, monocyte-enriched PBMCs present allergen to T cells 100- to 1000-fold more effectively if the allergen has been targeted to FcεRI on these cells via allergen-specific IgE. This mechanism may critically lower the atopic individual's threshold to mount allergen-specific T cell responses capable of promoting IgE production and delayed-type hypersensitivity reactions. *The Journal of Immunology,* 1995, 154: 6285–6290.

Whereas the role of IgE is clearly established in immediate type (type I) allergic reactions, the pathophysiologic contribution of allergen-specific IgE to T cell-mediated, delayed type (type IV-like) atopic immune responses, e.g., late phase allergic reactions (LPRs)[3] and atopic eczema, has been less well defined. Support for a role of IgE in the pathogenesis of these type IV-like reactions of atopy came from the findings that the occurrence of LPRs is IgE-dependent (1) and that the skin of atopic patients harbors IgE-bound APCs, i.e., epidermal Langerhans cells and dermal dendritic cells (2, 3). More recently, it has been demonstrated that Langerhans cells (4, 5), dermal dendritic cells (4, 6), and peripheral blood monocytes of atopic patients (7) express the high affinity receptor for IgE (FcεRI) and that this structure functions as an IgE binding moiety on these cells. As the development of LPR lesions is characterized by an influx of peripheral blood leukocytes into the tissue and because monocytic cells comprise a sizable portion of the inflammatory infiltrate in this reaction (8), we asked whether FcεRI on monocytes serves as an allergen-focusing structure and, furthermore, whether IgE-dependent targeting of allergens to FcεRI on monocyte-enriched PBMCs (ME-PBMCs) modifies their allergen presentation capacity and, thus, the magnitude of ensuing allergen-specific T cell responses.

Materials and Methods

mAbs and immunoreactants

Chimeric (human Fc/mouse Fab) IgE anti-4-hydroxy-3-nitrophenacetyl (cIgE anti-NP; Serotec, Oxford, United Kingdom), ME.133 Fab (anti-IgE; Maine Biotechnology Services, Scarborough, ME), anti-Leu-M3 FITC (CD14; Becton Dickinson Co., Mountain View, CA), 15–1 (anti-FcεRI; Ref. 4), MHM6 (CD23; Dakopatts, Glostrup, Denmark), BIP 1 (anti-*Bet v* I; Ref. 9), IgG1 control mAbs MOPC-21 (Sigma Chemical Co., St. Louis, MO) and VIAP Fab (anti-alkaline phosphatase; provided by Dr. O. Majdic, Institute of Immunology, Vienna, Austria) were used. Fab fragments of mAb VIAP were generated by using a kit from Pierce Chemical Company, Rockford, IL. Streptavidin-phycoerythrin (SA-PE) was from Becton Dickinson.

Recombinant allergens and protein-NP conjugation

Recombinant major birch (r*Bet v* I) and grass (r*Phl p* II) pollen allergens were expressed as nonfusion proteins and purified as described (10, 11).

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[3] Abbreviations used in this paper: LPRs, late phase allergic reactions; SA-PE, streptavidin-phycoerythrin; NP, nitrophenacetyl; E^--PBMCs, E^--peripheral blood mononuclear cells; ME-PBMCs, monocyte-enriched PBMCs; MFC, mean fluorescence channel number; TCC, T cell clone; AA, amino acid; cIgE, chimeric IgE.

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NP-haptenization of proteins was performed to allow cIgE anti-NP-dependent allergen or BSA (Behringwerke AG, Marburg, Germany) binding. Briefly, r*Bet v* I, r*Phl p* II (1 mg/ml), and BSA (25 mg/ml) were dialyzed against 10 mM phosphate buffer (pH 7.2) and, thereafter, reacted for 3 h at room temperature with 190, 350, and 4650 μg/ml dimethylformamide-dissolved NP-caproic acid-sucrose (Cambridge Research Chemicals, Cambridge, United Kingdom), respectively. Samples were dialyzed extensively against PBS (Life Technologies, Inc., Ltd., Paisley, Scotland) to remove uncoupled hapten molecules. The molar protein:NP coupling ratios were determined photometrically.

