

Role of Dendritic Cells in Atopic Dermatitis: An Update

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Abstract Dendritic cells (DCs) have been recognized as key players bridging innate and adaptive immune systems. They control the balance of the adaptive immune response, and the functional behavior of DCs is mainly dictated by their microenvironment. Atopic dermatitis (AD) is a paradigmatic disease where the inflammatory microenvironment has a deep impact on DCs. The emergence of IgE-mediated sensitization is tightly related to the impact of locally released cytokines by either keratinocytes, T cells, or other cells involved in the inflammatory reaction. This review will focus on the recent and relevant findings in the field of immunobiology of DCs and their role in AD.

Keywords Atopic dermatitis · Dendritic cells ·
Innate immunity

Introduction

Dendritic cells (DCs) have been recognized as key players in the regulation of the immune response. They are responsible for keeping the balance between tolerance and immunity. More recently, they also have been identified as key cells bridging the innate and the adaptive immune systems. At least two main families of the DCs have been identified nowadays (Fig. 1). The plasmacytoid DCs (pDCs) which are mainly responsible for the defense against virus and the myeloid DCs (mDCs), which are themselves divided into two main subpopulations [29]: (1)

the resident type such as epidermal Langerhans cells (LCs) are supposed to play a major role in the homeostasis of the immune response, possibly by their default behavior in inducing tolerance. On the other hand, (2) the inflammatory type of mDCs such as the inflammatory dendritic epidermal cells (IDECs) have been suspected to play a major role in the generation and maintenance of inflammation by their production of large amounts of proinflammatory cytokines. Since the description of the presence of IgE molecules on the surface of skin LCs in lesional skin of atopic dermatitis (AD) in the late 1980s [6, 10] and the demonstration of the high-affinity receptor for IgE on these cells in AD [7], cutaneous mDCs have been suspected to play a major role in the pathophysiology in this condition.

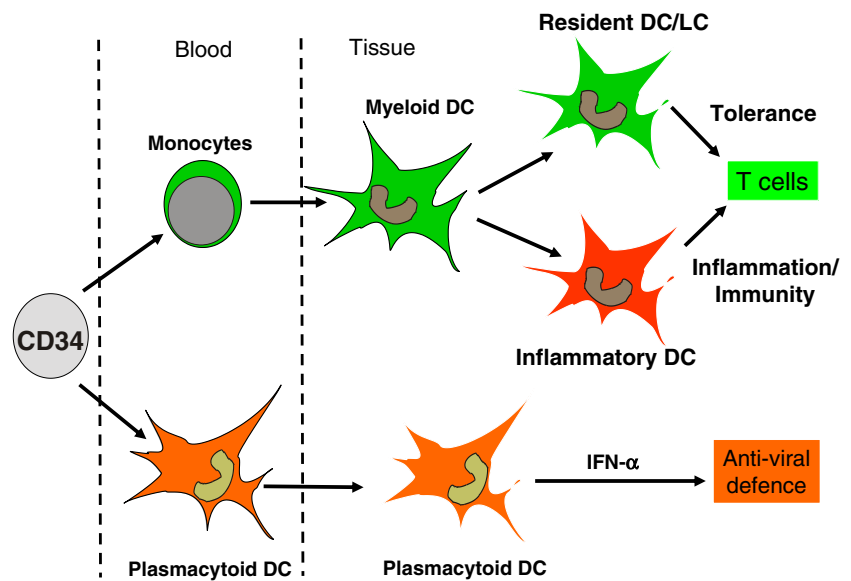
In the following review, the more recent findings and developments concerning the biology of mDCs with regard to AD as well as their significance in the mechanism of sensitization and finally the prospective of targeting epidermal mDCs by pharmacological compounds or purposes of immunotherapy will be considered.

