Immunoglobulin E-Binding Structures on Antigen-Presenting Cells Present in Skin and Blood

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In atopic individuals, cutaneous antigen-presenting cells (APC), i.e., Langerhans cells and dermal dendritic cells, frequently display anti-IgE reactivity. Although earlier observations suggested that this phenomenon results from the binding of (complexed) IgE to the low-affinity IgE receptor (FceRII/CD23), we and others demonstrated recently that Langerhans cells, dermal dendritic cells, and peripheral blood monocytes from atopic individuals can bind monomeric IgE via the high-affinity receptor for IgE (FceRI). These new observations re-stimulated investigations aiming to unravel the nature and functionality of the relevant in vivo IgE-binding moiety(-ies) on APC. New data demonstrate that FceRI, both quantitatively and qualitatively, is the pivotal serum IgE-binding structure on APC of atopers and, even more important, that FceRI on APC functions as an allergen-focusing molecule. Thus, it is likely that allergens may be more efficiently taken up, processed, and presented to T cells after targeting to APC via FceRI as compared with allergen binding to APC in the conventional manner. In vivo, FceRI-IgE-dependent allergen presentation may critically lower atopic individuals’ threshold to mount allergen-specific T-cell responses. This would result in the perpetuation of allergen-specific IgE production (type I reactions) and perhaps even the occurrence of T-cell-mediated, delayed-type hypersensitivity reactions in allergen-exposed tissues. J Invest Dermatol 104:707–710, 1995

The syndrome of atopy consists of three major symptoms, i.e., allergic rhinoconjunctivitis, allergic asthma, and atopic dermatitis [1], and is usually associated with elevated serum immunoglobulin E (IgE). Whereas the pathogenetic role of allergen-specific IgE is clearly established in the case of allergic rhinoconjunctivitis and allergic asthma, the manifestation of atopic dermatitis cannot be easily explained by the occurrence of type I allergic immune reactions. In fact, the clinical and histopathologic picture as well as the emergence kinetics of atopic eczema roughly follow the criteria of delayed-type (type IV) immune reactions. It is presently unclear whether IgE-mediated (type I) and T-cell-mediated (type IV) allergic reactions of atopy are events occurring independently of each other or are pathogenetically linked.

IgE-BINDING STRUCTURES ON LANGERHANS CELLS AND DERMAL DENDRITIC CELLS

The first evidence for a possibly causative role of IgE in the pathogenesis of atopic dermatitis was derived from studies showing that skin from patients with atopic dermatitis harbors IgE+ dendritic cells in the epidermis (Langerhans cells) as well as in the dermis (dermal dendritic cells) [2,3]. Initial attempts to characterize the critical IgE-binding structure on Langerhans cells suggested that these cells express the low-affinity IgE receptor (FceRII/CD23) in situ [4] and that this receptor is up-regulated after exposure of Langerhans cells to certain cytokines [5]. However, the failure of specific anti-CD23 monoclonal antibodies (MoAbs) to block entirely IgE binding to Langerhans cells [4], the obvious high affinity of this IgE-binding structure, and the fact that Langerhans cells of both normal and atopic skin are capable of IgE binding [2,6] prompted the search for IgE-binding moieties other than CD23. Recently, this issue was clarified by the demonstration that epidermal Langerhans cells and dermal dendritic cells of healthy persons bind monomeric IgE via the high-affinity IgE receptor FcεRI [6–9], previously thought to be expressed exclusively on mast cells and basophils. Recently, our group has shown that the high-affinity IgE receptor FceRI is the biologically relevant IgE-binding structure on epidermal Langerhans cells and dermal dendritic cells in diseased atopic skin (Klubal R et al, in preparation). The functional significance of FceRI expression on dendritic antigen-presenting cells (APC) is only poorly understood but could be similar to that observed for other FcRs on APC, i.e., the binding of monomeric or antigen-complexed IgE followed by signal transduction and internalization of FcR-bound immune complexes [10–12]. More rapid progress in this research has been hampered by the relative sparsity of these cells and by difficulties in isolating and purifying them from tissue samples. This problem may soon be circumvented by experimental protocols allowing the in vitro generation of Langerhans-cell–like dendritic cells from the pool of CD34-expressing stem cells from cord [13] and peripheral blood (Strunk D et al, submitted) or by the cytokine-driven expansion of FcεRII-expressing dendritic cells from as yet poorly characterized CD34-negative precursor cells present in human peripheral blood [14,15]. In the meantime, a valuable experimental tool for the investigation of FcεRI function on APC was gained by our recent finding that Langerhans cells are not the only APC capable of FcεRI expression.