Cell preparations

After informed consent was obtained, E^--mononuclear cells (E^--PBMCs) from atopic donors, i.e., birch and/or grass pollen allergic patients (as defined by clinical criteria, skin prick test, and radioallergosorbent test), were prepared by Ficoll-Hypaque (Pharmacia, Uppsala, Sweden) density gradient centrifugation of heparinized venous blood followed by depletion of SRBC binding T lymphocytes. Monocytes were enriched from E^--PBMCs by anti-CD19 immunomagnetic depletion of B cells (Pan-B (CD19) Dynabeads M-450; Dynal A.S., Oslo, Norway). The resulting ME-PBMC population consisted of 78 ± 5% (mean ± SD) CD14-positive, 1.5 ± 0.6% CD3-positive, and no CD19-positive cells. Lactic acid and lactose treatment was performed as previously described (12, 13).

Immunofluorescence double labeling and flow cytometric analysis

To determine monocyte-bound serum IgE or cIgE, lactic acid-, lactose-, or medium-treated E^--PBMCs of atopic individuals were incubated either with 5 μg/ml biotinylated Fab fragments of the anti-IgE mAb ME.133 or of the control mAb VIAP or with 5 μg/ml biotinylated cIgE or medium. To investigate the receptors critically involved in serum IgE- and cIgE-mediated binding of r*Bet v* I and r*Bet v* I-NP to monocytes, lactic acid-treated E^--PBMCs from atopic donors were exposed to 50 μg/ml of either an IgG1 control mAb, 15–1, or MHM6 before incubation in undiluted sera from *Bet v* I-sensitized allergic individuals or 5 μg/ml cIgE anti-NP. After two washes in ice-cold PBS, cells were incubated with 20 μg/ml biotinylated r*Bet v* I or biotinylated r*Bet v* I-NP in either the presence or absence of excess amounts of unlabeled r*Bet v* I or r*Bet v* I-NP, respectively. To visualize monocyte-bound biotinylated mAbs, r*Bet v* I, or r*Bet v* I-NP, all cell samples were reacted with SA-PE (1 μg/ml) and anti-LeuM3 FITC (5 μg/ml) and analyzed by flow cytometry (FACScan; Becton Dickinson). Phycoerythrin fluorescence of CD14-positive monocytes was recorded and expressed as the mean fluorescence channel number (MFC). Specific anti-IgE and cIgE binding (Δ-MFC) was calculated by subtracting the MFC obtained with either the control mAb VIAP (Fab) or with medium from the MFC of anti-IgE or cIgE reactivity, respectively. Specific r*Bet v* I or r*Bet v* I-NP binding (Δ-MFC) was calculated by subtracting the MFC of biotinylated r*Bet v* I or biotinylated r*Bet v* I-NP reactivity in the presence of the appropriate non-biotinylated competitor from the MFC measured in its absence. Data were compared by using paired Student's *t*-test; *p* values of <0.05 were considered to be significant.

Western blotting

A total of 400 ng of either native or NP-conjugated r*Bet v* I and r*Phl p* II were subjected to electrophoresis on 15% SDS-polyacrylamide gels and blotted onto nitrocellulose (Trans-Blot Transfer Medium; Bio-Rad Laboratories, Richmond, CA). Membranes were blocked in 5% dry milk/0.05% Tween 20 (Sigma Chemical Co.)/PBS, and incubated with either 0.2 μg/ml of the *Bet v* I-specific mAb BIP 1, 1 μg/ml cIgE anti-NP, or 1:2 diluted sera from monosensitized birch or grass pollen-allergic individuals. Membrane-bound mouse IgG or human IgE was reacted with 1:40,000 or 1:10,000 dilutions of polyclonal goat anti-mouse IgG (Bio-Rad Laboratories) or rabbit anti-human IgE horseradish peroxidase conjugates (Accurate Chemical and Scientific Cooperation, Westbury, NY), respectively. Membrane-bound second-step Abs were visualized with ECL developing solution (Amersham International, Little Chalfont, United Kingdom) and exposed to Kodak X-OMAT S films.

