

Human skin and oral mucosal dendritic cells as 'good guys' and 'bad guys' in allergic immune responses

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Summary

Recent progress achieved by an impressive number of studies focusing upon the ontogenesis and immunobiology of epidermal Langerhans cells (LCs) and other cutaneous dendritic cell (DC) populations as well as DCs at oral mucosal tissue has profoundly revised our understanding of the role of DCs in different tissues and microenvironments. By sensing their environment for microbial signals or allergens and bridging innate and adaptive immunity in a sophisticated manner, subtypes of DCs play a critical role in the maintenance of the immunological homeostasis in the periphery. Thereby, DCs, located directly at the interface to the environment, fulfil opposing tasks as they are key players in both the control and the generation of allergic inflammation. Furthermore, it is under ongoing debate whether DCs attenuate or aggravate allergic inflammation. As a consequence, accumulated knowledge gained in this field within the last few years has provided an excellent basis for innovative therapeutic opportunities which tend to target specifically the multi-faceted properties of DCs at distinct anatomical sites.

Keywords: allergy, dendritic cells, mucosa, skin, tolerance

Introduction

Since the discovery of the classical epidermal dendritic cells (DCs) by Paul Langerhans in 1863 [1], DCs have fascinated researchers all over the world, but still remained enigmatic due to their complex characteristics and roles in our immune system. However, all DC subtypes display a few common features, such as their localization at the border zones to the environment, which is associated directly with their pivotal role as sentinels of the immune system. Furthermore, they act as sensors for foreign danger signals and connect the innate and adaptive part of the immune system. Another, unique feature is their capability to prime naive T cells and direct the nature of T cell responses. Fulfilling these different tasks, several DC subtypes can act either as 'good guys' or as 'bad guys' in allergic immune responses.

Human DCs can be subdivided into two major subtypes, myeloid DCs (MDCs) and plasmacytoid DCs (PDCs). MDCs are localized in the peripheral tissue, the blood or secondary lymphoid organs [2]. PDCs can be detected in the blood and lymphoid organs and are characterized by expression of the α -chain of the interleukin (IL)-3 receptor (CD123) and the blood-derived DC antigen (BDCA)-2.

They are interferon (IFN)-producing cells recognizing viral antigens by Toll-like receptor (TLR)-7 and TLR-9 [2]. Variations of the DC character depend upon the subtype of DCs, the microenvironment, the quantitative and qualitative nature of other DC subtypes and cells in the environment and their cross-talk and interaction with DCs, the maturation stage of DCs, pattern of surface receptors, etc. Having these many-sided properties of DCs in mind it is important to understand, in as detailed a manner as possible, how DCs manage to induce or accelerate allergic immune responses as well as which qualities enable them to attenuate or prevent allergic inflammation or, moreover, promote the development of allergen-specific tolerance. One of the most impressive examples for these variations are DCs which express the high-affinity receptor for immunoglobulin (Ig)E (Fc ϵ RI). Depending upon the context, i.e. cell type and location of Fc ϵ RI-bearing DCs, allergic immune responses can be promoted such as in atopic dermatitis (AD) [3], prevented, as thought for Fc ϵ RI^{pos} oral mucosal DCs during sublingual immunotherapy [4], or functions involved in virus defence may be altered, as observed for Fc ϵ RI^{pos} PDCs [5]. In this work we summarize the versatile character of Fc ϵ RI^{pos} human DCs exemplified in the context of allergic immune reactions.