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IgE-BINDING STRUCTURES ON MONOCYTES/MACROPHAGES

Until recently, it was generally believed that monocytes/macrophages express only low-affinity IgE binding sites, i.e., the inducible form of the low-affinity IgE receptor CD23 [16] and the IgE-binding protein eBP [17]. This led to the assumption that these cell types preferentially bind preformed IgE complexes rather than monomeric IgE. We have found recently that monocytes of atopic individuals can bind monomeric IgE and that this binding occurs via FcεRI [18]. In particular, monocyte FcεRI expression was detected in most patients with atopic dermatitis (70% to 80%) and in a proportion of those with allergic rhinoconjunctivitis (approximately 50%). However, this demonstration of FcεRI on monocyte surfaces does not exclude the possibility that, under in vitro conditions, the binding of polyclonal serum IgE to monocytes occurs predominantly via FcεRII or eBP. We have addressed this issue experimentally and have found that freshly isolated monocytes of atopic, but not of nonatopic, carry cell-surface-bound IgE in vivo and that the majority of IgE-binding sites are occupied by (elevated) serum IgE (Maurer D et al, submitted). The further observation that lactic acid treatment but not lactose treatment of the cells almost completely removed in vivo-bound IgE molecules argued against a possible role of eBP in this process, but did not exclude an important role for CD23 as a relevant IgE-binding molecule in vivo. For this purpose, we exposed lactic-acid-treated monocytes to sera from birch-pollen-sensitized individuals, either in the presence or absence of inhibiting MoAbs to FcεRI or CD23, and visualized the binding of birch-pollen-specific serum IgE by a subsequent incubation step with biotinylated recombinant Bet v 1, the major birch-pollen allergen. The MoAb to FcεRI selectively abolished the binding of polyclonal serum IgE to monocyte surfaces (Maurer D et al, submitted). These results indicate that, in analogy to Langerhans cells, monocytes of allergic individuals carry FcεRI-bound, allergen-specific IgE in vivo and that the interaction with polyvalent allergen is followed by the triggering of FcεRI rather than CD23.

STRUCTURAL AND FUNCTIONAL ANALYSIS OF FcεRI ON APC

On basophils and mast cells, FcεRI is expressed as a tetrameric holoreceptor composed of one α-chain, one β-chain, and one γ-chain homodimer [10]. Molecular and biochemical studies have revealed that Langerhans cells [6,7] and monocytes of atopic persons [18] co-express the IgE-binding FcεRα/γ-chain and the signal-transducing FcεRγ-chain at both the mRNA and protein levels and that the monocyte FcεRα and FcεRγ protein chains are physically associated and thereby form functional FcεRγ complexes (Fiebiger E, unpublished observations). For reasons yet unknown, our attempts to detect FcεRβ mRNA and protein in Langerhans cells and monocytes have so far been unsuccessful [6,18]. Apart from procedural considerations, it is possible that the high-affinity IgE receptor on APC consists of α- and γ-chains only. In fact, transfection experiments have shown that this chain composition suffices for functional cell-surface expression of the human receptor [19,20]. However, the COOH-terminal intracytoplasmic portion of the β-chain has been found to contain a conserved protein sequence motif (antigen recognition activation motif) [21], which allows the physical association with members of the src protein tyrosine kinase (PTK) family. Accordingly, recent findings have re-emphasized an eminent functional importance of the β-subunit, showing that the constitutively β-associated src PTK lyn is crucial for phosphorylation and activation of the FcεRIγ subunit. FcεRIγ thus modified can then activate the PTK syk and downstream signaling events, allergen binding and activation of phospholipase C, breakdown of phosphoinositols, and elevation of the cytosolic calcium concentration [22]. Despite the apparent lack of β, FcεRI on APC is capable of mediating PTK activation [23] and calcium mobilization [18,23], indicating competent signaling via this receptor. At the moment, it is tempting to speculate about the presence of a putative β-like structure that functionally substitutes for the “classic” FcεRIβ-chain in APC.

