Immunoglobulin E–bearing Antigen-presenting Cells in Atopic Dermatitis

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Human antigen-presenting cells (APCs) bind monomeric immunoglobulin E (IgE) via the high-affinity IgE receptor, FcεRI. Surface expression of this trimeric structure is strongly associated with the atopic status of the donors, and maximal levels are observed on Langerhans cells (LC) and inflammatory dendritic epidermal cells (IDEC) in atopic dermatitis (AD). Although intracellular expression of the FcεRI α-chain is induced by interleukin-4 (IL-4), the upregulation of surface levels on dendritic cells (DC) from atopics is due to enhanced expression of the FcεRIγ-chain and stabilization by binding of its ligand IgE. A characteristic function of FcεRI-bearing APCs is the specific uptake and processing of IgE-bound allergens, which is followed by T-cell stimulation. In AD, DC-mediated presentation of aeroallergens penetrating the epidermis is thought to induce an IgE-mediated, delayed-type hypersensitivity reaction. In addition, different FcεRI-bearing APC subsets in AD skin might regulate inflammatory processes through the production of Th1/Th2-polarizing signals, proinflammatory cytokines, chemokines, and factors that are involved in the induction of tolerance.

Introduction

Atopic dermatitis (AD) represents a chronic, relapsing inflammatory skin disease with a very classic phenotype and typically distributed skin lesions. Both the underlying pathophysiologic and genetic mechanisms leading to the manifestation of this complex disease are still not completely understood, but scientific approaches in recent years have made considerable progress in gaining insights into the mechanisms that cause AD. IgE-bearing professional antigen-presenting cells (APC), especially dendritic cells (DC), which, in the normal epidermis, are represented by Langerhans cells (LC), have become an important part of the pathophysiologic concept of AD. This review is focused on the multifaceted role that IgE-bearing APCs might play in atopic diseases, and especially in the pathophysiology of AD.

Immunoglobulin E–bearing Antigen-presenting Cell Populations of the Skin

Professional APCs are represented by monocytes and macrophages as well as DC. The latter are known for their very high immunostimulatory activity toward T cells, and their unique ability to prime naïve T cells [1]. IgE-binding APC in the skin are mainly of the DC type. Besides epidermal DC, a few dermal dendrocytes have been shown to bear the high affinity receptor for IgE in AD skin [2]. Various DC subpopulations reside at the outposts of the immune system in the skin, the airways, and the gut. In these peripheral tissues, they act as primary sentinels of the immune system. Immature DC are derived from hematopoietic progenitors in the bone marrow and traffic from the blood to peripheral tissues to capture foreign antigens [1]. Upon antigen capture and additional maturation stimuli, they migrate to the draining lymphoid organs to prime naïve T cells and gear their development into Th1 or Th2 effector cells. DC1 are driving Th1 responses, and mainly belong to the myeloid lineage, whereas DC2 induce Th2 responses and mainly belong to the plasmacytoid DC lineage. The oldest member of the DC system are the epidermal LC, which are characterized by their primary ultrastructural marker, the tennis racket–shaped Birbeck granules, in combination with their surface expression of CD1a. LC form a network in the basal and suprabasal layers of the epidermis and are present in normal, uninflamed skin. Their primary function in uninflamed skin is to maintain a state of tolerance against invading antigens and allergens under an immunologic steady-state condition. LC are long-term residents of the skin compared with other DC types in peripheral tissues. In a mouse model, LC have been shown to remain in the skin for at least 18 months without being replaced by new LC precursors [3]. In contrast, in response to arriving danger signals, such as inflammation, multiple changes occur. Among these is the