Role of cutaneous dendritic cells in immunological homeostasis

Epidermal DCs, which comprise about 2–5% of all epidermal cells, belong in non-inflamed skin mainly to the classical Langerhans cells (LCs) which are characterized by the so-called Birbeck granules, visible by electron microscopy as tennis racquet-shaped vesicles. The Birbeck granules are thought to be connected to the C-type lectin Langerin expressed by these cells and involved in antigen presentation [6]. LCs are derived from monocytes as their direct precursors and are localized in the basal and suprabasal layers of the upper epidermis, where they reside in an immature state without renewal for months [7]. Transforming growth factor (TGF)- β is required for their differentiation [8]. In healthy, non-inflamed skin, LCs represent the only epidermal DC type. To some extent, LCs are believed to be able to maintain a state of tolerance in the skin [9]. Because epidermal LCs express surface molecules involved in the inhibition of T cell responses, such as the inducible co-stimulatory molecule ligand ICOS-L (B7-H2) or the immunoregulatory enzyme indoleamine 2,3-dioxygenase (IDO), both of which are known to function as strong inducers of peripheral tolerance [10], they are thought to display somewhat tolerogenic properties (Table 1). Mainly, the tolerogenic functions of LCs in non-inflamed skin are based on their immature state, low migratory properties and low expression of co-stimulatory molecules, as well as release of proinflammatory soluble mediators [11]. Moreover, data from a murine model system using the receptor activator of nuclear factor kappa B (NF- κ B) ligand (RANKL), overexpressing keratinocytes showed that LCs down-regulate co-stimulatory molecule expression and induce regulatory T cells, thereby modulating the skin immune response and attenuating overactivation even in an inflamed state [12]. However, under some circumstances LCs might also lose their tolerogenic properties and induce immunogenic immune responses during inflammatory conditions.

Cutaneous dendritic cells as key players in allergic skin diseases

Several Fc ϵ RI-bearing subtypes have been identified so far in human skin of AD patients. Concerning myeloid DCs, both CD207⁺/CD1a⁺, i.e. LCs as well as CD207⁺/CD1a⁺/Fc ϵ RI⁺ DCs, are located in the epidermis [13]. While low numbers of CD207⁺/CD1a⁺/Fc ϵ RI⁺ DCs occur in the dermis, CD1c⁺/Fc ϵ RI⁺ DCs represent the major DC subpopulation of the dermal compartment [14]. DC subtypes expressing Fc ϵ RI in the skin and blood of AD patients are IgE receptor-bearing epidermal LCs, which predominate in non-lesional AD (Table 1). Further, a subtype of DC, which in contrast to LCs does not have any Birbeck granules but expresses the mannose receptor (CD206), the so-called inflammatory dendritic epidermal cells (IDEC), invades the skin in the

acute phase and persists during the chronic phase of AD [15]. PDCs detectable in the epidermal skin of patients with psoriasis, lupus erythematoses or allergic contact dermatitis are almost absent in patients with AD [16].

We know from atopy patch test models that after allergen application to the skin, an eczematous skin reaction develops within 24–48 h in sensitized patients. This mechanism is in addition to the induction and release of a plethora of chemokines in the upper part of the skin [17] and recruitment of inflammatory cell subtypes such as IDECs from their dermal and blood precursors [18]. The initial predominance of T helper type 2 (Th2) cytokines during the acute phase is attenuated and the amount of Th1 cytokines, in particular IFN- γ , increases [19]. Other exogenous trigger factors such as microbial antigens might lead to very similar recruitment mechanisms. During the flare-up phase of AD, epidermal LCs up-regulate their Fc ϵ RI and co-stimulatory and major histocompatibility complex (MHC) expression [18]. Furthermore, they release chemotactic factors, but prime naive T cells primarily into T cells of the Th2 type. IDECs recruited into the skin express co-stimulatory surface molecules and Fc ϵ RI in relatively high amounts. Stimulation of IDECs by Fc ϵ RI cross-linking or *Staphylococcus aureus* enterotoxins *in vitro* induces the release of a high number of proinflammatory cytokines such as IL-8 and TNF- α or chemokines, as well as soluble factors which promote Th1 immune responses including IL-12 (Table 1) [20]. Therefore, IDECs are regarded as the main amplifiers of the allergic-inflammatory reaction in the epidermis on level of DCs and are designated as 'bad guys', while counter-regulatory, anti-inflammatory and pro-tolerogenic properties are allocated to epidermal LCs, which are considered as 'good guys' in this context.