T cell clones (TCCs) and cytokine secretion-based definition of Th2, Th0, and Th1 TCCs

Bet v I- or *Phl p* II-specific TCCs from atopic individuals were established and characterized by techniques previously described (14, 15). TCCs used during this study included: WD18 (epitope specificity *Bet v* I, amino acids (AA): 1–16), WD22 (*Bet v* I, AA: 1–16), WD24 (*Bet v* I, AA: 143–156), WD25 (*Bet v* I, AA: 143–156), WD27 (*Bet v* I, AA: 1–16), HC8 (*Bet v* I, AA: 77–92; Ref. 15), HC33 (*Bet v* I, AA: 111–126; Ref. 14), RR4 (*Bet v* I, AA: 143–156), RR6 (*Bet v* I, AA: 13–27), RR9 (*Bet v* I, AA: 4–18), TF1M (*Bet v* I, AA: 94–108), TF7B (*Bet v* I, AA: 13–24), GZ10A (*Bet v* I, AA: 127–141), GZ1A (*Bet v* I, AA: 127–141), and GZ1M (*Phl p* II, AA: 37–51). To determine the cytokine secretion pattern of individual TCCs, 10^6 TCC cells were incubated in 1 ml serum-free medium (UltraCulture; BioWhittaker, Walkersville, MD) with 10^6 autologous, irradiated (60 Gy) PBMCs in the presence of 10 μg/ml *Bet v* I. Twenty-four-hour supernatants were collected and analyzed for IL-4 and IFN-γ content by using cytokine-specific ELISAs (IL-4: R&D Quantikine, Minneapolis, MN; IFN-γ: Medgenix Diagnostix, Fleurus, The Netherlands). Clones yielding a IL-4:IFN-γ (pg:pg) ratio of <0.5 or >5 were designated Th1 or Th2 TCCs, respectively. Ratios from 0.5 to 5 were classified as Th0 responses.

Proliferation assays

Five × 10^4 lactic acid-treated ME-PBMCs from atopic donors or 5 × 10^4 mitomycin C (Sigma Chemical Co.)-treated EBV-transformed B cells were dispensed in individual wells of 96-well round-bottom microtiter plates (Nunc, Roskilde, Denmark). Thereafter, cells were incubated with 10 μg/ml IgG1, 15–1, or MHM6 before exposure to 0.5 μg/ml cIgE or medium and the indicated concentrations of NP-conjugated or native allergens. Thereafter, 5 × 10^4 autologous TCC cells were added as responders. All proliferation assays were performed in recombinant human granulocyte-macrophage-CSF (100 U/ml; Sandoz, Vienna, Austria)-supplemented, serum-free UltraCulture (BioWhittaker) medium to maintain optimal viability of lactic acid-treated ME-PBMCs (unpublished observations). Cultures were incubated for 48 h before pulsing with 0.5 μCi [^{3}H]thymidine (Amersham International) per well for an additional 16 h. Incorporation of [^{3}H]thymidine was measured by liquid scintillation spectroscopy. The results are expressed as the mean ± SD of cpm obtained in duplicate cultures. Background counts of controls (ME-PBMCs, ME-PBMCs plus Ag, TCC, ME-PBMCs plus TCC, TCC plus Ag) were always <1000 cpm.