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release of monocyte-chemoattractant protein (MCP) chemokines by skin cells, which induce the recruitment of new LC progenitors from the bone marrow [3]. Other factors, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β initiate the migration of activated immunostimulatory LC to peripheral lymph nodes, which is directed by binding of the chemokines CCL19 and CCL21 to their receptor CCR7. In this manner, in the acute phase of allergic and inflammatory skin diseases, LC precursors are immediately recruited by chemotactic signals to the site of inflammation and replace activated DC, which leave the skin to enhance immune reactions further. However, inflammatory skin diseases, such as AD, are characterized by the presence of a second epidermal DC type, the so-called inflammatory dendritic epidermal cells (IDEC). The ultrastructure of IDEC resembles that of LC, but IDEC do not contain any Birbeck granules [4]. Although it has been assumed for a long time that LC represent a single IgE-binding and high-affinity IgE receptor (FcεRI) expressing epidermal cell population in AD lesions, it has become obvious that both IDEC and LC are the relevant IgE-binding and FcεRI-expressing cells. In comparison with LC, IDECs additionally express CD1b, CD11a, CD11b, and CD11c, the thrombospondin receptor CD36, and the mannose receptor (CD206), which is known to be involved in the uptake of bacterial components [5]. Using an atopy patch test as a model, it has been shown that in the early phase of AD, IDEC are rapidly recruited into the inflammatory skin lesions, where they amplify the allergic inflammatory immune reaction [6•]. It is of special interest that plasmacytoid DC (pDC), which are involved in antiviral defense by the production of large amounts of interferon (IFN)α and IFNβ, are present only in low amounts in the epidermis of AD patients. This is in contrast with other inflammatory skin diseases, such as psoriasis vulgaris, contact dermatitis, or lupus erythematosus. The lack of this pDC subset in the skin of AD patients might be one reason for their high predisposition for viral infections, such as herpes virus infections, which cause eczema herpeticatum, known as a frequent complication of AD [7].

The High Affinity IgE Receptor FcεRI Is the Major Immunoglobulin E–binding Structure on Antigen-presenting Cells in Atopic Dermatitis

At the molecular level, human APCs have been found to express three IgE-binding structures: the high-affinity IgE receptor FcεRI; the CD23 molecule, which represents the low-affinity IgE receptor FcεRII; and εBP/galectin-3 [8–11]. However, two studies have shown that on LC and in AD skin, FcεRI represents the predominant IgE-binding structure on APC [2,10]. Therefore, in this review, we focus on FcεRI-bearing APCs. We explain the molecular characteristics of FcεRI on APCs, and describe the multifaceted role that FcεRI-bearing APCs might play in the pathophysiology of AD.

FcεRI on Antigen-presenting Cells Exhibits a Trimeric Structure

The classic, tetrameric FcεRI expressed on effector cells of anaphylaxis, such as mast cells and basophils, consists of three, distinct protein species (αβ2γ) [12] (Fig. 1). The α-chain mediates binding to the Fc portion of the IgE molecule. The β-chain acts as an amplifier of signaling downstream of the receptor [12]. In addition, the β-chain augments the maturation of the α-chain and its intracellular trafficking to the cell surface, thus leading to increased surface expression [12]. The γ-chain dimer, which is shared with other Fc receptor complexes, carries two immunoreceptor tyrosine-based activation motifs (ITAMs) in its cytoplasmic tail for downstream signal propagation. ITAMs are phosphoacceptors, through which the β- and γ-chains of FcεRI interact with signaling proteins. Transfection studies have suggested that the γ-chain masks an endoplasmic reticulum (ER)-retention motif in the α-chain, which leads to export and full maturation of the FcεRI complex, making it an essential prerequisite for the FcεRI surface expression [13].

In contrast, human APCs express the minimal trimeric FcεRI structure (α2γ) lacking the β-chain (Fig. 1). This structure has been shown for LC, monocytes, and peripheral blood DC [14–16]. The absence of the FcεRIβ chain might explain the much more variable surface expression of FcεRI on APC, ranging from FcεRI-negative cells to expression densities that are comparable with mast cells and basophils. However, the trimeric FcεRI complex can activate cells by inducing signaling events, such as tyrosine phosphorylation or calcium mobilization [14,16–18], although signals tend to be weaker than those for the tetrameric structure, due to the absence of the FcεRIβ ITAM and usually lower surface expression. Interestingly, a trimeric FcεRI complex cannot reach the surface of rodent cells [12]. Therefore, humans have a much broader FcεRI tissue distribution than rodents. This explains the lack of a rodent model for IgE-mediated epicutaneous sensitization and the lack of an AD correlate in rodents, although AD-like skin reactions can be induced in rodents using repetitive application of high-antigen doses under occlusion.