In line with this hypothesis, recent data from *in vitro* systems showed that topical immunomodulators such as tacrolimus impact upon restoring the overbalance of epidermal LCs as good guys in inflamed skin [21]. Tacrolimus and TGF- β seem to act synergistically on the generation of LCs and to lower the stimulatory capacity of LCs towards T cells. *In vivo*, the number of epidermal LCs, characterized by Lag and Langerin-expression in tacrolimus-treated skin, increased after 1 week of treatment with tacrolimus. While the amount of TGF- β 1, - β 2 and - β 3 produced by skin cells in response to treatment with tacrolimus remained unchanged, tacrolimus increased the responsiveness of differentiating cells towards TGF- β by up-regulating their TGF- β RII expression. The synergism between TGF- β 1 and tacrolimus might promote the generation of LCs from invading precursor cells, reduce expression of co-stimulatory as well as MHC II molecules and reduce the stimulatory activity of the differentiating cells. The synergistic effect of TGF- β and tacrolimus on LC development and function might underlie the restoration of the physiological LC dominance after tacrolimus treatment of AD. Therefore, supporting the TGF- β -related differentiation and function of LCs by tacrolimus

Table 1. Dendritic cell (DC) subtypes in human skin and mucosal epithelium.

DC subtype	Localization	Characteristic surface molecules and receptors	Cytokine/chemokine production	References
Myeloid DCs				
Skin DCs				
LCs	(Supra-) basal layers of the upper epidermis	CD1a ⁺⁺⁺ , MHC class II, Birbeck granules Langerin ⁺ (CD207) Lag ⁺ FcεRI ⁺⁺ (absent in healthy skin) ICOS-L ⁺ (B7-H2) IDO ⁺	Proinflammatory soluble mediators, chemotactic factors	[6,7,9,10,11,13,18]
IDECs	Inflamed epidermis	CD1a ⁺ , MHC class II ⁺ FcεRI ⁺ CD11c ⁺ , CD11b ⁺ , CD1b ⁺ , CD206 ⁺	Proinflammatory cytokines (TNF-α IL-8), chemokines and soluble factors (IL-12)	[13,15,20]
Dermal DCs	Dermis	CD1c ⁺ /FcεRI ⁺ (Langerin/CD1a/ FcεRI)		[14]
Mucosal DCs				
oLCs	Oral mucosal epithelium	CD1a ⁺⁺ , MHC class II ⁺⁺ , Birbeck granules Langerin ⁺ (CD207), CD14 ⁺⁺ (increased compared to nDC) FcεRI ⁺ (irrespective of atopic status, increased in atopic donors, higher expression level compared to nDCs) CD205 ^{+/+} , CD206 ^{+/+} , CD11b ⁺ TLR-4 ⁺ B7-H1 ⁺ , B7-H3 ⁺ (up-regulated upon TLR-4 ligation)	Anti-inflammatory cytokines (IL-10, increased upon TLR-4 ligation, TGF-β)	[4,29,31,35,37]
nDCs	Nasal mucosal epithelium	CD1a ⁺ , MHC class II ⁺ Langerin ⁺ (CD207), CD14 ⁺ CD205 ⁺ , CD206 ⁺ (increased compared to oLCs) CD209 ⁺ FcεRI ⁺ (mainly on oLCs of atopic donors)	Proinflammatory (TNF-α, IL-6, increased in atopic individuals) and anti-inflammatory cytokines (IL-10, increased in non-atopics) upon FcεRI activation	[29,30]
PDCs				
	Epidermal skin (of patients with psoriasis or allergic contact dermatitis, but nearly absent in patients with AD), nasal mucosa and peripheral blood	CD123 ⁺ BDCA-2 ⁺ MHC class II ⁺ TLR7 ⁺ TLR9 ⁺ FcεRI ⁺	IFN IL-10	[2,5,16,22,23,25,28,33,34]

BDCA, blood derived dendritic cell antigen; ICOS-L, inducible co-stimulator ligand; IDECs, inflammatory dendritic epidermal cells; IDO, indoleamine-2,3 dioxygenase; IL, interleukin; LCs, Langerhans cells; MHC, major histocompatibility complex; nDCs, nasal mucosal dendritic cells; oLCs, oral mucosal Langerhans cells; PDCs, plasmacytoid dendritic cells; TGF, transforming growth factor; TLR, Toll-like receptor; TNF, tumour necrosis factor.

represents a new approach to influence the balance between protective and disease promoting DC populations during the course of AD [21]. In conclusion, a threshold of activating signals has to be exceeded so that up-regulation of co-stimulatory molecule expression and expression of receptors involved in antigen uptake and presentation, as well as the release of chemokines, changes the qualitative and quantitative nature of DC subtypes in the epidermis to initiate flare-ups of AD, while restoring these mechanisms is in addition

to the clinical improvement of the lesions and reduction of inflammatory markers in the skin.