BILOGIC CONSEQUENCES OF ALLERGEN-IgE BINDING TO FcεRI ON APC

The binding of allergen-specific IgE to FcεRI on mast cells and basophils, followed by bridging of the membrane-bound IgE molecules by soluble, multivalent allergens, results in cellular degranulation and consequently in the release of proinflammatory substances such as histamine, serotonin, prostaglandins, and leukotrienes [24-26], as well as in the synthesis and secretion of cytokines such as interleukin (IL)-3, IL-4, IL-5, IL-6, granulocyte-macrophage colony-stimulating factor, and interferon-γ [27-29]. Because FcεRI on APC constitutes a functional cell-surface receptor and APC are potent producers of cytokines [30-34] and eicosanoids [35,36], it is likely that FcεRI induces the release of biologic effector molecules by APC and critically modulates or even initiates allergic inflammatory responses in allergen-exposed tissues.

We recently found that, besides its putative cytokine-inducing properties, FcεRI on professional APC functions as an allergen-focusing receptor structure. Using sera from grass- or birch-pollen-sensitized donors and recombinant birch (Bet v 1) and grass pollen (Phl p 11) allergens as well as hapten (hydroxy-nitrophenacyl, NPY)-specific, monomeric IgE (clgE) and NP-conjugated allergens, we observed that the presence of cell-surface-bound IgE results in efficient allergen binding to the monocytes of atopic, MoAb-blocking experiments revealed that FcεRI, rather than FcεRII, is the pivotal moiety that mediates this event. Even more important, clgE-mediated allergen binding to monocyte-enriched, peripheral blood mononuclear cells of atopic persons resulted in a 100-1000-fold amplification of Bet v 1 or Phl p 11 presentation to autologous T-cell clones with peptide specificities for Bet v 1 or Phl p 11. The addition of the anti-FcεRIα-chain MoAb, but not of an anti-CD23 MoAb, reduced this clgE-enhanced, allergen-specific T-cell–clone response to levels seen in the absence of clgE. This demonstrates that FcεRI, but not FcεRII, mediates IgE-dependent allergen uptake, processing, and presentation by professional APC from atomics (Maurer D et al, submitted). Thus, our findings emphasize an as yet unknown function of FcεRI in atopic diseases and provide clear evidence that the presence of this receptor on APC critically lowers the threshold of atopic individuals to mount allergen-specific T-cell responses.

With regard to IgE-mediated cutaneous allergy, these findings may have pathogenetic significance for delayed-type allergic inflammation occurring in the skin and, perhaps, in other tissues. If repeated allergenic exposure of the skin and/or mucosal tissue results in the production of allergen-specific IgE (Fig 1A), then the interaction of allergen with IgE bound to FcεRI on skin APC may result in IgE-facilitated allergen presentation to T cells in lymphoid and non-lymphoid organs and, furthermore, in allergen/IgE-dependant activation and cytokine secretion by FcεRII-expressing cells within the tissue (Fig 1B). In particular, monocytes secrete IL-1 and tumor necrosis factor-α after cross-linking of cell-surface–bound IgE moieties in vitro [34]. These two cytokines have been shown to play an indispensable role in the elicitation of cutaneous late-phase atopic reactions [37,38]. IL-1 and tumor necrosis factor-α exert some of their biologic effects via induction of E-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 expression by endothelial cells [37,39]. Upregulated endothelial cell adhesion molecules promote and reinforce leukocyte-endothelial-cell interactions and, therefore, are a prerequisite for transmigration of inflammatory cells into inflamed tissue [40]. In delayed-type atopic reactions, the latter event is characterized by extravasation of (Fc-IgE receptor-bearing) eosinophils and macrophages, as well as by a pronounced accumulation of T lymphocytes [3]. At this particular step, IgE-amplified allergen presentation by FcεRI-expressing skin APC may decisively control the quality and quantity of allergic tissue inflammation. Even in the presence of minute allergen concentrations, this mechanism may allow effective activation and clonal expansion of skin-infiltrating,
allergen-specific T helper cells, with a Th2-like cytokine secretion pattern [41-43] and with the capacity of mediating (IL-4-dependent) allergic tissue reactions [44]. Moreover, activated allergen-specific Th2-like cells should possess the capability to promote B cells to secrete allergen-specific IgE, which again binds to FcεRI-expressing APC in skin and other tissues. If this allergen-driven, self-amplifying mechanism is operative in atopic diseases in vivo, then therapeutic strategies should aim to interrupt this vicious circle by interference with FcεRI expression, IgE binding to FcεRI, and/or FcεRI-mediated signal transduction by APC.

This work was supported in part by grants from the Austrian Science Foundation (S06702-MED) and from the Sandoz Research Institute, Vienna, Austria.

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