Results and Discussion

FcεRI serves as the pivotal monocyte receptor for polyclonal, allergen-specific IgE under serum conditions and mediates IgE-dependent allergen focusing

Our first goals were to analyze whether serum IgE is fixed to monocytes of atopics in vivo, to see whether allergen-specific IgE actively binds to these cells under atopic serum conditions, and to determine which of the known IgE receptors (16–18) is (are) the most relevant serum IgE binding site(s). As shown in Figure 1, freshly isolated CD14-positive monocytes of atopics, but not of non-atopics (data not shown), carry cell surface-bound serum IgE in vivo. The fact that the same cells are hardly capable of IgE binding in vitro suggests that most receptors for monomeric IgE are already occupied by serum IgE moieties. Indeed, lactic acid treatment almost completely removes in vivo-bound serum IgE and, concomitantly, dramatically increases the capacity of monocytes to bind monomeric IgE de novo (Fig. 1). The fact that a mAb to the high affinity IgE receptor (FcεRI) abolishes this IgE binding capacity (Ref. 7; data not shown) strongly suggests that

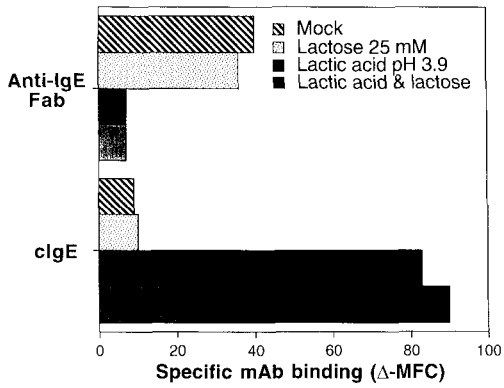

FIGURE 1. Lactic acid treatment, but not lactose treatment, of peripheral blood monocytes from atopic individuals removes in vivo cell surface-bound IgE and allows de novo binding of monomeric IgE. Mock-treated (hatched bars), lactose-treated (dotted bars), lactic acid-treated (solid bars), or lactose and lactic acid-treated (shaded bars) E^--PBMCs of an atopic individual were reacted with biotinylated Fab fragments of an anti-IgE mAb or with biotinylated cIgE. Binding of mAbs was visualized by SA-PE and flow cytometry. Specific anti-IgE or cIgE reactivity (Δ-MFC) of CD14-positive monocytes was calculated as described in *Materials and Methods* and is shown on the abscissa. Representative experiment of four.

monocyte FcεRI has been involved in serum IgE binding in vivo, but does not exclude a possible contribution of the IgE binding protein or of the low affinity IgE receptor (CD23/FcεRII), reportedly expressed on monocytes of atopic individuals (17, 19). A critical role for the IgE binding protein in this process is ruled out by the finding that lactose elution of the IgE binding protein from monocyte surfaces neither removes in vivo-bound IgE nor augments the de novo IgE binding capacity (Fig. 1). To test the relative contributions of FcεRI and CD23 to IgE binding in vivo, lactic acid-treated monocytes were incubated in serum from birch pollen-sensitized individuals in the presence or absence of blocking anti-FcεRI or anti-CD23 mAbs. Specific binding of labeled recombinant major birch pollen allergen *Bet v* I (10, 20) was assessed by flow cytometry. As demonstrated in Figure 2*A*, the mAb directed against the IgE binding α-subunit of FcεRI (mAb 15–1), but not the anti-CD23 mAb (MHM6) or IgG1 control mAbs, prevents almost completely the binding of r*Bet v* I-specific reactivity in patients' sera. Thus, we conclude that under serum conditions, monocytes of atopic individuals carry allergen-specific IgE bound to FcεRI rather than to FcεRII and that these FcεRI-bound molecules can serve as allergen-focusing structures.

Both allergen-specific serum IgE recognizing native allergen and monoclonal, hapten-specific IgE recognizing haptenized allergen use FcεRI as the principal monocyte receptor