FcεRI on PDCs modulates viral defence of the cells

Human PDCs, also known as IFN-producing cells [22], release high amounts of type I IFN after pathogen challenge. PDCs express TLR-7 and TLR-9 selectively and recognize microbes such as *Herpes simplex virus* (HSV) [23], linking

innate and adaptive immunity [24]. PDCs bear a trimeric variant of the high-affinity receptor for IgE (Fc ϵ RI) on their cell surface, which is occupied almost completely by IgE molecules [5,25]. Consequently, Fc ϵ RI expression on PDCs in the peripheral blood correlates directly with IgE serum levels [5]. Most interestingly, *in vitro* experiments revealed that Fc ϵ RI-aggregation and allergen challenge profoundly down-regulate the capability of PDCs to release IFN- α / β upon subsequent stimulation with cytosine–guanine dinucleotide (CpG) motifs [5]. Data showing lower production of IFN- α by human blood DCs from allergic individuals after TLR-9 stimulation [26], as well as down-regulation of Fc ϵ RI expression on PDCs after TLR-9 activation and reduced TLR-9 expression after Fc ϵ RI cross-linking [27], indicate that a direct counter-regulation and interaction of Fc ϵ RI/TLR-9 mediated mechanisms might be responsible for this effect. This implies that the amount of Fc ϵ RI expressed on the surface of PDCs, together with the strength and frequency of signals mediated via Fc ϵ RI attenuate the capacity of PDCs to defend the organism against invading microbial and, in particular, viral antigens.

Furthermore, increased IL-10 production of PDCs after Fc ϵ RI aggregation observed *in vitro* might enhance endogenously, together with the Th2-dominated microenvironment in the skin, PDC apoptosis and reduction of the number of PDCs recruited from the blood and detectable in epidermal AD lesions [5,16]. Taken together, a close cross-talk of Fc ϵ RI with TLR-9 and reduced capability of PDCs to release IFN in response to TLR stimulation by viral antigens after Fc ϵ RI activation/allergen challenge, together with the relatively lower number of epidermal PDCs in AD compared to other inflammatory skin diseases such as allergic contact dermatitis or psoriasis, might explain in part the increased susceptibility of AD patients to viral infections of the skin observable, for example, by the manifestation of eczema herpeticum, a severe HSV infection spreading over large body areas in AD patients *in vivo* [28].

Oral mucosal DCs facilitate and anticipate allergic immune responses

Although the oral mucosal epithelium is exposed to high numbers of bacterial products and allergens derived from food, chronic allergic inflammatory reactions are observed less frequently at this site [4]. This is in contrast to other mucosal surfaces such as the nasal and bronchial mucosa, where local chronic allergic and inflammatory reactions occur often. Most probably, DCs play a major role as both activators and silencers of allergic immune responses within the immunological network of mucosal surfaces. In this context, it has been reported that different DC subpopulations reside within the oral and nasal mucosa in humans. The predominant DC population within the oral epithelium consists mainly of classical Birbeck granules containing CD207^{pos}/CD1a^{pos} LCs, while significant numbers of PDCs

