

Network of Myeloid and Plasmacytoid Dendritic Cells in Atopic Dermatitis

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Abstract. Atopic dermatitis (AD) presents as a chronic relapsing skin disease with high prevalence in children. The typical distributed skin lesions make the clinical diagnosis of AD very simple and clear-cut in most of the cases. In contrast, the underlying mechanisms leading to the manifestation of AD are more than complex and consist of genetic components combined with various deficiencies on the level of innate and adaptive immune mechanisms. Challenged by this puzzle, scientific approaches of the last years have made considerable progress in gaining insights into the mechanisms, which cause AD. AD is a biphasic inflammatory skin disease characterized by an initial phase predominated by Th2 cytokines which switches into a second, more chronic Th1-dominated eczematous phase. Two different dendritic cell (DC) subtypes bearing the high-affinity receptor for IgE (FcεRI) have been identified in the epidermal skin of AD patients: FcεRI^{high} Langerhans cells (LCs) and FcεRI^{high} inflammatory dendritic epidermal cells (IDECs). These two DC subtypes are believed to contribute distinctly to the biphasic nature and the outcome of T cell responses in AD. In contrast, plasmacytoid DCs, which play an important role in the defence against viral infections, have been shown to bear the high-affinity receptor for IgE too but are nearly absent from the epidermal skin lesions of AD patients. In light of recent developments, the picture emerges that different IgE-receptor bearing DC subtypes in the blood and skin of AD patients play a pivotal role in the complex network of DCs, which is highlighted in this review.

1. Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease, which currently affects 10–30% of children and 1–3% of adults worldwide (Leung and Bieber 2003). The pathophysiology of AD is complex, and several lines of evidence indicate that multifaceted genetic and environmental factors contribute to the clinical manifestation of the disease (Novak et al. 2003a). Food allergens, aeroallergens in addition to microbial components, and stress are regarded as important trigger factors and impact on both the severity and the duration of the disease. Besides that, chronic tissue damage and frequent allergen challenges seem to predispose subgroups of patients to

the manifestation of immunoglobulin E (IgE) hyperreactivity, which together with numerous other factors paves the way for the chronification of AD and the concomitant development of other atopic disorders such as allergic rhinoconjunctivitis and asthma (Mothes et al. 2005). Although there is incontrovertible evidence for a capability of environmental allergens to initiate severe flare-ups of eczema or contribute to the impairment of the characteristic, xerotic and itchy skin lesions which predominate the clinical picture of AD, the main mediators of these reactions on the cellular level, were elusive for a long time. This changed over a decade ago, when IgE-bearing dendritic cells (DCs) have been discovered in the epidermal skin lesions of AD for the first time. Later on, the high-affinity receptor for IgE (Fc ϵ RI) has been identified as main IgE-binding structure on these cells (Bieber et al. 1992; Wang et al. 1992). In contrast to the classical tetrameric Fc ϵ RI on the surface of effector cells of allergic reactions such as mast cells and basophils, Fc ϵ RI on DC has a trimeric structure and consists of the IgE-binding α -chain and the γ -chain dimer which are responsible for downstream-signal propagation, while the β -chain is absent. Further on, it has been shown that the Fc ϵ RI surface expression is regulated distinctly in antigen-presenting cells of atopic and non-atopic donors. In DCs of non-atopic individuals, most of the IgE-binding α -chain remains in the intracellular space, while only few γ -chain dimers are present. In contrast, in DCs of atopic individuals, a second variant of the α -chain can be detected, which is capable of associating with the γ -chains present in high levels in these cells. This is the basis for the transportation of the complete trimeric Fc ϵ RI complex to the cell surface and accounts for the high capability of DCs in the skin of AD to bind IgE molecules (Novak et al. 2004b; 2003b; 2003c).

2. Network of Myeloid DCs in AD

DCs as antigen-presenting cells are outposts of the immune system, which are located at the border zones of the body to the environment. Since they have been discovered over a century ago in 1868 by Paul Langerhans, they remained enigmatic and fascinated researchers all over the world (Jolles 2002). With the help of their dendrites, they form a sophisticated network within the epidermis and encounter foreign antigens. Subsequently, they internalize these antigens, secrete cytokines, process them, migrate to the lymph nodes, and present the processed antigens to T cells. Obviously, their function of antigen uptake and presentation as well as T cell priming is of particular immunologic importance in diseases with an impaired epidermal skin barrier such as AD (Cork et al. 2006). This impaired skin barrier has been shown to result partially from genetic modifications in genes encoding important proteins of the epidermal differentiation complex such as Filaggrin or S100 (Weidinger et al. 2006; Palmer et al. 2006; Cookson 2004). Together with an increased water loss and shift of the pH, this contributes to the fatal "loss" of the skin barrier as a protective shield in AD patients, which allows foreign antigens to invade easily into the skin (Strid and Strobel 2005). As a basic principle, two different types of DCs are known to regulate the immune haemostasis in our body: First, the so-called myeloid DCs, which express the DC marker CD1a. Myeloid DCs are

CD11c+CD123– and suspected to encounter a high number of immune reactions, which lead to immunity (Bonasio and von Andrian 2006).