The availability of recombinant allergens, i.e., recombinant birch (r*Bet v* I; Ref. 10) and grass pollen allergens (r*Phl p* II; Ref. 11), permitted the design of an allergen-focusing model that uses standardized, monoclonal, hapten (NP)-specific chimeric IgE (cIgE). This allows the targeting of haptenized (NP-conjugated) allergen in a fashion similar to that observed with polyclonal serum IgE and native allergen. This strategy bypasses the need for affinity-based purification of polyclonal, allergen-specific serum IgE, a complex procedure that often destroys IgE immunoreactivity. As shown in Figure 2*B*, haptenization of r*Bet v* I and r*Phl p* II results in a 3000 and 1000 m.w. shift because of the apposition of 10 and 4 NP/spacer residues to each recombinant molecule, respectively. This figure also demonstrates the immunoreactivity of NP-conjugated r*Bet v* I and r*Phl p* II allergens with polyclonal birch and grass pollen-specific serum IgE, respectively, as well as the reaction specificity of cIgE anti-NP and the *Bet v* I-specific mAb BIP 1. Figure 2*B* also shows that the anti-r*Bet v* I-NP reactivity of mAb BIP 1 is considerably weaker than its anti-r*Bet v* I reactivity. Although haptenization of the molecule seems to decrease the accessibility of the epitope recognized by this mAb, polyclonal serum IgE showed equal binding to native and NP-haptenized material (Fig. 2*B*). As shown in Figure 2*C*, cIgE-dependent focusing of NP-conjugated r*Bet v* I to monocytes of atopic individuals is strictly dependent on the expression of FcεRI moieties and, therefore, mimics the FcεR binding characteristics of allergen-specific serum IgE and native allergen (Fig. 2*A*).

The presence of allergen-specific IgE amplifies the allergen presentation capacity of ME-PBMCs

After having established that lactic acid treatment of B and T cell-depleted ME-PBMCs has no deleterious consequences for their capacity to stimulate alloantigen- and allergen-specific proliferative T cell responses (data not shown), we decided to use the above described allergen-focusing model to investigate whether the presence of hapten-specific IgE modifies the capacity of ME-PBMCs from atopics to take up and present immunogenic peptides to allergen-specific, peptide-mapped autologous TCCs. Allergen-specific TCCs used in this study exhibited TCR-$\alpha\beta^+$, $CD3^+$, $CD4^+$, and $CD8^-$ Th2 ($n = 8$), Th0 ($n = 6$), or Th1 ($n = 1$) cell phenotypes. Epitopes recognized by the 14 *Bet v* I-specific TCCs were scattered over the entire *Bet v* I molecule (one TCC recognized AA positions 37–51 of the *Phl p* II molecule) (15; unpublished observations). Both r*Bet v* I and NP-conjugated r*Bet v* I were presented comparably well to TCCs of various peptide specificities, indicating that the biologically relevant T cell epitopes had remained immunogenic after NP conjugation (Fig. 3). This figure also shows that the presence of NP-specific IgE increased substantially the presentation of *Bet v* I-epitopes, especially when suboptimal allergen concentrations were used. This phenomenon occurred only when