The Behavior of the mDCs is Dictated by Their Microenvironment

Three decades ago, the prototypic mDC in the skin, i.e., the LC, was considered as a highly professional and more or less stable antigen-presenting cell which is always fulfilling its duties in a predetermined way. More recently, we have learned that the functional behavior of these mDCs is under the tight control of their microenvironment. Although it is not excluded that some intrinsic properties of the mDCs which may be determined by genetic polymorphism, such as the high or low expression of distinct surface molecules, it is now clear that a number of environmental and/or

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Fig. 1 The two main families of dendritic cells



tissue-derived signals deeply impact the phenotype and function of mDCs. Consequently, this has dramatic consequences on the outcome of the T-cell response initiated during the antigen presentation. In the following, the most recent advances in this area will be summarized.

Impact of Cytokines and Chemokines on mDCs in the Skin

Interleukin-31 (IL-31) has been identified as one of the key cytokines produced by T cells in the context of AD [30]. These cytokines have been shown to be responsible for the generation of pruritus, possibly also in response to the stimulation by *Staphylococcus aureus*-derived products [22]. Recent reports have shown that IL-31 is able to induce proinflammatory effects on human monocytes and macrophages. Among the other cytokines which may play a key role in the generation of the inflammation in AD, interleukin-25 (IL-25) has been shown to be produced in high amounts by mDCs [20]. Most interestingly, IL-25 is also able to downregulate the synthesis of filaggrin in keratinocytes. Thus, besides skewing the immune response in the Th2 direction, IL-25 seems also to contribute to the impairment of the epidermal barrier function. Similarly, human LCs have been reported to induce interleukin-22 in a subpopulation of CD4-positive D cells lacking interleukin-17 production [16].

Epidermal mDCs have been shown to not only be an important source of chemokines but also to respond to such mediators produced in the local microinflammatory milieu. Indeed, the influx of Langerin-negative CD1a-positive mDCs, i.e., IDEC, seems to be driven by the expression

of CCR5 and CCR6 [17]. Interestingly, it is possible to distinguish an initial acute phase and a later chronic phase of AD based on the profile of chemokines produced in this skin. Thus, a complex network of chemokines produced in the skin is able to selectively recruit and to induce the differentiation of mDCs from their circulating or dermal precursors in the skin.

Regulation of mDCs by Toll-like Receptors

Toll-like receptors (TLRs) are known to have a profound impact on the biology of mDCs and pDCs [8, 21]. Cutaneous mDCs including DCs and IDECs express a distinct profile of TLR which can profoundly differ in human and animal models [25]. In contrast to the murine system, our knowledge about the biological impact of TLR binding proteins for the functional behavior of human cutaneous mDCs in the skin still remains limited. From animal models, we have learned that TLRs can direct mDCs to the generation of Th1 response, i.e., the induction of IL-12 and interferon-gamma-producing T cells. Much less is known currently for the relevance of these findings in the human system. This is of particular importance since the expression of TLR2 on mDCs in the skin seems to be restricted to a subpopulation of patients suffering from AD (Bieber et al, in preparation). Besides the issue of the biological relevance of genetic polymorphisms of the TLR2 gene, the impact of the binding of TLR2 ligands such as *Staphylococcus aureus*-derived proteins, proteins derived from *Malassezia sympodialis*, herpes simplex virus, β -defensins, and others on the function of mDCs in the skin in the context of AD remains

unknown. Similarly, while there is some evidence for an effect of TLR9 polymorphisms on pDCs expressing the high-affinity receptor for IgE (FcεRI) in AD [24, 27], the possible cross-talk between TLR2 and FcεRI expressed on mDCs in AD may provide interesting insights in the role of infections in the regulation of IgE synthesis.

Histamine as a Regulator of the mDC Biology

Since therapeutic attempts to control the pruritus in AD by antihistamines usually failed, it was assumed that histamine does not play a significant role in the itching and in the overall pathophysiology of this condition. However, the description of a functional histamine H4 receptors (H(4)R) on human mDCs suggested that this mediator may indeed influence these key players in the skin immune system [11, 13]. In a murine model of skin inflammation that mimics AD, the treatment with H(4)R antagonists has been shown to reduce the inflammatory response. It was speculated that this antagonist may inhibit the migration of mDCs to the regional lymph nodes. In other experiments performed on human mDCs [18], the role of histamine as a proinflammatory mediator has been suggested. Indeed, the fact that IDECs express a functionally active H(4)R [13] strongly suggests that histamine is able to control the secretion of cytokines and chemokines by these cells. Here, H(4)R agonists could be beneficial as they potentially down-regulate inflammation induced by IDECs.