FcεRI Expression on Antigen-presenting Cells Is Associated with Atopic Status

Mast cells and basophils express high constitutive levels of FcεRI on their surface. As mentioned earlier, APC show a much broader expression density. One of the most important observations suggesting a role for FcεRI-bearing APC in AD and atopy in general is that surface expression of FcεRI on APC is tightly associated with the atopic status of the individual donors [19]. FcεRI on epidermal LCs is absent or expressed at very low levels in the skin of healthy donors, but is elevated in the skin of patients with AD and shows maximal levels in skin lesions [4,16]. IDEC present in skin lesions of AD generally show an even higher FcεRI expression than LCs [4]. This upregulation on both DC

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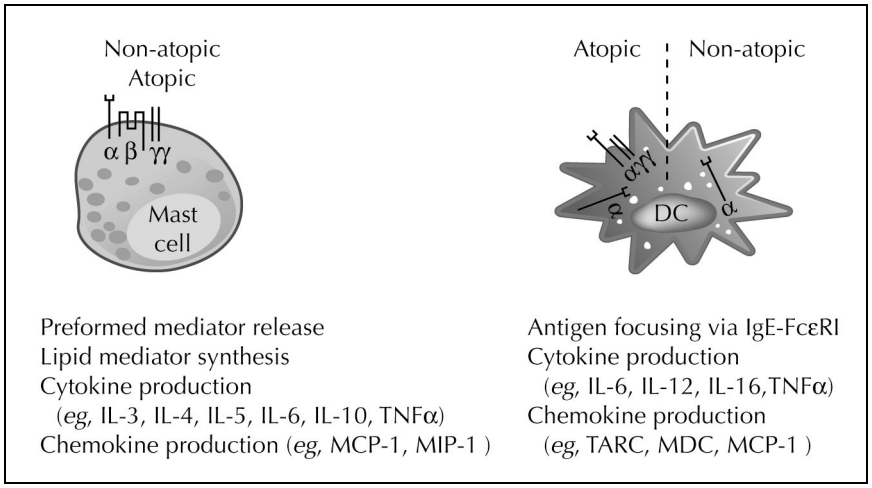

Figure 1. Structure, expression, and function of FcεRI on mast cells and DC from nonatopics and atopics. Mast cells from nonatopic and atopic donors exhibit a high constitutive surface expression of tetrameric FcεRI. Upon crosslinking of FcεRI-bound IgE by antigen, they release preformed mediators, synthesize lipid mediators, such as prostaglandins and leukotrienes, and produce a broad array of cytokines and chemokines. In contrast, DC show a trimeric FcεRI structure lacking the β-chain. Although DC from both nonatopics and atopics show high levels of intracellular FcεRI α-chain, only DC from atopics exhibit significant amounts of FcεRI on their surface. This is associated with coexpression of the γ-chain in atopics, and higher IgE levels in these donors further enhance FcεRI surface expression. Importantly, due to this association of FcεRI surface expression with atopic status, FcεRI-dependent functions on DC are mainly restricted to DC from atopic donors. These include specific antigen focusing via FcεRI and IgE, the production of proinflammatory or Th-polarizing cytokines, and the production of chemokines. DC—dendritic cell; IL—interleukin; MCP—monocyte chemoattractant protein; MDC—marophage-delivered chemokine; MIP—macrophage inflammatory protein; TARC—thymus and activation-regulated chemokine; TNF—tumor necrosis factor.

types correlates well with the serum IgE level of the atopic donors [4]. Not unexpected, given the common pathophysiology with other atopic diseases, FcεRI surface expression in the skin appears to be upregulated on LC from patients with allergic asthma and rhinitis [20]. In addition, peripheral blood monocytes from atopic donors show significant correlation of FcεRI expression with the atopic status of donors [14]. However, this upregulation of FcεRI surface expression cannot be observed when monocytes from patients with intrinsic AD are analyzed [21]. Lesional skin from intrinsic AD, although clinically similar to extrinsic AD, can be distinguished by a much lower FcεRI surface expression on epidermal DC [22].