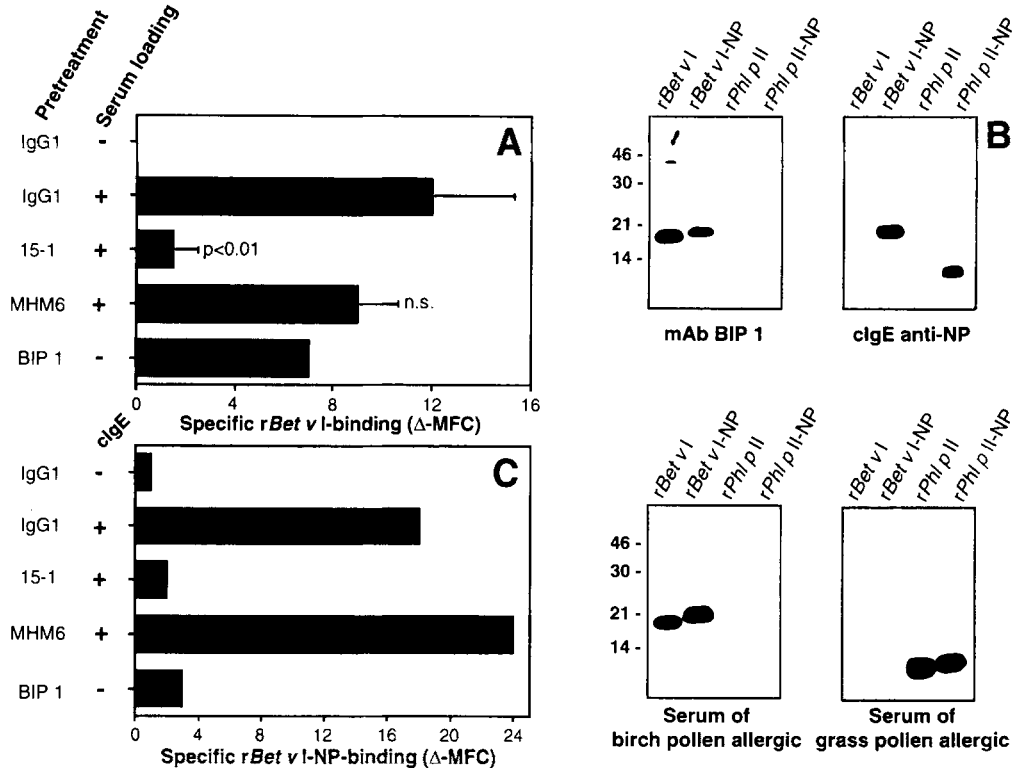

FIGURE 2. FcεRI is the pivotal monocyte receptor for allergen-specific IgE under atopic serum conditions as well as for monomeric, hapten-specific IgE. *A*, lactic acid-treated E^--PBMCs from an atopic donor were exposed to either an IgG1 control mAb, 15–1, or MHM6 before incubation in undiluted sera from *Bet v* I-sensitized allergic individuals (n = 5). The capacity of monocytes to bind biotinylated r*Bet v* I was visualized by SA-PE and analyzed by flow cytometry. r*Bet v* I or r*Bet v* I-NP reactivity of monocyte FcγR-bound anti-*Bet v* I mAb BIP 1 (10 μg/ml) served as a positive control. Specific r*Bet v* I binding (Δ-MFC; abscissa) to CD14-positive monocytes was calculated as described in *Materials and Methods*. The MFC in the presence of excess doses of r*Bet v* I, i.e., nonspecific fluorescence, ranged from 8 to 10. *B*, Native or NP-conjugated r*Bet v* I and r*Phl p* II were size fractioned by SDS-PAGE and analyzed by Western blotting for reactivity with mAbs BIP 1 (*upper left*) and cIgE anti-NP (*upper right*) as well as for reactivity with serum IgE from birch (*lower left*) or grass pollen (*lower right*) -allergic individuals. Molecular mass calibration is shown on the *left* in kDa. *C*, Lactic acid-treated E^--PBMCs from the same donor as in *A* were exposed to either an IgG1 control mAb, 15–1, or MHM6 before incubation with cIgE anti-NP. Binding of biotinylated r*Bet v* I-NP was visualized by SA-PE. Specific r*Bet v* I-NP binding (Δ-MFC) to CD14-positive monocytes is given on the abscissa; nonspecific fluorescence equals a MFC of 8.

NP-derivatized rather than native material was used. Figure 4, *A* and *C* demonstrate data representative of results obtained in 12 independent experiments using ME-PBMCs and TCCs of various peptide specificities from five atopic donors. Note that the presence of hapten-specific IgE reduces the amount of NP-conjugated allergen required to yield a 50% maximal TCC response by a factor of 100 to 1000. It should be emphasized that this IgE-mediated enhancement of allergen presentation occurred equally well with both allergens as well as with all their peptide specificities tested, and was independent of the cytokine secretion pattern of the TCC (data not shown). These findings suggest that ME-PBMCs are capable of inducing massively amplified specific Th2, Th0, or Th1 cell responses when the allergen is targeted to these cells via allergen-specific IgE.