TSLP, a Key Cytokine in the Regulation of TH2 Response via DC

The thymic stromal lymphopoietin (TSLP) is an interleukin-7-related cytokine expressed by keratinocytes and which has been identified as a key cytokine driving allergic skin inflammation [30, 33]. TSLP has been recognized to drive mDCs in the skin, particularly LCs, to induce a Th2 response and thus to largely contribute to the generation of the IgE response. In animal models, TSLP derived from the skin has been shown to trigger the progression from epidermal barrier defects to allergic asthma [12] whereby the key role of epidermal LCs has been highlighted in this model [15]. Not only genetic polymorphisms of the TSLP gene could be responsible for an upregulation of its production by keratinocytes in AD but also the lack of epidermal anti-proteolytic activity such as SPINK5 [9] in the skin may be instrumental in the upregulation of TSLP ultimately leading to the phenotype of AD-like inflammation in murine skin [14]. All these findings gained mostly in murine models strongly support the key role of TSLP in a skin-driven upregulation of the IgE immune response in AD.

The Significance of the Microenvironment of mDCs in the Pathophysiology of Atopic Dermatitis

The natural history of AD has been divided into three main phases [5] (Fig. 2). The initial phase representing the early onset in infants still represents an enigmatic condition where skin inflammation gradually appears in these individuals who initially lack any kind of IgE-mediated sensitization. This observation, which has been the key result of many epidemiological studies, supports the concept that IgE sensitization is acquired during this initial phase of the disease and that the chronic inflammation in the skin can be considered as the point of entry for this sensitization. However, it remains unclear what could be the *primum movens* of this apparently allergen-independent generation of chronic inflammation in the skin. According to recent experiments in animal models [9, 14], genetically determined intrinsic defects in either anti-proteases systems and/or defects in signaling molecules such as Notch could deliver some important information for our understanding of the very initial triggers in this very early stage of the disease. As a consequence of these local disturbances, an increased production of TSLP by the surrounding keratinocytes seems instrumental in directing the local LC to induce a Th2 T-cell response in response to the penetration of environmental allergens through the impaired epidermal barrier function. Moreover, besides the impact of this local inflammation on the behavior of the LC, the systemic impact of locally produced and remotely active cytokines and chemokines should be considered and implies that AD should be considered more as a systemic disease. Thus, although in this very initial phase, cutaneous LCs and IDECs do not yet express the receptor for IgE and do not yet bind specific IgE, they are already considered as the key players in the generation of an IgE response.

In the second phase of the natural history of AD, once the IgE response is established and the mDCs in the skin are expressing their IgE receptors, they can handle very low amounts of allergens penetrating the epidermal compartment and trigger AD as a true IgE-mediated cellular immune response [26]. Thereby, it is now well accepted that LCs are initially driving a Th2 response locally while the influx of IDECs is subsequently followed by a Th-2 to Th1 switch of the cutaneous T-cell response.

The third phase of the natural history of AD is characterized by a sensitization towards self-proteins, mainly derived from keratinocytes [3]. Here again, the cutaneous mDCs could play an important role. Indeed, they are capturing the keratinocyte-derived proteins locally released due to scratching and induce a Th2 response to these structures which seem to have some homology to environmental allergens such as *M. sympodialis* antigens