In the past decade, some of the factors regulating FcεRI expression have been identified. These are also thought to play a role in allergic diseases, which further strengthened the hypothesis of an involvement of FcεRI-bearing APCs in AD. Despite the highly variable surface expression of FcεRI, many human DC types exhibit a constitutive intracellular expression of the FcεRI α-chain (Fig. 1): freshly isolated LC from atopic and nonatopic donors show high levels of intracellular FcεRIα protein, irrespective of their atopic status [20,23]. The observation that in vitro cultured DC from monocyte precursors, which lack an intracellular pool of FcεRIα, and DC, cultured from hematopoietic progenitor cells, both acquire an intracellular pool upon addition of the Th2 cytokine IL-4, suggested that it might play a role in regulation of FcεRIα expression in DC [24,25]. However, IL-4 is also affecting DC differentiation, and, therefore, it was left unclear whether increased FcεRIα expression was directly due to regulation by IL-4 or an epiphenomenon of an altered DC expression program. Recent studies on the human FcεRIα distal promoter confirmed that IL-4 directly increases the intracellular expression of FcεRIα. Interestingly, a comparable promoter region has not been found in the rodent FcεRIα gene, which explains that IL-4 cannot enhance FcεRIα expression in rodent cells. In contrast, FcεRI surface expression appears to be regulated by other, unrelated factors [26]. Therefore, the presence of the Th2 cytokine IL-4 in sufficient amounts acts as a prerequisite for FcεRI expression on human DC, but other factors must account for the elevated surface expression on APC from atopic donors.

First, variable FcεRI surface levels on DC might result in part from differences in the γ-chain expression of atopic and nonatopic individuals (see Fig. 1). In LC and in vitro–generated DC from nonatopic donors, FcεRIγ expression is low or absent [23,24]. DCs from these donors exhibit mainly immature α-chains, which accumulate in the ER, and show core glycosylation, whereas DC from atopics coexpressing the γ-chains exhibit mature, terminally glycosylated α-chains associated with γ-chains in the Golgi compartment and on the cell surface [24]. To understand how coexpression of the FcεRIγ chain could result in the export

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of mature complexes, it is necessary to mention three earlier studies that investigated the assembly of FcεRI complexes in transfection systems. It has been shown that N-linked glycosylation is necessary for efficient folding of FcεRIα and its ability to leave the ER [27]. In addition, intracellular association of FcεRIα with the γ-chains is mandatory for surface expression [13]. It leads to the masking of a retention signal and export of the receptor complex from the ER to the Golgi compartment, where terminal maturation occurs [28]. Mature FcεRI complexes can then exit to the cell surface. Further support for this concept comes from a recent observation that high doses of tumor growth factor (TGF)-β can downregulate FcεRIγ expression on human myeloid cells, including monocytes [29]. Because FcεRIγ is a common subunit that is shared with the Fcγ receptors FcεRI/CD64 and FcεRIII/CD16 but not FcεRII/CD32, this leads to downregulation of CD64 and CD16 surface expression as well, but does not affect CD32 surface expression. TGFβ is a crucial factor for the generation of LC [30], which makes it tempting to speculate that TGFβ might account for downregulation of FcεRIγ expression leading to the very low or negative expression levels observed in LC from nonatopic donors [23]. Some studies have reported that IL-4 alone can upregulate FcεRI surface expression in monocytes and monocytic cell lines [31,32]. This is not in contrast to a significant role for FcεRIγ. In contrast with DC, normal monocytes express sufficient amounts of FcεRIγ to allow surface expression of FcεRIα, which can be seen by the absence of an intracellular FcεRIα pool [24]. However, it is not understood which factors present in atopic donors upregulate expression of the FcεRIγ chain and thus support expression of a fully functional FcεRI complex on the surface of DC from these donors. Analysis of the FcεRIγ promoter region identified an IFNγ-responsive element [33], but IFNγ addition to DC cultures downregulates FcεRI surface expression, presumably due to downregulation of FcεRIα production and negative effects on DC differentiation (S. Kraft, Unpublished observations). Upon in vitro differentiation of DC from monocyte precursors, a reducing microenvironment achieved by the addition of antioxidants can counteract the downregulation of FcεRIγ expression, resulting in significantly higher FcεRI surface levels, but the biologic significance of this phenomenon is unclear [34].

