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Review

# Harnessing dendritic cells in inflammatory skin diseases

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ABSTRACT

The skin immune system harbors a complex network of dendritic cells (DCs). Recent studies highlight a diverse functional specialization of skin DC subsets. In addition to generating cellular and humoral immunity against pathogens, skin DCs are involved in tolerogenic mechanisms to ensure the maintenance of immune homeostasis, as well as in pathogenesis of chronic inflammation in the skin when excessive immune responses are initiated and unrestrained. Harnessing DCs by directly targeting DC-derived molecules or selectively modulate DC subsets is a convincing strategy to tackle inflammatory skin diseases. In this review we discuss recent advances underlining the functional specialization of skin DCs and discuss the potential implication for future DC-based therapeutic strategies.



## 1. Introduction

The skin is an organ rich in easily assessable immune cells that are ready to provide the first line immune defense mechanisms against a multitude of internal and external pathogen-derived and environmental challenges. As the primary immunological barrier to the external environment, the skin is equipped with a complex network of immune cells, originally described as "skin-associated lymphoid tissue (SALT)" [1] and later as "skin immune system" [2]. Skin immune sentinels consist of both innate and adaptive immune cells [3]. Dendritic cells (DCs), as professional antigen presenting cells, are the main gate-keepers of the immune system, bridging innate and adaptive immunity. It is now becoming clear that DCs with their inherent plasticity can initiate a diverse range of immune responses in addition to conventional functions in the generation of immunity against pathogens [4,5]. In the steady-state, DCs have an essential role in maintaining tissue homeostasis. In pathology, DCs are able to mature into inflammatory DCs at sites of inflammation in both autoimmune and allergic disease, thereby sustaining a continuous activation of the adaptive immune system at sites of inflammation [6].

DCs have a central role in many aspects of skin immunity. Understanding the skin DC network is critically important to tackle skin immune pathology. Over the years much effort has been devoted to characterize skin DC subsets and their functions. Many studies have taken advantage of genetically engineered animal models that allow researchers to selectively examine or target DC subsets under defined conditions. Although breakthrough findings in the murine system have brought valuable insights into our understanding of the skin DC network, the discrepancy between human and murine skin immune systems, in particular the heterogeneity of DCs, donor variability, and diverse markers for DC subsets identification, poses a challenge for translational findings from the murine to the human system (Fig. 1). Different experimental approaches (i.e. *in situ* or *ex vivo* examination; enzymatic digestion or naturally crawl-out methods to isolate skin DCs) applied in various studies have increased the complexity of data analysis. Thus, the functional characteristics of human skin DC subsets are only partially understood.

In this review we discuss the current understanding of the skin DC network, emphasizing the functional specialization of skin DC subsets in the steady-state conditions (Fig. 2) and pathology, using the common inflammatory skin diseases psoriasis and atopic dermatitis (AD) as examples. This review also highlights current therapeutic approaches as well as new concepts related to harnessing DCs as a convincing immunological intervention for the treatment of chronic inflammatory immune-mediated skin diseases.

## 2. Skin DC subsets and functions

### 2.1. Epidermis (Langerhans cells)

Langerhans cells (LCs) are the primary DC subset in the epidermis of healthy skin. They are radio-resistant and are phenotypically characterized by the expression of langerin (CD207),

*Abbreviations:* SALT, skin-associated lymphoid tissue; DCs, dendritic cells; AD, atopic dermatitis; CHS, contact hypersensitivity; DDCs, dermal DCs; MHC, major histocompatibility complex; pDCs, plasmacytoid DCs; TLR, toll-like receptor; SLE, systemic lupus erythematousus; HEL, hen egg lysozyme; iNOS, inducible nitric oxide synthase; TIP-DCs, TNF- and iNOS-producing DCs; NO, Nitric oxide; IDECs, inflammatory dendritic epidermal cells; NR-UVB, narrow-band UVB; PML, progressive multifocal leukoencephalopathy; TCI, transcutaneous immunization.