were detected in nasal mucosal epithelium [29]. The myeloid CD1a^{pos} DC subpopulation within oral and nasal mucosal epithelium differs further in the expression of various lectins, such as CD206 and CD209, which are expressed only by nasal DCs (nDCs) (Table 1) [29]. However, myeloid DCs in both regions express Fc ϵ RI constitutively, which is involved in mediating allergic inflammation [29–31]. Higher expression of Fc ϵ RI was detected on nDCs of individuals suffering from atopic diseases such as allergic rhinitis. Activation of Fc ϵ RI on nDCs induced the production of proinflammatory cytokines such as TNF- α and IL-6, as well as the anti-inflammatory cytokine IL-10. Interestingly, nDCs of atopic individuals displayed increased production of TNF- α and IL-6, while nDCs of non-atopic individuals displayed elevated production of IL-10 upon Fc ϵ RI activation [30]. Moreover, IL-4 inhibited Fc ϵ RI-induced IL-10 production. Because Th2 cytokines such as IL-4 are elevated in the nasal mucosal tissue, IL-4 might inhibit the anti-inflammatory effect mediated after Fc ϵ RI activation on nDCs and in turn facilitate allergic immune responses in the nasal mucosa [32]. Furthermore, it has been reported that PDCs within the nasal mucosa propagate an allergic Th2 immune response in allergic rhinitis [33,34]. However, nasal mucosal PDC activation by CpG motifs skewed co-cultured T cells towards Th1 cells, producing IFN- γ and IFN- α [34]. The functional properties of Fc ϵ RI on oral LCs (oLCs) remain to be elucidated, although preliminary data suggest an increased production of the anti-inflammatory cytokines IL-10 and TGF- β 1 [35]. This could result from the microenvironment within the oral mucosa. In this regard, it has been shown recently in mice that oral mucosal tissue harbours limited numbers of proinflammatory cells but significant numbers of T cells with regulatory functions [36]. The oral mucosal microenvironment itself is related predominantly to microbial products, which originate from local microflora [4] and which might influence local DCs. In this context, it has been demonstrated that oLCs also express the lipopolysaccharide (LPS) receptor/CD14 and TLR4 [37]. Interestingly, its ligation on oLCs by TLR4-ligands leads to up-regulation of the expression of co-inhibitory molecules such as B7-H1 and B7-H3 as well as to the induction of IL-10 released by oLCs. Moreover, activation of TLR4 on oLCs induces forkhead box protein 3 (FoxP3)(+) regulatory T cells, which produce IL-10 as well as TGF- β 1, suggesting that innate immune receptors such as TLR-4 as well as Fc ϵ RI on oLCs are involved critically in the maintenance of tolerance towards bacterial components and allergens within the oral mucosa. The predominant tolerogenic character of oral mucosal tissue is reflected further by the success of sublingual immunotherapy (SLIT), which together with subcutaneous immunotherapy represents the only causal therapy in the treatment of IgE-mediated allergies such as allergic rhinitis [38]. Although detailed immunological mechanisms underlying SLIT remain to be elucidated, allergen-specific tolerance induction next to a Th2/Th1 shift are considered to be key mechanisms [39]. Most probably, oLCs are thought to

play a central role, as they initiate and perpetuate the allergen-specific immune response during SLIT [40]. It has been shown recently in a murine model that local oral DCs bind and process topically applied ovalbumin (OVA), which leads to the induction of IFN- γ - and IL-10-producing T cells [41]. Furthermore, it is tempting to speculate that TLR-4 activation by components originating from commensal bacteria or supplemented to SLIT formulations might serve as adjuvants. In this regard, a recently published study in a mouse model supports the assumption that TLR-2 activation on purified murine oral mucosal DCs promotes IFN- γ - and IL-10-producing T cells [42], resulting in stronger Th1 and tolerogenic immune responses.

Altogether, the published data suggest that mucosal DCs are prone to induce proinflammatory as well as tolerogenic immune responses. Nasal mucosal DCs facilitate allergic immune responses in atopic individuals, while oral mucosal DCs such as oLCs induce preferentially a regulatory immune response, which on one hand supports the immunological homeostasis within oral mucosal tissue, and on the other hand propagates the desired allergen-specific tolerance induction during SLIT.

Conclusion and perspectives

The variable subtypes of DCs, as well as functions of DCs located in different microenvironments such as non-inflammatory *versus* inflammatory skin or mucosal tissue, account for the highly versatile character of DCs, ranging from good to very bad players of allergic-inflammatory immune responses. The notion that regulatory missions of DCs are modulated directly by the character of the microenvironment provides several exciting ways in which DCs might be decisive for the prevention or promotion of allergic-inflammatory reactions and a healthy or diseased immune state, both under physiological conditions or as therapeutic target cells.

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