Second, the concentration of the FcεRI ligand IgE regulates the surface expression of the FcεRI complex: IgE binding to the α-chain appears to be the minimal requirement for the induction of FcεRI upregulation in the monocytic cell line U937 and NIH3T3 FcεRI-transfectants [35•]. Recently, it could be shown that monomeric IgE upregulates the FcεRI expression on monocyte-derived DC of atopic individuals in vitro [24]. This mechanism is distinct from the effect of IL-4 and the upregulated FcεRIγ expression mentioned earlier, because it does not affect the production of both the FcεRIγ and FcεRIα chains, but rather stabilizes FcεRI complexes on the cell surface. These observations explain the correlation of FcεRI surface expression on LC and monocytes with IgE serum levels of donors. In summary, upregulation of FcεRI surface levels observed in atopic donors appears to be a result of a sufficient IL-4 level, elevated IgE levels, and less-defined factors regulating the availability of the FcεRIγ chains.

FcεRI on Antigen-presenting Cells Is Involved in Antigen Focusing and Induces the Production of Multiple Inflammatory Mediators

Before focusing on the role of FcεRI-bearing APC in AD in more detail, some of its most important molecular functions on APC with relevance for atopy are explained here. Aggregation of tetrameric FcεRI on effector cells of anaphylaxis is involved in immediate-type hypersensitivity reactions by the release preformed mediators stored in granules, which contain proteases and amines such as histamine or heparin, and by the rapid synthesis of prostaglandins and leukotrienes [12]. In contrast, the main role of trimeric FcεRI on APC is believed to be antigen focusing. Early observations on LCs suggested that allergen presentation by these cells is mediated by IgE [36]. Detailed studies using birch and grass pollen allergen, which were recognized by antigen-specific IgE bound to APC via FcεRI, showed that FcεRI is the pivotal structure mediating IgE-dependent antigen presentation to T-cells [15,37]. Importantly, this is a much more efficient process than nonspecific uptake of allergens: 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. After polyvalent ligation, FcεRI-bound IgE is internalized into acidic, proteolytic compartments, degraded, and delivered into organelles containing MHC class II, HLA-DM, and lysosomal proteins [38]. Thus, multimeric ligands captured by FcεRI and IgE are channeled efficiently into MIIC (MHC class II compartment)-like organelles of DC, instead of being delivered into a recycling MHC class II pathway. In MIIC, cathepsin S-dependent ligand peptide loading of newly synthesized MHC class II molecules occurs. Thus, the decision to take up and to present Ag in an IgE-dependent manner is made on the basis of whether Ag or pathogens carry repetitive or multiple distinct IgE epitopes. Together, these observations led to the concept of an "IgE-mediated delayed-type hypersensitivity reaction" by which FcεRI-bearing APC play a role in the pathophysiology of atopic diseases.