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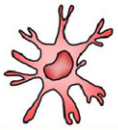
| | Localization | Cell Type | [a]Cellular Markers |
|---|---|---|---|
| Human | Epidermis |  LC | CD45, MHC class II, CD1a<br>CD207 (langerin), E-cadherin, EpCAM |
| | Dermis |  $CD14^-$ DDC | CD1c , $CD1a^{+or-}$, CD45<br>CD11b, CD11c, MHC class II |
| | |  $CD14^+$ DDC | CD1c, CD45, CD11b, CD11c, CD14<br>MHC class II, CD209 (DC-SIGN) |
| Mouse | Epidermis |  LC | CD45, CD11b, CD11c, MHC class II<br>CD205, CD207, E-cadherin, EpCAM |
| | Dermis |  $CD11b^+$ DDC | CD45, $CD11b^{hi}$, CD11c<br>MHC class II, CD205 |
| | |  $CD207^+$ DDC | CD45, $CD11b^{dim}$, CD11c, CD103<br>MHC class II, CD207 |

**Fig. 1.** Dendritic cell populations in the skin of human and mice. [a]Common cellular markers associated with human and mice skin DC subsets.

CD1a, E-cadherin and epithelial-cell adhesion molecule (EpCAM) [7]. Morphologically, they are typified by the presence of Birbeck granules, a tennis racket-shaped cytoplasmic organelle mainly composed by langerin [8]. In the steady state, LCs are situated in the basal and suprabasal layers of epidermis, where they interact with keratinocytes through E-cadherin [9]. E-cadherin ligation may act to maintain LCs in an immature state [10]. Keratinocytes are believed to be an important source of mediators that help to support the development of LCs [11]. In adult quiescent skin, LCs are maintained at a stable density in the epidermis potentially through self-renewal or by skin-resident radio-resistant LC precursor cells [12]. During injury or inflammation when the skin is depleted of resident LCs as in the case of UV-B irradiation, circulating progenitors such as monocytes may enter the inflamed skin and replenish LCs in the epidermis [12–14]. In humans, $CD34^+$ hematopoietic progenitor cells [15,16], monocytes [17], as well as dermal $CD14^+$ DCs [18] were shown to give rise to LC-like cells *in vitro*. TGF-β is a critical factor for LC development both *in vitro* and *in vivo*, as LCs are absent in the epidermis of TGF-β deficient mice [19].

Despite the abundance of studies in the past decades aiming to uncover the functional role of LCs, the *in vivo* function of LCs is still not fully understood. As one of the first DCs coming into contact with invading pathogens, LCs were believed to have the capacity to sense infection, capture antigens and acquire a strong immunogenic function [20,21]. The classical LC paradigm states that LCs are maintained in an immature state in quiescent skin. Upon encountering pathogens, LCs can capture antigens and undergo a maturation process which involves up-regulation of major histocompatibility complex (MHC) class I and class II molecules, costimulatory molecules including CD40, CD80 and CD86, and chemokine receptors such as CCR7, as well as down-regulation of E-cadherin that allows them to migrate out of the skin to draining lymph nodes, where they present antigens to T cells [22]. Both *ex vivo* isolated LCs or *in vitro* generated LC-like DCs display a strong T-cell stimulatory capacity [23]. In addition, LCs present exogenous antigens to $CD8^+$ T cells via the MHC class I pathway, a process referred to as "cross-presentation" and promote a strong cytotoxic T cells responses [23,24].

Early work addressing *in vivo* function of LCs has focused on a mouse model of contact hypersensitivity (CHS) and demonstrated the potential role of LCs in CHS reactions [25]. This however has been challenged as removal of LCs by topical application of steroids [26] or using an inducible or constitutive LC ablation model (LC-deficient mice) showed no difference [27] or even an enhancement in the magnitude of CHS responses [28]. These reports suggested that LCs are dispensable in CHS reactions and raises the possibility that LCs may have an immune inhibitory role. The redundant role of LCs in CHS reaction is proposed to be compensated by a recently characterized subset of dermal resident $CD207^+$ DCs. Notably, the concentration of sensitising antigens may be essential for dermal $CD207^+$ DC-mediated CHS responses. When only a low concentration of antigens was applied to LC-deficient mice, a diminished CHS reaction was observed potentially due to limited access of antigens by dermal DCs (DDCs) [29,30]. The role of LCs in antimicrobial immunity has also been questioned by the finding that LCs were unable to generate $CD8^+$ T cell immunity when the