

The central role of FcεRI in allergy

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Summary

The high-affinity receptor for immunoglobulin E (IgE), FcεRI, plays a central role in the initiation and control of atopic allergic inflammation. On mast cells and basophils, the function of the receptor is well known and constitutes cellular degranulation and the release of various mediators. FcεRI on antigen-presenting cells (APCs), however, does not lead to degranulation of preformed granula, but has different functions: signal transduction pathways like the activation of NF-κB are initiated to induce inflammatory cytokine gene expression. In addition, FcεRI on APCs acts as an allergen-focusing structure and can efficiently amplify allergen presentation in an IgE-dependent manner. Recently, we and others have gained new insight into the regulation and function of FcεRI on APCs, which has shed new light on the modulating effects of the immune system in atopic inflammation.

Atopy

The clinical triad of atopic eczema/dermatitis syndrome (AEDS), allergic rhinitis and allergic asthma and their cosegregation in affected family members within allergic pedigrees suggest that atopy underlies specific common pathophysiologic dysregulations.¹ With the beginning of the new millennium, it is clear that the hereditary predisposition to produce immunoglobulin E (IgE) with an immune response that is dominated by the Th2 subset of CD4⁺ T cells represents only one feature of a large, complex network. On a cellular basis, AEDS is an inflammatory skin disease with histological features of an eczematous reaction. Clinically, AEDS can be divided into two distinct forms: the extrinsic form, which ultimately results from sensitization to environmental allergens with elevated specific IgE levels, and the intrinsic form, occurring in the absence of sensitization and specific IgE.² While the pathophysiology of the nonallergic form is poorly understood, progress has

been made in understanding the underlying mechanisms of the allergic form of AEDS (Fig. 1).

The high-affinity receptor for IgE, FcεRI

Receptors for the Fc domain of IgE (FcεRs) provide a key to the onset and propagation of allergic diseases. There are two classes of FcεRs on cells of the immune system: the high-affinity receptor for IgE, FcεRI, capable of binding monomeric IgE, and the low-affinity receptor for IgE, FcεRII or CD23, which interacts preferentially with complexed IgE.³ The classical FcεRI is tetrameric: it consists of an α-chain which provides the binding site for IgE, a β-chain, and homodimeric γ-chains. The latter subunits are responsible for transducing the initial cross-linking signal into the cell.⁴ The β-chain of FcεRI enhances receptor maturation, leading to an increase of FcεRI surface expression and signal transduction capacity within the cells.⁵ In humans, the classical FcεRI (αβγ₂) is constitutively expressed on effector cells of anaphylaxis (i.e. mast cells and basophiles), whereas the expression of a trimeric form of FcεRI (αγ₂) is variably present on antigen-presenting cells (APCs) such as monocytes, and dendritic cells (DCs) including Langerhans cells (LCs).⁶ Although it lacks the classical β-chain, FcεRI on APCs confers full function on these cells.

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Accepted for publication 22 October 2002