In addition to their function in antigen focusing, it has been shown recently that FcεRI-bearing APC can produce a broad range of cytokines and chemokines. FcεRI ligation on monocytes and DC can induce some important signal transduction events, such as tyrosine phosphorylation, calcium mobilization, and activation of the transcription factor nuclear factor (NF)-κB [16,17,39]. The latter is involved in the production of the proinflammatory

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cytokines TNF-α and the chemokine MCP-1 by APC. DC generated from monocyte precursors in a reducing milieu resemble IDEC in their immunophenotype and produce IL-1α, IL-1β, MCP-1, MCP-3, released on activation, normal T-cell expressed and secreted (RANTES), TNF-α, and MIP-1α on FcεRI crosslinking [34]. Using subtractive hybridization, it could be shown that monocytes from atopic donors can produce transcripts for some of the above-mentioned factors as well as MIP-1β, IL-6, IL-1R antagonist, and kynurenine 3-monooxygenase [40]. LC-like DC produce IL-16 upon FcεRI ligation, which serves as a chemoattractant for other DC [41•]. By the production of these proinflammatory factors and also recently described tolerizing factors [42,43], FcεRI-bearing APC might have an important impact on the inflammatory microenvironment in AD, as discussed later. Another interesting observation is that FcεRI ligation on monocytes from atopic donors can extend their lifespan by an anti-apoptotic effect, which might play a role in the establishment and sustainment of chronic atopic diseases [44]. For a brief overview of FcεRI-induced functions in DC, see Figure 1.

Multiple Roles for IgE-bearing Antigen-presenting Cells in the Pathogenesis of Atopic Dermatitis

Although the factors mentioned earlier provide multiple lines of evidence that FcεRI-bearing APC play an important role in the pathophysiology of AD, it is challenging to develop a coherent model and to obtain causal proof. This can be attributed to difficulties in establishing an appropriate animal model because of the above-mentioned critical differences in FcεRI structure, regulation, and tissue distribution between humans and rodents. However, from a transgenic mouse model, there is some evidence that FcεRI might play a role in the control of bacterial pathogenicity and intestinal inflammation [45]: transgenic mice expressing a humanized FcεRI, both on APC and effector cells of anaphylaxis, were compared with wild-type mice, which express murine FcεRI only on effector cells of anaphylaxis and on FcεRα-deficient mice. In the transgenic mice, levels of colonic IL-4 were higher, the composition of the fecal flora was modified, and bacterial translocation toward mesenteric lymph nodes was increased. In addition, they showed more pronounced trinitrobenzene sulfonic acid (TNBS)-induced colitis, which indicates that the presence of FcεRI might favor the creation of an inflammatory tissue environment. However, it is not clear whether these observations are due to an additional expression of FcεRI on APC or other mechanisms—for example, higher overall surface expression of FcεRI in these mice.

From an immunologic viewpoint, AD is a biphasic inflammatory skin disease characterized by an initial phase predominated by Th2 cytokines that switches into a second and chronic Th1-dominated eczematous phase [46]. FcεRI-expressing LC residing in the epidermis might play a crucial role, especially in the initial events of AD, because they might represent the missing link between aeroallergens penetrating the epidermis and antigen-specific cells infiltrating the skin lesions. Allergens penetrating into the epidermis due to the reduced skin barrier in AD skin might be taken up by the FcεRI-bound IgE molecules of epidermal LC. In this way, LC could extend their ability to react toward allergens by binding large amounts of IgE molecules with various specificities, which are efficiently processed and targeted to MHC class II-rich compartments, ultimately leading to a higher density of specific peptides in the grooves of surface MHC class II molecules [37,38]. The initial contact of LC with antigens in AD reprograms them from an immature phenotype to a mature phenotype. This leads to increased expression of molecules that are necessary for them to migrate to the lymph nodes and activate T cells, which ultimately boosts the secondary immune response. The polarization of naïve T cells is a unique feature of APC, and it might play a pivotal role in the outcome and the course of AD. It has been shown recently that LC activated via FcεRI drive naïve T cells into IL-4–producing T cells that exhibit a Th2 profile (Novak *et al.*, Unpublished data). Th2 polarization is characteristic for the initial phase of AD [46]. Further on, FcεRI-mediated activation of LC leads to the release of chemokines, such as MCP-1, IL-16, thymus and activation-regulated chemokine (TARC), and macrophage-derived chemokine (MDC), which might be responsible for the recruitment of other immune cells into the skin [34,39,41•,47; Novak *et al.*, Unpublished data]. For example, messenger RNA expression for IL-16, the natural soluble ligand of the CD4 molecule that induces chemotactic response of CD4+ T cells, monocytes, and eosinophils is enhanced in active AD lesions [48]. Furthermore, IL-16 production can be induced by the aggregation of FcεRI on LC of atopic donors in vitro. Thus, it is likely that IL-16 plays a major role in the initiation phase of AD [41•].

