

FcεRI-expressing antigen-presenting cells: new players in the atopic game

Thomas Bieber

What is the role of FcεRI on professional antigen-presenting cells (APCs)? Here, Thomas Bieber speculates how FcεRI-expressing APCs may trigger primary and secondary immune responses, T-cell skewing and inflammation.

Atopy is defined as a genetically inherited predisposition to develop allergic diseases such as asthma, rhinoconjunctivitis and atopic eczema, associated with an exaggerated production of IgE antibodies to environmental allergens. This immunoglobulin and its cellular receptors – the high-affinity receptor FcεRI and the low-affinity receptor FcεRII (CD23) – are known to play a pivotal role in the physiopathology of atopic diseases. Human professional antigen-presenting cells (APCs), such as monocytes¹, peripheral blood dendritic cells (DCs)², epidermal Langerhans cells (LCs)³⁻⁵ and related DCs (Ref. 6), as well as APCs in the lung^{7,8}, may express FcεRI. However, detailed structural analysis has shown that the receptor on APCs differs from the FcεRI expressed on basophils and mast cells (the effector cells of anaphylaxis) in that it lacks the classical β chain. Another characteristic of FcεRI on APCs is its highly variable expression, which is dictated by the microenvironment of the cells⁹ and determines their activation capacity: only APCs expressing high levels of FcεRI are fully activated upon receptor ligation¹⁰. Since APCs are not equipped with granules or preformed mediators able to induce an immediate, allergic reaction or to kill parasitic invaders, new roles for the FcεRI have to be considered.

The role of FcεRI in antigen focusing by APCs

Antigen uptake, processing and presentation are the main functions of APCs. FcεRI expression enables specific antigen uptake via receptor-mediated endocytosis in APCs and implies several important features. First, depending on the density of FcεRI expressed on APCs, these receptors extend the ability to react with allergens by binding large amounts of IgE molecules with

various specificities; this significantly enhances the probability of FcεRI crosslinking by a defined allergen at the cell surface. Second, IgE-FcεRI complexes allow capture of large allergens that are not normally engulfed via the usual pathway, i.e. by pinocytosis. Third, receptor-mediated endocytosis following aggregation of FcεRI on APCs results in transfer of the receptor to coated pits, coated vesicles and endosomes¹⁰. By analogy to B-cell receptors, where Ig-α and Ig-β are targeted to different endosomal compartments¹¹, the route used for antigen uptake by APCs may target foreign structures specifically to major histocompatibility complex (MHC) class II-rich compartments, ultimately leading to a higher density of specific peptides in the grooves of surface MHC class II molecules. Finally, as mentioned above, APCs expressing high receptor densities display full cell activation upon FcεRI ligation, which most probably induces the synthesis and release of yet-to-be-defined mediators. Such mediators may on the one hand enhance/influence the outcome of subsequent antigen presentation and on the other hand have proinflammatory capacities and recruit inflammatory cells to sites of allergen penetration (see below).

This scenario allows for efficient antigen presentation of even minute amounts of allergens. Interestingly, while it was reported in 1990 that LCs isolated from atopic skin use IgE for antigen uptake, which was followed by presentation to autologous T cells¹², formal proof that FcεRI enables APCs to provide IgE-mediated antigen focusing has been provided only recently for monocytes¹³, circulating DCs (Ref. 2) and LCs (Ref. 14).

FcεRI⁺ APCs as tuners of specific immune responses

As a consequence of the ability to capture allergens via FcεRI and present them efficiently, FcεRI⁺ APCs armed with specific IgE antibodies should be able to boost the secondary immune response and trigger further IgE synthesis by recruiting and activating more antigen-specific T helper 2 (Th2) cells. In addition, it is possible that FcεRI⁺ APCs (in particular DCs, which are potent stimulators of naive T cells) may initiate a primary immune response. At first glance, FcεRI-mediated antigen uptake and subsequent presentation would appear unlikely in the primary reaction, since specific IgE would have to be present early in the response. However, it is possible that complex allergenic structures efficiently captured via FcεRI on DCs are processed in a way that leads to the unmasking and presentation of cryptic peptides/epitopes not previously encountered by T cells. This would result in a primary reaction against these antigens, thereby contributing to the extension of the IgE repertoire. Furthermore, some epitopes may not be efficiently loaded on to MHC class II molecules for presentation because of a high-affinity interaction between IgE and the allergen. A third possible function of FcεRI⁺ APCs is suggested by considering the putative role of APCs and especially DCs in the mechanisms leading to skewing T cells to secrete a particular cytokine profile – a topic attracting much recent interest^{15,16}. The possibility of simultaneous antigen uptake and FcεRI aggregation on APCs leading to the *de novo* synthesis and release of mediators capable of skewing naive or memory T cells towards a defined phenotype and/or function, i.e. towards Th0, Th1 or Th2 cells, is a seductive working hypothesis.

