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Invited Review Article

# Human skin dendritic cells in health and disease

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SUMMARY

Dendritic cells (DCs) are specialized antigen presenting cells abundant in peripheral tissues such as skin where they function as immune sentinels. Skin DCs migrate to draining lymph node where they interact with naïve T cells to induce immune responses to microorganisms, vaccines, tumours and self-antigens. In this review, we present the key historical developments and recent advances in human skin DC research. We also integrate the current understanding on the origin and functional specializations of DC subsets in healthy skin with findings in inflammatory skin diseases focusing on psoriasis and atopic eczema. A comprehensive understanding of the dynamic changes in DC subsets in health and disease will form a strong foundation to facilitate the clinical translation of DC-based therapeutic and vaccination strategies.


**Contents**



## 1. Introduction

Dendritic cells (DCs) are a heterogeneous population of leukocytes that are critical in orchestrating immune responses. In humans, the logistical difficulties of studying tissue DCs have led to the extensive use of peripheral blood *in vitro* monocyte-derived DCs (mo-DCs) as an experimental tool. The *in vivo* equivalent of mo-DCs may be DCs seen in inflammation rather than healthy tissue. The skin is an accessible epithelial barrier rich in antigen presenting cells (APCs) and has been used as a model tissue to study primary DCs in humans. In this review, we will outline the current understanding of the composition, function and origin of human skin DCs in health and two common inflammatory skin diseases, psoriasis and atopic eczema.

## 2. Skin dendritic cells

The demonstration of MHC Class II, Fc and C3 receptors on epidermal Langerhans cells (LCs) 109 years after their initial discovery by Paul Langerhans in 1868, confirmed their identity as immune cells and promoted the use of human skin as a convenient source to study tissue DCs [1–3]. These initial studies on murine and human LCs formed the paradigm for 'migratory' tissue DCs which sample antigen in their local microenvironment and migrate to draining lymph node where they interact with T

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lymphocytes to initiate a specific immune response [4]. The first interrogation of DCs in the human dermis was undertaken by immunostaining for Factor XIIIa (FXIIIa) which identified branching spindle shaped cells called 'dermal dendrocytes' [5]. This was followed by the observation in 1993 that dermal myeloid DCs, distinct from epidermal LCs, spontaneously migrated from skin explants cultured *ex vivo*. Analysis of migrated cells identified two dermal DC subsets characterized by the expression of CD1a and CD14 [6,7]. However, *in situ* analysis of the human dermis revealed $CD1c^+$ DCs which co-express CD1a and $FXIIIa^+CD14^+CD163^+$ dermal macrophages [8]. The puzzling observation of two myeloid DCs within cells migrating spontaneously from skin explants but only one subset identifiable *in situ* was explained by the overlapping antigen profile of $CD14^+$ DCs with dermal macrophages. There are several features that distinguish $CD14^+$ DCs from macrophages: (1) morphology: macrophages contain dense cytoplasmic melanin granules, (2) flow cytometry: macrophages have high scatter properties which result in autofluorescence easily identifiable in the FITC channel (excitation/emission: 488/530(20)), (3) migratory behavior: only dermal $CD14^+$ DCs migrate spontaneously from skin explants cultured *ex vivo*, (4) adherence: macrophages are adherent to tissue culture plastic and (5) turnover kinetics: macrophages are reconstituted at a significantly slower rate by donor-derived cells following hematopoietic stem cell (HSC) transplantation [9].

In addition to $CD1c^+$ DCs and $CD14^+$ DCs, $CD141^{hi}$ DCs were recently identified in skin and other peripheral tissues [10]. Although high expression of CD141 characterize this subset, this antigen is also expressed by all $CD14^+$ DCs and a subset of $CD1c^+$ DCs [11]. An important distinction of $CD141^{hi}$ DCs from the other DC subsets is the lack of CD14 expression and lower expression of CD11c [10]. In the dermis, myeloid DCs are located more superficially than macrophages, which are present deeper and primarily perivascular in distribution [12]. Whether the three myeloid DC subsets occupy distinct microanatomical spaces is unknown. Gene expression studies suggest that human skin $CD141^{hi}$ DCs are homologous to murine $CD103^+/CD8^+$ DCs and $CD1c^+$ DCs are homologous to $CD11b^+CD24^+CD64^-$ DCs (reviewed in [13]). Our recent analysis showed that dermal $CD14^+$ 'DCs' are monocyte-derived cells, which are transcriptionally similar to $FXIIIa^+$ macrophages [14]. In contrast to myeloid DCs, plasmacytoid DCs (pDCs) are virtually undetectable in healthy skin but are recruited during inflammation [8,15,16]. pDCs are located in lymphoid tissues such as lymph node and tonsil [17,18]. In addition to pDCs and tissue 'migratory' myeloid DCs, draining lymph node also contains 'resident' myeloid DCs. Lymph node 'resident' $CD1c^+$ and $CD141^+$ DCs are $HLADR^{lo}$ and $CD11c^{hi}$, distinguishable from $HLADR^{hi}CD11c^{lo}$ 'migratory' DCs [10].