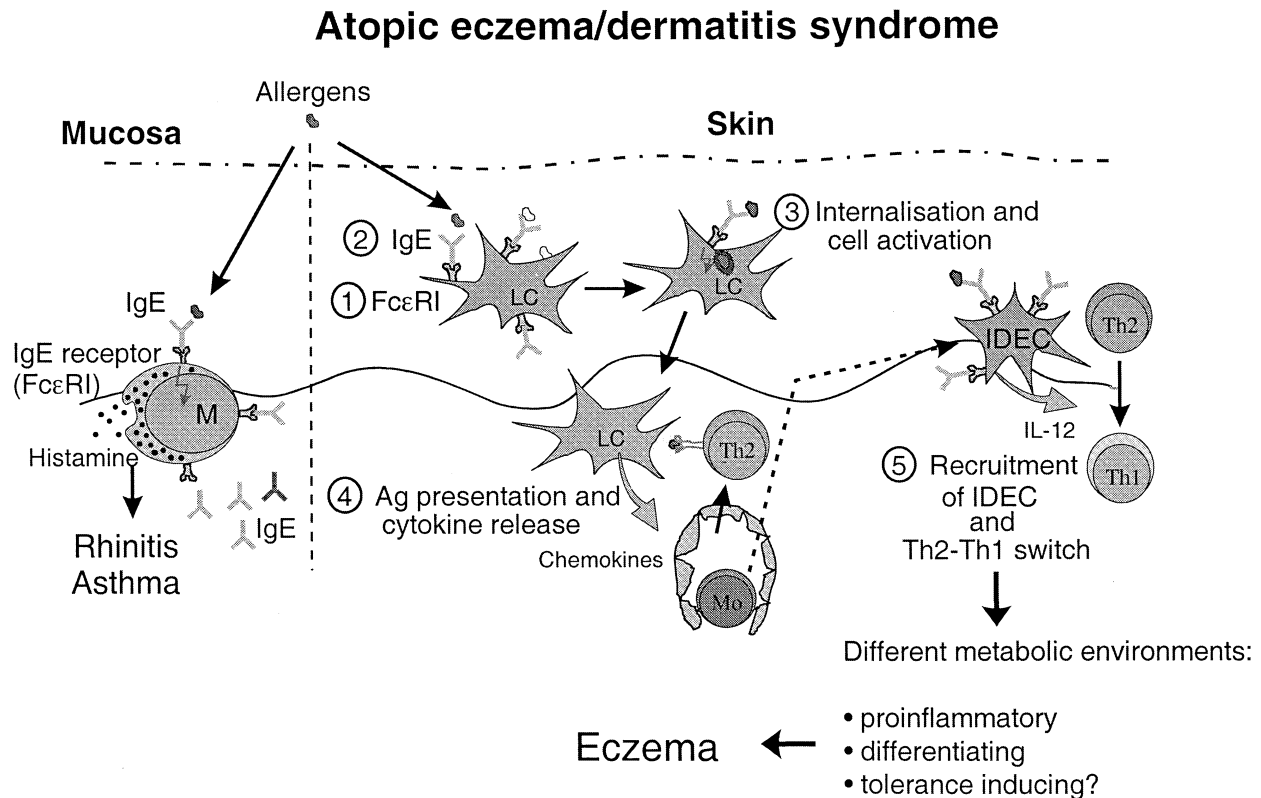


Figure 1 The role of FcεRI⁺ Langerhans cells (LCs) and inflammatory dendritic epidermal cells (IDECs) in the pathogenesis of atopic eczema/dermatitis syndrome (AEDS). In allergic rhinitis and allergic asthma, FcεRI cross-linking leads to the degranulation of mast cells, which may initiate immediate and late-phase events. In AEDS, LCs are activated through the cross-linking of FcεRI and trafficking ensues. The activation of T cells will lead to an inflammatory cascade, thus contributing to the recruitment of IDECs that stimulate autologous T cells. IDECs may induce a switch of Th2 to Th1 cell responses and probably contribute to the chronicity of AEDS. M, mast cell; Mo, monocyte.

Allergic reactions

The sensitization phase

In the phase of sensitization, an allergen is encountered for the first time. Immature DCs, monocytes or macrophages which reside in tissues function as the first barrier and capture the antigen by phagocytosis, macropinocytosis or receptor-mediated uptake. The antigen is directed into the endocytic pathway of the cell where degradation of the protein and assembly into MHC class II-peptide complexes take place.⁷ During their characteristic maturation process, DCs prepare to migrate to regional lymph nodes and stimulate naive T cells. There is up-regulation of MHC class II, accessory molecules such as CD40, CD80, CD83 and CD86, and down-regulation of Fc receptors.⁸ Data indicate that, at the moment of priming, naive T cells receive signals driving them into Th1- or Th2-type CD4⁺ T cells.⁹ It is the hallmark of atopic individuals that

their immune system selects a Th2 skewed memory and thus favours immune responses seen in allergic diseases, the ultimate product being the production of allergen-specific IgE.¹⁰ IgE then binds to FcεRI on mast cells, basophils or APCs thus increasing the efficacy of allergen defence upon re-exposure.