Thus, depending on the highly variable expression of FcεRI on APCs, which seems to be dictated by their

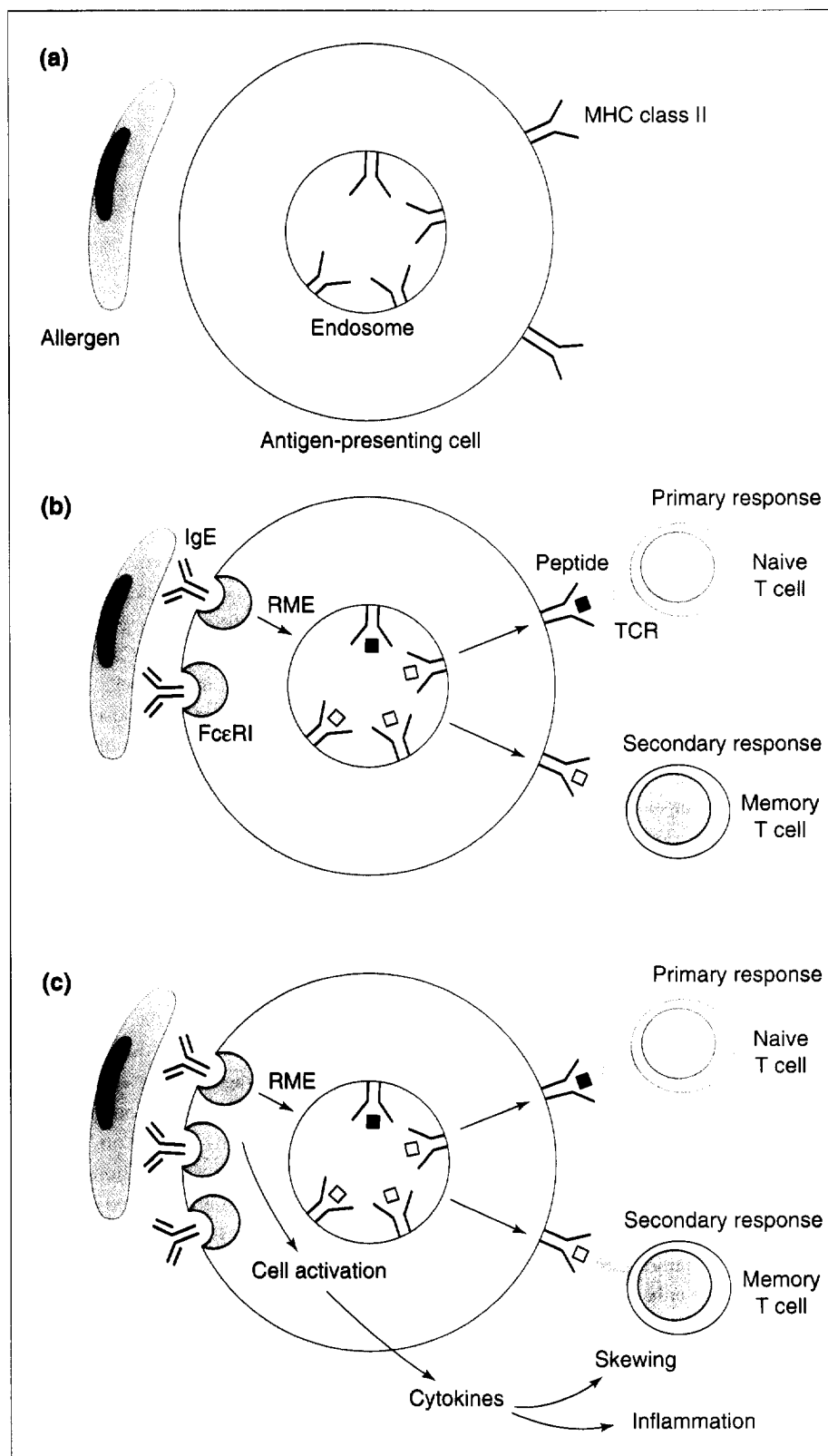


Fig. 1. Role of FcεRI-expressing antigen-presenting cells (APCs) in tuning the antigen-specific immune response. Depending on the receptor density on APCs, three situations may be envisaged, each having different outcomes. (a) Absence of FcεRI-expression, resulting in no IgE-mediated capture of allergens. (b) Expression of low amounts of FcεRI, resulting in binding of antigen-specific IgE and therefore of allergen, receptor-mediated endocytosis (RME), and loading onto major histocompatibility complex (MHC) class II molecules. This allows efficient presentation to specific memory T cells (secondary immune response) via the T-cell receptor (TCR), or even to naive T cells in the case of cryptic epitopes (primary immune response). (c) Expression of high amounts of FcεRI, resulting in the responses described in (b) but also full FcεRI-triggered activation with subsequent putative alteration of the repertoire of cytokines and/or costimulatory molecules produced by APCs. The situation in (c) may lead to skewing of the stimulated T cells to a different cytokine-secretion profile than in (b).

