The role of dendritic cell subtypes in the pathophysiology of atopic dermatitis

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Background: Atopic dermatitis (AD) is an inflammatory, immunologically mediated skin disease characterized by a T helper type 2 cell—predominant phenotype initially with additional acquisition of T helper type 1 cell phenotype during the chronic eczematous phase. Compelling evidence presented here suggests that two types of dendritic cells (DC), myeloid DC (mDC) and plasmacytoid DC (pDC), are important in the pathogenesis of AD.

Methods: We reviewed the current literature and summarized key information about the role of mDC and pDC in the pathogenesis of AD.

Results: Langerhans cells and inflammatory dendritic epidermal cells, which bear the high-affinity receptor for immunoglobulin E on their cell surface, are hypothesized to contribute to the pathogenesis of AD. pDC, Which play an important role in the defence against viral infections, have also been shown to express high-affinity receptor for immunoglobulin E.

Conclusion: Immunoglobulin E receptor—bearing mDC and pDC subtypes in the blood and the skin of patients with AD are of critical immunologic importance in the complex pathophysiologic network of AD. Targeting mDC and pDC subtypes may lead to effective new therapies for the management of AD. (J Am Acad Dermatol 2005;53:S171-6.)

Dendritic cells (DC) are highly specialized professional antigen-presenting cells usually located at surveillance interfaces of the human body such as the skin or mucosa, and are thought to play an important role in the generation and regulation of immune responses. Two distinct subtypes of DC with different cell-surface markers and functional duties have been discovered: myeloid DC (mDC) and plasmacytoid DC (pDC).[1] Compelling evidence suggests that both mDC and pDC are instrumental in the pathophysiology of atopic dermatitis (AD) (Table I).[2,3]

AD represents a chronic, relapsing inflammatory skin disease with characteristic clinical features. Genetic background; environmental exposures such as food allergens, aeroallergens, microbial antigens, or stress; and distinct immunologic predispositions all contribute to the development of recurrent, itchy eczematous skin lesions in afflicted patients. Although the relevance of allergens from the environment, which elicits or aggravates eczematous skin lesions, is obvious, the exact pathophysiologic pathway underlying this phenomenon is unclear. Recent evidence suggests DC subtypes in the skin and the blood of patients with AD play a pivotal role in the generation and/or control of inflammation. In particular, DC subtypes are considered to represent the missing link between allergen uptake and the clinical manifestation of allergic diseases.[4]

Abbreviations used:

AD:	atopic dermatitis
DC:	dendritic cells
DC1:	dendritic cells 1
DC2:	dendritic cells 2
FcεRI:	high-affinity receptor for immunoglobulin E
IDEC:	inflammatory dendritic epidermal cells
IFN:	interferon
IgE:	immunoglobulin E
IL:	interleukin
LC:	Langerhans cells
mDC:	myeloid dendritic cells
pDC:	plasmacytoid dendritic cells
Th2:	T helper type 2 cell
TSLP:	thymic stromal lymphopoietin

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Supported by grants from the Deutsche Forschungsgemeinschaft No 454/2-1 and No 454/1-1 and BONFOR.
Conflicts of interest: None identified.
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0190-9622/$30.00

doi:10.1016/j.jaad.2005.04.060

Table I. Summary of the different phenotypical and functional characteristics of high-affinity receptor for immunoglobulin E–bearing dendritic cell subtypes in the skin of atopic dermatitis

Dendritic cell type	Phenotype	Function	AD lesional skin observations
LC	$CD1a^{+++}$ $Fc\epsilon RI^{++}$ IgE^{+} $CD206^{-}$ $CD207^{+}$ $MHCII^{+}$	• Antigen uptake • Antigen presentation • Priming of T cells • Initiation of allergic-inflammatory reaction in skin • Recruitment of inflammatory cells • Tolerogenic	• High number of $Fc\epsilon RI^{++}$ LC
IDEC	$CD1a^{++}$ $Fc\epsilon RI^{+++}$ $Fc\epsilon RII^{+}$ IgE^{+} $CD206^{+}$ $CD207^{-}$ $CD11b^{+}$ $CD1b^{+}$ $MHCII^{+}$	• Antigen uptake • Antigen presentation • Priming of T cells • Recruitment of inflammatory cells • Amplification of allergic-inflammatory reactions • Contribution to Th2/Th1 switch in AD • Immunogenic	• High number of $Fc\epsilon RI^{+++}$ IDEC
pDC	$CD1a^{-}$ $CD123^{+}$ $BDCA2^{+}$ $MHCII^{+}$ $Fc\epsilon RI^{+++}$ IgE^{+}	• Defense against viral infections • Production of Interferon-α/-β • Priming of naïve/memory T cells >Th2	• Deficiency of pDC

AD, Atopic dermatitis; *BDCA*, blood dendritic cells (DC) antigen; *FcεRI*, high-affinity receptor for immunoglobulin E (*IgE*); *IDEC*, inflammatory dendritic epidermal cells; *LC*, Langerhans cells; *MHC*, major histocompatability complex; *pDC*, plasmacytoid DC; *Th1*, T helper type 1 cell; *Th2*, T helper type 2 cell.

In patients with atopy, including AD, the high-affinity receptor for immunoglobulin E (IgE) (FcεRI) is strongly up-regulated on DC, including epidermal Langerhans cells (LC).[5,6] In addition, FcεRI, which, in contrast to effector cells of anaphylaxis, on antigen-presenting cells, consists of 3 subunits (α, 2γ), is differentially regulated in individuals who are atopic and nonatopic.[7] The FcεRIγ chain, which stabilizes surface expression of the FcεRI complex, is present in low amounts in professional antigen-presenting cells from nonatopic individuals, limiting the surface expression of the FcεRI complex and their IgE-binding capacity.[8,9] In contrast, DC of individuals who are atopic express substantial amounts of FcεRI and the IgE/FcεRI binding stabilizes and increases the surface expression of this receptor. This also explains, at least in part, why FcεRI expression on mDC and pDC in the peripheral blood and on distinct DC subtypes in the skin of patients with AD correlates with their serum IgE level.[10]

mDC Or DC1

The role of mDC in the skin

Two distinct FcεRI-bearing mDC types have been identified in the eczematous skin lesions of AD. LC, which are characterized by their primary marker, the tennis racket–shaped Birbeck granules that are composed by the newly characterized protein langerin, and the surface expression of CD1a represent the oldest members of the DC system. LC reside in the basal and suprabasal layers of the epidermis and are present in normal skin. The second mDC subpopulation, which is detectable in inflammatory skin disease, is inflammatory dendritic epidermal cells (IDEC).[11,12] In skin biopsy specimens from patients with AD, both LC and IDEC express high amounts of the FcεRI on their cell surface. This high FcεRI surface expression can be used to phenotypically differentiate eczematous skin lesions of patients with AD from other inflammatory skin diseases such as psoriasis, contact dermatitis, or cutaneous T-cell lymphoma.[13]

Sequential skin biopsy specimens from patients with AD subjected to allergen-induced lesions by atopy patch test are characterized by a biphasic cytokine profile. Although early lesions are characterized by the expression of a T helper type 2 cell (Th2)-predominant pattern, a T helper type 1/0 cell dominant pattern emerges during the subacute and chronic phase. This observation challenges the current belief that AD is a typical Th2 disease. Studies