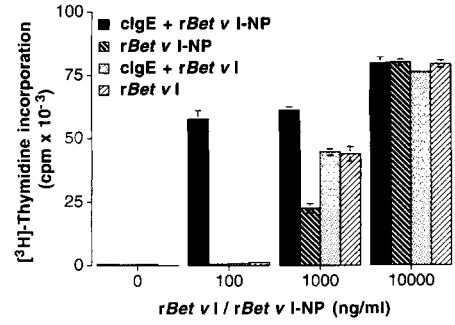

FIGURE 3. Allergen-specific IgE amplifies the capacity of ME-PBMCs to present allergen to HLA-DR-restricted, peptide-mapped TCCs. Lactic acid-treated ME-PBMCs from an atopic donor were exposed to either medium or 0.5 μg/ml cIgE before incubation with either r*Bet v* I or r*Bet v* I-NP. Allergen-specific proliferation of the autologous TCC WD24 is given on the ordinate in cpm. Representative experiment of five.

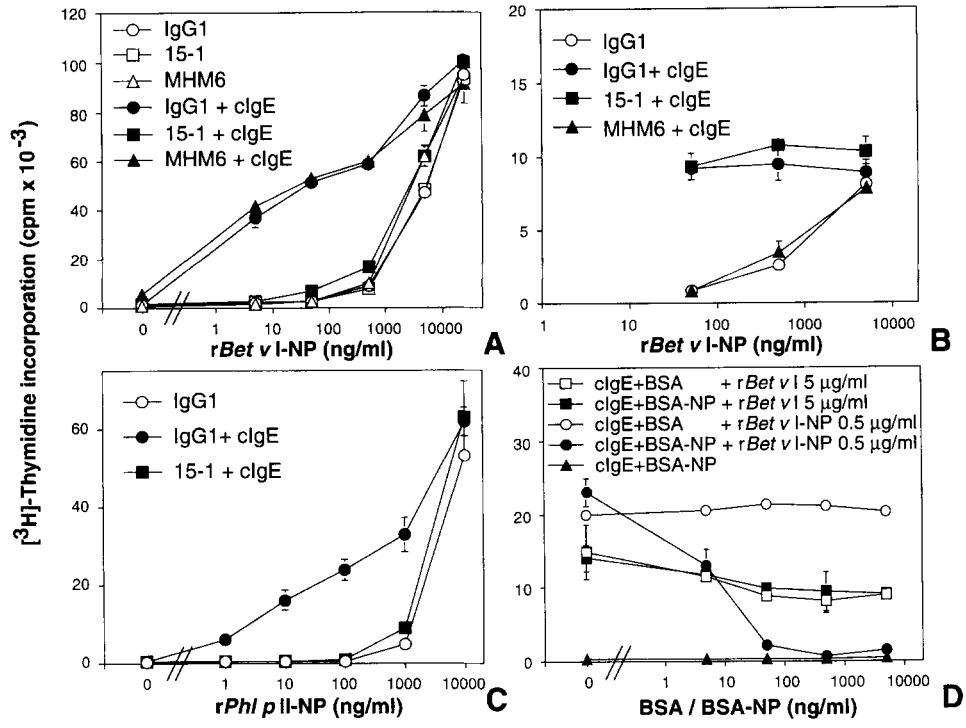

FIGURE 4. The high-affinity IgE receptor FcεRI mediates IgE-facilitated allergen presentation by ME-PBMCs. Lactic acid-treated ME-PBMCs (*A*, *C*) or mitomycin C-treated EBV-transformed B cells (*B*) were reacted with IgG1 (circles), 15–1 (squares), or MHM6 (triangles) followed by the addition of the indicated concentrations of NP-conjugated allergen in the absence (open symbols) or in the presence of cIgE (closed symbols). T cells of TCC TF1M (*A*), HC8 (*B*), or GZ1M (*C*) were added as responders. *D*, Lactic acid-treated ME-PBMCs were incubated with cIgE in the presence of various concentrations of BSA (open symbols) or BSA-NP (closed symbols). Thereafter, r*Bet v* I (squares), r*Bet v* I-NP (circles), or medium (triangles) was added to the wells. T cells of TCC TF7B were added as responders and [^{3}H]thymidine uptake was measured (cpm; *ordinate*).