What is the biological need for different DC subsets? It is important that division into DC subsets is not simply a trivial classification exercise. A considerable body of evidence has accumulated over the years demonstrating specialized immune functions for the various DC subsets. These studies have used migrated primary cells or from enzymatically-digested skin and in vitro $CD34^+$ hematopoietic stem cell (HSC)-derived $CD14^+$ DCs and $CD1a^+$ LCs [19–24]. A summary of the different functions described for skin DC subsets can be found in Table 1.

A further consideration is the phenotypic stability of skin DCs. DC subsets identified from enzymatic-digestion and spontaneous migration have been shown to have similar antigenic profile. Although this suggests phenotypic stability, altered proportion of DC subsets upon *ex vivo* cytokine treatments has been documented suggesting cellular plasticity [22,25,26]. Whether plasticity within differentiated resident populations is an important feature *in vivo* is uncertain. The demonstration of long-lived recipient-derived macrophages after allogeneic HSC transplant, despite the rapid repopulation of dermal DCs by donor-derived cells, suggests that dermal macrophages do not differentiate into resident skin DCs [9].

## 3. Origin of human skin dendritic cells

DCs arise from a bone marrow HSC-derived lineage dependent on the receptor tyrosine kinase FLT3 [27–29] (Fig. 2). Patients deficient in blood monocytes and DCs due to IRF8 and GATA2 mutation lack dermal DC subsets, have reduced numbers of macrophages but intact LCs [30,31]. This implies that dermal DCs are directly dependant on circulating monocytes and/or DCs or a shared HSC-derived precursor. In contrast, macrophages and LCs are likely to arise from alternative precursors *e.g.* embryonic or tissue-resident precursors, or are simply long-lived and turnover very slowly. In mice, LCs were shown to arise from embryonic progenitors which seed the skin prior to birth [32,33]. It is possible that similar embryonic precursors directly contribute to human LCs. Both human and murine LCs also possess local proliferative potential [34,35].

The specific contributions of circulating blood DCs and monocytes to skin DC subsets are still unclear. Human blood DCs were identified in 1982 as cells expressing MHC Class II, negative for lineage markers defining T, B and NK cells (CD3, CD19, CD20 and CD56) with potent allostimulatory properties [36,37]. The $Lin^-ClassII^+$ blood compartment contains human monocytes and DC subsets, which all except pDCs, express the integrin CD11c. Human monocyte subsets can be identified by the expression of CD14 and CD16. DCs are found within the $CD14^-CD16^-$ fraction and can be characterized by the expression of CD1c and CD141/BDCA3 [38]. The phenotypic differences between DCs initially identified in peripheral tissues ($CD1c^+$ and $CD14^+$ 'DCs') and blood ($CD1c^+$ and $CD141^+$ DCs) was an obstacle to establish their precise relationships easily. As skin $CD14^+$ 'DCs' also express CD141, which is further upregulated during spontaneous migration from skin explant culture, it was initially thought to be the equivalent of blood $CD141^+$ DCs [11]. The identification of tissue $CD14^-CD141^{hi}$ DCs, distinct from $CD14^+$ 'DCs' and $CD1c^+$ DCs, corresponding to blood $CD141^+$ DCs, has facilitated the alignment of DC networks in peripheral blood and skin as shown in Fig. 1. A proportion of cells within peripheral blood $CD16^+$ monocyte population expressing 6-Sulfo LacNAc (SLAN), called SLAN DCs, have also been described [39]. In healthy skin, $SLAN^+$ cells have been found but unlike other DCs, do not express CD11c [40].

The human and mice DC networks appears to be conserved (Fig. 2) [10,41–46]. Inter-species homology predicts that the human $CD141^+$ DCs in blood and skin arise from a precursor that precludes a monocyte stage. Blood $CD141^+$ DCs upregulate CD1c and CD1a upon co-culture with skin and express the the skin homing receptor CLA suggesting that blood $CD141^+$ DCs may be the immediate precursors of skin $CD141^{hi}$ DCs [10]. Human $CD141^+$ and $CD1c^+$ DCs possess a unique phenotype transcription signature distinct from monocytes and macrophages. The murine homologs of dermal $CD14^+$ cells are dermal $CD11b^+CD64^+$ macrophages (Fig. 2).

## 4. Skin dendritic cells in inflammation and disease

The function of DCs as cutaneous sentinels and instigators of T cell responses suggests a key role for these cells in inflammatory skin diseases. We are beginning to understand the contribution of DC to the pathogenesis of psoriasis and atopic dermatitis (AD). An important consideration in studying DCs in inflamed skin is to distinguish resident DCs that are normally present in skin from