FcεRI⁺ APCs as triggers for IgE-mediated DTH reactions

As is the case for mast cells, FcεRI ligation on APCs may trigger the synthesis and release of mediators that initiate a local inflammatory reaction. Thus, FcεRI⁺ APCs in the lung and the skin may play a crucial role in asthma and atopic dermatitis, respectively, since they could represent a link between transepithelial-penetrating aeroallergens and antigen-specific T cells infiltrating the tissues. The presence of FcεRI⁺ epidermal DCs, bearing IgE molecules, seems to be a prerequisite to provoking eczematous skin lesions after application of aeroallergens to the skin of atopic patients¹⁷. Consequently, atopic dermatitis and asthma may represent IgE-FcεRI-mediated, delayed-type hypersensitivity (DTH) reactions triggered by FcεRI⁺ APCs.

Future prospects

Once the mechanisms of APC involvement in tolerance are better understood, it might be possible to use *in vitro*-generated APCs expressing FcεRI to induce allergen-specific tolerance/anergy in patients exhibiting exaggerated immune responses towards environmental allergens.

microenvironment, the cells may display different functional capacities. Three main scenarios may be envisaged (Fig. 1): APCs that do not express FcεRI are not able to capture allergen-specific IgE; APCs expressing only low amounts of FcεRI can capture allergens via specific IgE, leading to secondary and possibly primary im-

mune reactions, but their cytokine secretion program is not altered; and APCs expressing high amounts of FcεRI not only efficiently capture and internalize allergens, but are also activated upon receptor ligation, with subsequent modification of their cytokine secretion and skewing of T-cell function.

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CSF-1 signal transduction: what is of functional significance?

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There have been many discrepant findings in the field of colony-stimulating factor 1 (CSF-1) signaling. Here, John Hamilton highlights some of the issues that need to be resolved.

Colony-stimulating factor 1 (CSF-1), also known as macrophage-CSF (M-CSF), is a homodimeric glycoprotein that binds to a high-affinity receptor, c-Fms, which is expressed mainly on cells of the monocyte/macrophage lineage¹. The c-Fms protooncogene product comprises an extracellular ligand-binding domain joined through a single membrane-spanning helix to a cytoplasmic protein tyrosine kinase (PTK) domain. c-Fms is more closely related structurally to the α and β receptors for platelet-derived growth factor (PDGF), the c-Kit protooncogene product and Flt3/Flk2 than to other PTK receptor subfamilies. The PTK domain of each of these receptors is interrupted by kinase insert (KI) sequences of variable lengths¹ (see below and Fig. 1).

Studies of CSF-1 signal transduction have led to many different conclusions. This article summarizes some of the differences that need to be resolved if we are to improve our understanding of CSF-1 and monocyte/macrophage biology.

Roles for c-Fms autophosphorylated tyrosines

Upon CSF-1 binding and receptor dimerization, the PTK domain of c-Fms is activated, resulting in *trans*-phosphorylation of specific tyrosine residues within the cytoplasmic domain. These residues may then serve as high-affinity binding sites for *src*-homology 2 (SH2) domains contained within cytoplasmic signaling proteins². Several autophosphorylation sites have been identified in the murine c-Fms protein: Y697, Y706 and Y721 in the KI region, Y807 in the PTK domain, and Y559 in the juxtamembrane region² (Fig. 1); the equivalent tyrosines in human c-Fms are at positions 699, 708, 723, 809 and 561, respectively¹. Current evidence supports the following associations of cytoplasmic signaling proteins (given here using

the residue numbers of murine c-Fms): phosphoinositide 3-kinase (PI 3-kinase) at Y721 (Ref. 2), Grb2 at Y697 (Ref. 3), STAT1 at Y706 (Ref. 4) and Src at Y559 (Ref. 5) (Fig. 1).

Residue Y809/Y807

Ligand-activated human c-Fms can induce continuous proliferation when ectopically expressed in murine NIH 3T3 fibroblasts⁵. By contrast, a receptor mutant containing a phenylalanine for tyrosine substitution at codon 809 (here designated c-Fms Y809F) was mitogenically inactive. Although the cells expressing c-Fms Y809F exhibited normal PTK activity *in vitro* and *in vivo*, and unimpaired *c-fos* and *c-jun* expression, c-Myc mRNA was poorly induced⁶. Enforced expression of c-Myc in these cells overcame the arrest at cell-cycle stage G1, suggesting that c-Myc is required for CSF-1-induced mitogenesis⁷. By contrast, the equivalent murine c-Fms Y807F mutant had decreased autophosphorylation *in vivo* and PTK activity *in vitro*, and induced lower c-Fos and c-Jun mRNA expression, but was able to