Of the cell types potentially recruited by these chemotactic factors, the invasion of IDEC into the epidermis is assumed to boost inflammatory processes and to cause the switch of the initial Th2-dominated acute phase of AD into an immune response in which IFNγ-producing Th1 cells predominate [46]. Indeed, there are three findings supporting a role for IDEC in the exacerbation of AD. First, after successful treatment and clinical improvement of the AD skin lesions with topical immunomodulators, such as FK506/tacrolimus, the number of IDEC decreases substantially [49]. Second, in vitro data suggest that FcεRI-activated IDEC, like DC, prime naïve T cells into IFNγ-producing T cells of the Th1 type by the release of the Th1-polarizing cytokines IL-12 and IL-18 (Novak *et al.*, Unpublished data). Third, in vitro data suggest that IDEC, like DC, which express high FcεRI receptor densities after their migration into the skin lesions, display a full activation on FcεRI ligation and induce the synthesis and release of proinflammatory mediators, which contribute to an enhancement of subsequent antigen presentation [34].

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Inflammatory dendritic epidermal cells seem to be of monocytic origin, because DC with a comparable immunophenotype can be generated from monocyte precursors in vitro. Recently, their rapid influx into skin lesions induced by atopy patch tests has been shown [6•]. Interestingly, upregulation of FcεRI on IDEC occurs later during the development of the skin lesions, which suggests the presence of local factors involved in regulation of FcεRI surface expression. Importantly, in vitro data suggest that higher FcεRI expression on DC from atopics and especially from lesional skin of AD and the higher expression of signaling enzymes, such as protein-tyrosine kinases, leads to a massive enhancement of proinflammatory functions mediated by APC in AD [17,34]. On LC, cell activation by FcεRI, as judged by the phosphorylation of phospholipase C-γ, is mostly restricted to atopic donors [17]. FcεRI-induced calcium mobilization, which follows phospholipidase-γ activation, can only be detected when LC from lesional skin of AD are analyzed [16]. Activation of the transcription factor NF-κB, which regulates expression of many proinflammatory genes, such as TNF-α, is only detectable in LC from atopic donors [39]. In addition, IgE-mediated upregulation of FcεRI on DC has been shown to have a significant enhancing effect on IgE-mediated antigen presentation [24].

However, unexpected functions of a potential tolerogenic role for FcεRI-bearing APC have been described recently. Cross-linking of FcεRI on APC leads to profound alterations in the phenotype and functional characteristics of the developing DC. This effect is mainly mediated by an elevated production of the tolerogenic cytokine IL-10, which is released by the activated cells themselves [42]. In addition, FcεRI ligation on monocytes of atopic donors induces indolamine dioxygenase, which is similar to IL-10 involved in the control of T-cell responses and the induction of tolerance in the immune system [43]. However, it is unclear whether FcεRI-bearing APC are involved in the downregulation of AD in vivo, and further studies clarifying this role are required.

Conclusions

Taken together, the observations described in this review indicate a major role for IgE-bearing APC in the pathophysiology of AD. IgE-bearing APC are ideally equipped for very efficient presentation of allergens to T cells, thus acting as amplifiers of an allergen-specific immune response. In addition, there is mounting evidence that their activation by IgE and allergen can influence inflammatory reactions by a host of other functions, such as the production of Th1/Th2-polarizing cytokines, proinflammatory cytokines, chemokines, tolerizing factors, or even factors affecting their own lifespan and differentiation. The remaining challenges are to obtain causal proof for their specific involvement in AD and to dissect potentially difficult roles played by different APC populations in the skin.

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