The elicitation phase: FcεRI in the early- and late-phase reaction

Upon a second encounter of an allergen, FcεRI is of central importance in both phases of the allergic reaction, the so-called early and late phases. The interaction of IgE with antigen leads to a variety of immunological sequelae. Ligation of FcεRI by binding of IgE-allergen complexes on mast cells triggers the release of preformed vasoactive mediators, synthesis of prostaglandins and leukotrienes, and the transcription of cytokines. In FcεRI-deficient mice, free IgE or

antigen-complexed IgE does not augment allergen-dependent inflammation in previously sensitized mice, thus underlining the importance of this receptor in allergic asthma.¹¹ In the bronchial mucosa, these mediators of immediate-hypersensitivity reactions rapidly induce mucosal oedema, mucus production, and smooth muscle constriction. In asthmatics, this acute reaction is often followed by a late-phase reaction which is dependent upon eosinophils and manifests 4–8 h after the initial reaction.¹² It has been postulated that the state of chronic and relapsing airway constriction results from persistent late-phase inflammatory responses sustained by the exposure of perennial allergens.¹³ In human and animal studies, it is postulated that mast cells are initiators of both the early and the late phases of bronchial hypersensitivity.¹⁴ Depending on the target organ, late-phase reactions can be also be provoked by the activation of T cells.

In the skin of atopic individuals, degranulation of mast cells by cross-linking of FcεRI can also trigger both immediate-hypersensitivity and late-phase reactions. But the cellular and molecular basis of the cell-mediated hypersensitivity reaction in atopic patients with AEDS and high levels of IgE remained unclear until FcεRI was described on LCs in lesional skin of patients with AEDS.¹⁵ The infiltrate in AEDS is histologically characterized by high numbers of LCs, inflammatory dendritic epidermal cells (IDECs), macrophages and T cells. IDECs constitute a cell population that is mainly found in AEDS but is also seen in other inflammatory diseases such as psoriasis and allergic contact dermatitis.¹⁶ Ultrastructurally, these cells resemble LCs but lack Birbeck granules. The presence and activation of FcεRI on these cells provide evidence in support of the pathophysiological concept that this receptor acts as a link between (aero-) allergens and antigen-specific T-cell immunity: the presence of FcεRI⁺ LCs bearing IgE molecules is a prerequisite for provoking eczematous skin lesions by means of application of allergens on the skin of atopic patients.¹⁷ FcεRI–IgE–allergen complexes facilitate antigen uptake and antigen presentation: large molecules that are not usually engulfed via the normal pathway are able to be processed by receptor internalization. In addition, mediators and cytokines are released which, as well as recruiting other inflammatory cells, have an impact on skewing T cells towards a defined phenotype.¹⁹ A new concept involves FcεRI⁺ LCs as the pivotal cells in the sensitization phase of AEDS, as they are present in higher numbers in the skin of atopic persons compared with healthy individuals.²⁰ While LCs produce only small amounts of cytokines, IDECs are capable of secreting a substantial amount of

cytokines and are therefore thought to be the principal cells of the elicitation phase. Moreover, at the single-cell level, FcεRI density is higher on IDECS than on LCs, which might lead to full cell activation and IgE-mediated trapping of the allergen.¹⁶ Recently, new immunomodulatory functions of this receptor have been described: ligation of FcεRI prevents apoptosis of atopic monocytes induced by serum deprivation via Fas/Fas-ligand interactions.²¹ In addition, the aggregation of this receptor on monocytes prevents their differentiation into DCs *in vitro*, leading to macrophage-like cells with high phagocytic activity.²² The broad spectrum of reactions after cross-linking FcεRI on APCs may mirror the clinical variability among atopic patients: it is largely unknown why AEDS patients with high receptor expression and high IgE levels enter phases of remission or aggravation and why other family members or persons with the same parameters are clinically healthy. One can anticipate that the next few years will yield new insights into the genetic, environmental, cellular and molecular factors that underlie the development of atopic diseases.

Conclusions

Atopy defines a complex genetically and environmentally determined predisposition for the development of allergic asthma, allergic rhinoconjunctivitis and the atopic eczema/dermatitis syndrome (AEDS). The plasticity of FcεRI⁺ APCs as immunostimulating and/or immunoregulatory cells provides a key to the understanding of the dynamics of atopic diseases. It is thought that FcεRI⁺ APCs communicate with T cells in defined metabolic compartments, and that T cells can respond with either activation or arrest, depending on proinflammatory or regulatory forces.

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Key points

- Ligation of FcεRI triggers important functions involved in allergy development.
- FcεRI on antigen-presenting cells in the skin represents the link between (aero-) allergens and T-cell mediated inflammation.
- New functions of FcεRI and its immunomodulatory effects on the immune system are currently being investigated.