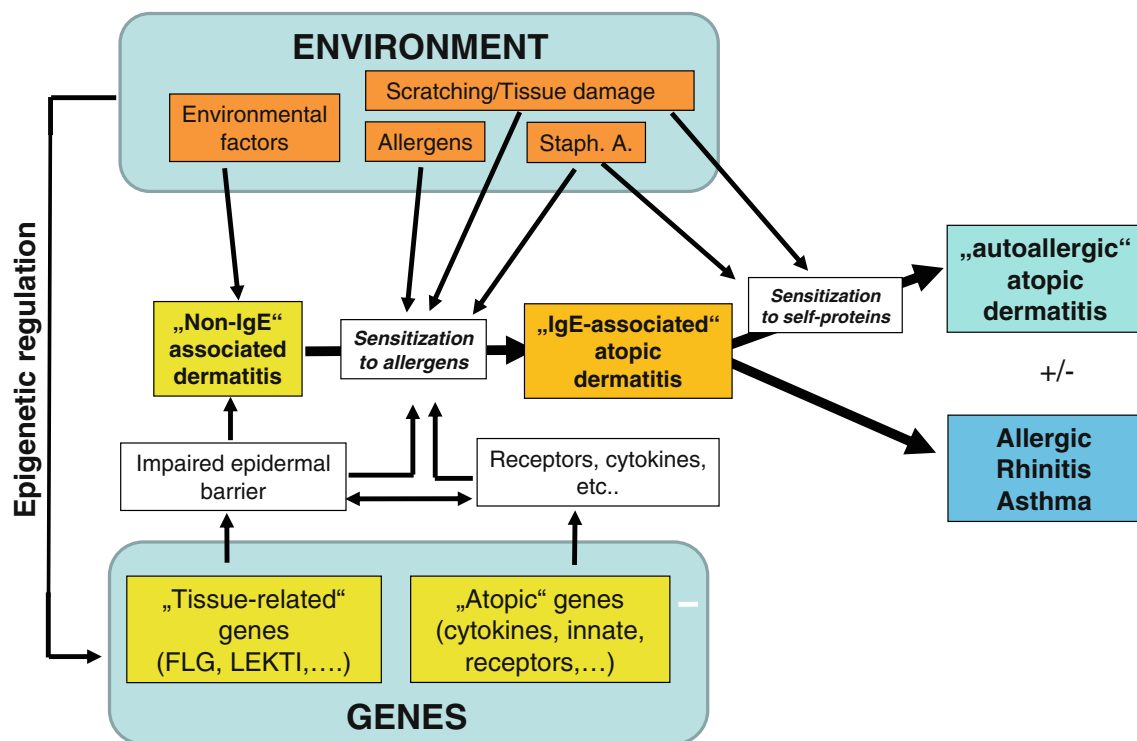


Fig. 2 A diagram showing the three main phases of the natural history of AD

[32]. These mechanisms of self-sensitization are supported by the increased local production of TSLP by the surrounding keratinocytes upon mechanic injury by scratching.

Dendritic Cells as Target for Established and New Therapies in Atopic Dermatitis

Due to the above mentioned characteristics and complex interactions between the inflammatory microenvironment and mDCs in the skin, these cells may be considered as ideal targets for immunopharmacological strategies. Indeed, it has already been shown that the binding of TLR4 on LCs from oral mucosa supports the generation of Th1 and regulatory T cells [1, 2]. Similarly, immunoregulatory compounds such as calcineurin inhibitors have been shown to target cutaneous mDCs by suppressing selectively the proinflammatory IDECs [23, 31] while steroids seem to affect both LCs and IDECs [19].

In animal models, the use of gene therapy using siRNA against costimulatory molecules such as CD86 as well as other interfering strategies in the treatment of murine skin allergic diseases have been reported with encouraging results [4]. Overall strategies aimed to induce regulatory/tolerogenic mDCs or to support the natural ability of tolerance induction by epidermal or oral LCs seems to be promising [1, 2]. Indeed, first attempts to use this particular property of epidermal LCs in applying allergens in a patch

test-like device on the skin of allergy patients with allergic rhinitis seems promising [28].

Conclusion

Recent progress in our understanding of the immunobiology of the mDCs in the context of the pathophysiology in AD has been largely influenced by the new paradigm of the impact of the microenvironment on their functional behavior. In the future, we will be able to understand not only what distinguishes normal from inflammatory micro-milieus but also how they are able to direct mDCs to induce either tolerance or immunity. Ultimately, we will use this knowledge for the development of new strategies aimed to target mDCs in the skin and to modulate their proinflammatory properties and/or to enforce their natural capacity to induce tolerance.

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