The most prominent members of this class of DCs are the classical Langerhans cells (LCs), which are characterized by the Birbeck granules, electron-microscopically visible as tennis racket-shaped organelles originating from the accumulation of the C-type lectin Langerin (Villadangos and Heath 2005). LCs reside in both, healthy and inflamed skin and are constantly renewed under steady-state conditions. As a characteristic feature of AD, LCs are equipped with the high-affinity receptor for IgE (FcεRI) on their cell surface, which enables them to take up allergens penetrating into the skin (Villadangos and Heath 2005). In vitro studies of LCs combined with Atopy-patch test results in which type I allergens applied to the skin induce an eczematous reaction within 24–48 h in sensitized individuals, provide evidence that LCs are in the foreground in the initial phase of AD (Novak et al. 2004b). LC are capable of taking up invading allergens and presenting these allergens to T cells (Kerschenlohr, Decard, Przybilla, and Wollenberg 2003). In this step, primarily T cells of the Th2 type are primed by LCs in vitro, which are characterized by the production of IL-4, IL-5, and IL-13, typical for the initial phase of AD (Novak et al., 2004b). Other factors, such as the release of thymic stromal lymphopoietin (TSLP) by keratinocytes, are suspected to aggravate this DC-mediated Th2-immune response (Wang et al. 2006). Further on, allergen challenge and concomitant IgE receptor cross linking on LCs or activation by microbial products such as staphylococcal enterotoxins lead to the release of different chemotactic mediators, which together with soluble factors contribute to the recruitment of other cell types such as inflammatory dendritic epidermal cells (IDECs) from their precursor cells from the blood into the skin (Gunther et al. 2005; Pivarsci et al. 2004; Homey et al. 2006).

IDECs are only present at inflammatory epidermal sites and bear significantly high numbers of FcεRI in combination with CD11b molecules and the mannose receptor (CD206) on their cell surface but are Langerin (CD207)-negative DCs (Wollenberg et al. 1995; Sary, Bangert et al. 2005). In time, kinetics acquired with the help of atopy patch tests, invasion of IDECs into the epidermis within 24–48 h after allergen application, and concomitant up-regulation of FcεRI expression on LCs and IDECs in the developing skin lesions has been observed (Kerschenlohr et al. 2003), supporting the view of a two-step model directed by DC subtypes in AD (Figure 1) Due to their high ability to release distinct pro-inflammatory mediators after IgE receptor-mediated allergen challenge, it is assumed that IDECs are the main dendritic amplifiers of the epidermal allergic-inflammatory reaction in AD. Allergen challenge of IDECs in vitro leads, beside the release of pro-inflammatory cytokines and chemokines, to the production of IL-12 and IL-18, which might contribute to the alteration of the initial Th2-immune microclimate to the predominance of interferon (IFN)-γ-producing T cells in the skin, which seem to be a crucial step for the chronification of the skin lesions (Novak et al. 2004b; Grewe et al. 1995).