FcεRI is the critical IgE receptor on ME-PBMCs that mediates IgE-dependent allergen presentation

To identify the IgE binding structure that mediates this IgE-dependent allergen presentation, we performed mAb-blocking experiments. These studies revealed that the presence of anti-FcεRI mAb 15–1 in cultures containing hapten-specific IgE plus haptenized allergen reduces the allergen-specific T cell responses to levels seen with allergen in the absence of cIgE (Fig. 4, *A* and *C*). In contrast to this inhibitory effect of mAb 15–1, the anti-CD23 mAb MHM6 failed to influence this enhanced response under the experimental conditions used (Fig. 4*A*). Furthermore, preliminary evidence suggests that the IgE-dependent Ag presentation capacity of FcεRI-expressing, plastic-adherent ME-PBMCs from an atopic donor is superior to FcεRI weakly positive, adherent ME-PBMCs from a non-atopic individual (data not shown). Conversely to the situation seen with the B cell-depleted ME-PBMCs, IgE-dependent allergen presentation by EBV-transformed B cells, which are known to be CD23 dependent (21–24), was abolished by the anti-CD23 mAb but was unaffected by the anti-FcεRI mAb (Fig. 4*B*). As CD23 is reportedly expressed on monocytes of atopic individuals (17, 19), the divergent usage of Fc-IgE receptors for IgE-mediated Ag presentation by B cells and ME-PBMCs may be surprising at the first glance. However, it should be kept in mind that monocytes express the cytokine-inducible CD23b isoform that has been shown to mediate phagocytosis rather than endocytosis of receptor-bound ligands (25). Taken together, our results suggest that high affinity IgE receptor-mediated endocytosis and, perhaps, sorting of allergen to specialized peptide-loading compartments, is superior to pinocytotic allergen uptake and processing. Finally, we entertained the possibility that cross-linking of FcεRI moieties by IgE and multivalent allergen may have contributed to the observed IgE-enhanced allergen presentation. Therefore, we asked whether IgE-dependent ligation of FcεRI by an irrelevant haptenized Ag (BSA) could influence allergen presentation by FcεRI-expressing ME-PBMCs. These experiments suggest that cross-linking of IgE binding moieties by cIgE and NP-conjugated BSA does not quantitatively alter IgE-independent r*Bet v* I-presentation, whereas IgE-dependent r*Bet v* I-NP-presentation is abrogated in a dose-dependent manner (Fig. 4*D*). Furthermore, cIgE and BSA-NP-induced complexation of IgE receptors on monocytes or on other IgE binding cells did not result in a nonspecific proliferative TCC response (Fig. 4*D*). Therefore, we propose that enhanced allergen uptake via IgE-FcεRI complexes,

rather than the mere cross-linking of FcεRI, is the functionally pivotal mechanism leading to IgE-dependent enhanced allergen presentation by FcεRI-positive ME-PBMCs.

In addition to their constitutive presence within environmentally accessible organs, e.g., skin (4–6) and mucosal tissue (26), FcεRI-expressing APCs are circulating in peripheral blood (7) and may, upon allergen challenge, enter sites of ongoing allergic inflammation, e.g., lesions of LPRs. With low concentrations of allergens within such lesions, the expression of FcεRI on APCs by atopic individuals may critically determine whether allergen uptake, processing, presentation, and ensuing allergen-specific T cell activation can occur. FcεRI-IgE-dependent allergen presentation may hence critically lower the atopic individual's threshold to mount allergen-specific T cell responses. Consequently, this activation of allergen-specific T helper cells may result in the perpetuation of allergen-specific IgE production and, thus, of type I reactions and, perhaps even, in the induction of delayed-type hypersensitivity reactions (27, 28) in allergen-exposed tissues.

Acknowledgments

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