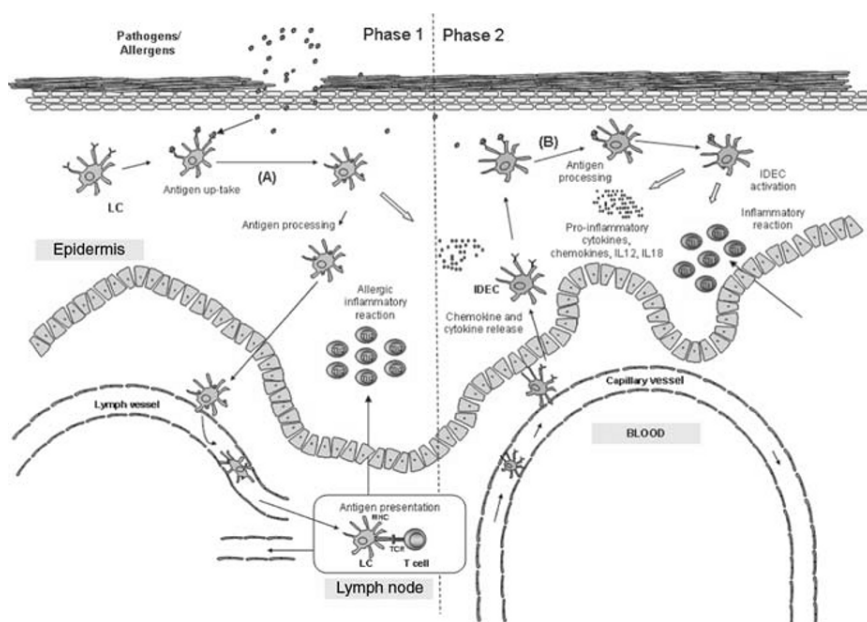


FIGURE 1. Network of Langerhans cells (LCs) and inflammatory dendritic epidermal cells (IDECs) in the epidermis of atopic dermatitis (AD) patients. (A) LC residing in the epidermis capture pathogens, secrete cytokines/chemokines, process antigens, migrate to the lymph nodes, and present them to T cells. In the lymph node, LC prime large amounts of Th2 cells, which produce high amounts of Th2 cytokines such as IL-4, IL-5, and IL-13. (B) Allergen challenge and concomitant IgE receptor cross linking on LC or activation by microbial products lead to the release of different chemotactic mediators, which together with soluble factors contribute to the recruitment of IDECs into the skin. IDEC present at inflammatory epidermal sites and bear significantly high numbers of Fc ϵ RI on cell surface. Allergen challenge of IDEC in vitro leads to the production of IL-12 and IL-18 and release of pro-inflammatory cytokines and chemokines, which might contribute to the amplification of the allergic-inflammatory reaction and alteration of the initial Th2-immune microenvironment to the predominance of IFN- γ -producing Th1 T cells in the skin, which seem to be a crucial step for the chronification of the skin lesions. MHC, major histocompatibility class; TCR, T cell receptor.

3. Balance of LCs and IDECs Predicts the Severity of AD

It is assumed that LCs are capable of maintaining, to some degree, a state of tolerance toward invading allergens and pathogens within the skin. Most likely, the intensity and number of danger signals and other yet-unidentified signals might lead to the break-down of this state of tolerance under certain conditions and an overbalance of inflammatory reactions accompanied by the invasion of cell types with

pro-inflammatory characteristics into the skin such as IDECs. After therapy with topical immunomodulators, for instance, the surface expression of the IgE receptors is reduced on both LCs and IDECs, and the number of IDECs within the epidermis decreases below the detectable level (Schuller et al. 2004; Novak et al. 2005; Simon et al. 2004). These findings support the view that IDEC should be the main DC subtypes targeted and eliminated by therapeutic approaches, while the rather anti-inflammatory and pro-tolerogenic functions of LCs should be sustained or even strengthened by therapeutic intervention.

4. Deficiency of Plasmacytoid DCs in AD

Plasmacytoid DCs are CD1a negative as well as CD11c negative but positive for the α -chain of the IL-3 receptor (CD123) and the blood-dendritic cell antigen (BDCA)-2. They are equipped with specific pattern recognition receptors of the innate immune system which enable them to sense microbial pathogens and thereby defend our organism against bacterial and viral infections (Soumelis and Liu 2006). Plasmacytoid DCs in the peripheral blood of AD patients have been shown to bear the Fc ϵ RI receptor on their surface which is densely occupied with IgE molecules (Novak et al. 2004a). IgE receptor expression of pDC correlates with the IgE serum levels, indicating that IgE in the micromilieu might be necessary to stabilize this structure on the cell surface of pDC. Further on, activation of Fc ϵ RI on pDC counter-regulates the toll-like receptor (TLR)-9 pathway involved in the regulation of the type I IFN production, which is required for the defence against virus infections (Schroeder et al. 2005). Aggregation of Fc ϵ RI on pDC induces the release of IL-10 and increases in an endogenous loop IL-10-mediated apoptosis of pDC in vitro. Further on, the pre-activation of pDC via allergen challenge significantly reduces the capacity of pDC to produce IFN- α and IFN- β in response to subsequent stimulation with viral DNA motifs (Novak et al., 2004a). The reduced capacity of pDC to produce type I IFN after allergen challenge might be one of the reasons for the high susceptibility of AD patients to viral infections. There is also evidence for a reduced amount of pDC in the epidermis of AD patients in comparison to other chronic inflammatory skin diseases such as psoriasis, allergic contact dermatitis, or lupus erythematoses which might be based on a lower recruitment of these cells into the skin due to reduced expression of skin homing molecules on pDC of atopic donors or a higher rate of apoptosis of pDC in the Th2-prone micromilieu of AD skin (Wollenberg et al. 2002). The Th2-predominated immune state (Wollenberg et al. 2003; Novak and Peng 2005), modifications on the level of pDC together with other deficiencies of the innate immune system, for instance, reduced amounts of antimicrobial peptides such as cathelicidin in the skin of AD patients (Ong et al. 2002; Howell et al. 2006) have been identified as important risk factors for the manifestation of bacterial and viral infections of the skin, which significantly aggravate the course of the disease in a subgroup of AD patients.

5. Conclusions

Distinct DC subtypes in the blood and in the skin of AD patients play a pivotal role in the pathophysiology of this chronic inflammatory skin disease. Targeting DC subtypes by boosting their anti-inflammatory, pro-tolerogenic capacities while impairing their pro-inflammatory, pro-allergic attributes would represent a promising therapeutic strategy to take advantage of DCs and the complex network of DCs in AD.

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