Invited Review Article

Human skin dendritic cells in health and disease

Muzlífah Haniffa,a,b, Merry Gunawan a, Laura Jardine a

a Institute of Cellular Medicine, Newcastle University, NE2 4HH, UK
b Department of Dermatology, Newcastle Upon Tyne NHS Trust, NE1 4LP, UK

1. Introduction

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.

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 epidermal Langerhans cells (LCs) 109 years after their initial discovery by Paul Langerhans in 1868, confirmed their identity as

4. Skin dendritic cells in inflammation and disease

4.1. Dendritic cell phenotype in inflamed skin

4.2. Origins of inflammatory dendritic cells and their homeostasis in inflammation

4.3. Functional properties of dendritic cells in inflammation

5. Conclusion

Acknowledgements

References
lymphocytes to initiate a specific immune response [4]. The first interrogation of DCs in the human dermis was undertaken by immunostaining for Factor XIa (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 only one subset 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, CD141hi 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 CD141hi 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 CD141hi 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 HLA-DR+ and CD11c+, distinguishable from HLADR+CD11c+ ‘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 IRAF 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+ ‘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+CD141hi DCs, distinct from CD14+ ‘DCs’ could correspond 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 skin homing receptor CLA suggesting that blood CD141+ DCs may be the immediate precursors of skin CD141hi DCs [10]. Human CD141+ and CD1c+ DCs possess a unique phenotype transcription signature distinct from monocytes and macrophages. The murine homologs of dermal CD141+ 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
### Table 1
Functional studies on skin DC subsets.

| Reference         | Subset | Isolation and generation | Function | Cytokine | Alloactivation | Th2 polarization | Th1 polarization | Cross-presentation | Cross-priming | Memory/recall response |
|-------------------|--------|---------------------------|----------|----------|----------------|------------------|------------------|-------------------|---------------|-----------------------|
| Caux et al. [19]  | CD1a+ (CD1a+CD14-) | Migrate Digest In vitro | ++       | IL-15, IL-8 | +++            | +++              | ++               | +++               | ++            | +                     |
|                   | CD14+ (CD1a-CD14+) |                      | ++       | IL-10, IL-6, MCP-1, IL-12p40, IL-1β, GM-CSF, TNFα | ++              | ++               | +++              | +++              | +++           | ++                    |
| Klechevsky et al. [20] | LCs (CD1a-CD14+CD207+) | CD14+ dDCs (CD1a-CD14+HLA-DR+) | +       | IL-15, IL-8 | +++            | ++               | +++              | +++              | +++           | +++                   |
|                   | CD1a+ CD14- LCs | CD1a+ CD14+ DCS | ++       | IL-10, TGFβ1 | +++            | ++               | +++              | +++              | +++           | ++                    |
| Morelli et al. [21] | CD1a+CD14- LCs | CD1a+CD14+ preLCs | ++       | IL-10, TGFβ1 | ++              | ++               | +++              | +++              | +             | +                     |
| Angel et al. [23]  | dLCs (CD1ahi CD207+ CD14-) | CD1a+ dDCs (CD1a+CD207- CD14-) | +       | IL-1, IL-6, IL-23, IL-10 | +++            | ++               | +++              | +++              | +++           | +                     |
| Haniffa et al. [9] | HLA-DR+CD14+CD1a+ dDCs | CD14+ dDCs (CD1a+CD14+) | ++       | TNFα, CXCL10 | +++            | ++               | +++              | +++              | +++           | +                     |
| Haniffa et al. [10] | CD141 DCs (CD141hiCD11clo-intCD1clo) | CD141 dDCs (CD141loCD11chiCD1c+) | +       | TNFα, IL-10, IL-8 | +++            | ++               | +++              | +++              | +++           | +                     |
| Matthews et al. [86] | CD14+CD1a+ migDCs | CD14+CD1a+ migDCs | +       | IL-6, IL-10, TNFα, IL-1β | +++            | +                | +++              | +++              | +             | +                     |
|                   | CD1a+CD14- migDCs | CD1a+CD14- migDCs | +       | IL-6           | +++            | +                | +++              | +++              | +             | +                     |
|                   | CD1a+ dDCs | CD1a+ dDCs | -       |               | -              | -                | -                | -                | -             | -                     |
| Polak et al. [24]  | LCs     | CD11c+ dDC | +       | TNFα, IL-6 | +++            | ++               | ++               | ++               | +             | +                     |
| Penel-Sotirakis et al. [87] | LCs | CD1c+CD14- dDCs | +       | TNFα, IL-6 | +++            | ++               | ++               | ++               | +             | +                     |
| Fujita et al. [78] | LCs (HLA-DR+CD207+) | CD1c+ dDC (HLA-DRhiCD11c+1c+) | +       | TNFα, IL-6 | +++            | ++               | ++               | ++               | +             | +                     |
cells recruited during inflammation. This is difficult for a number of reasons: (i) there are no unique markers to identify recruited cells and (ii) resident subsets may have an altered phenotype in inflammatory environment. Furthermore, ‘snapshot’ analysis of inflamed skin does not take into account the dynamic state of migratory DCs which affects the nature and quantity of skin DCs at a given time point during disease evolution. Functional differences of DC subsets in inflammation may also be skewed by the tissue microenvironment. In this section, we will review the contribution of DCs in psoriasis and AD pathogenesis with reference to these difficulties.

4.1. Dendritic cell phenotype in inflamed skin

Animal models suggest that inflammation is accompanied by monocyte-derived DC accumulation in tissues. Mice infected with Listeria monocytogenes accumulate DCs in spleen. These DCs produce TNFα and iNOS and are called TipDCs [47]. Inflammatory DCs have also been described in a murine cutaneous Leishmania model of skin inflammation [48]. In both models, infiltrating cells express murine DC markers (CD11c, MHC II, CD80, CD86 and DEC205) alongside monocyte (CD11b, Ly6C) and macrophage-associated antigens (Mac-3, F4/80).

A recent study on inflamed human synovial and ascitic fluid [49], compartments where few resident cells are present in healthy state, revealed inflammatory DCs which expressed HLA-DR, CD11c and CD1c. These cells also express varying levels of CD1a, CD14, CD206, FcER1 and SIRPα. It is difficult to translate this finding into skin where CD11c, HLA-DR and CD1c expression would also identify resident dermal CD1c DCs. In psoriasis, DCs have been recognized as a significant proportion of inflammatory lesions [50]. Chemerin production by dermal fibroblasts, endothelial and mast cells in psoriasis lesional and peri-lesional skin attracts pDC in the initial stage of plaque formation [16]. The downstream upregulation of Type I IFN genes results in subsequent myeloid inflammatory DC recruitment [51,52]. Dermal CD11c+ cells in psoriasis skin outnumber lymphocytes and coincide with areas of TNFα and iNOS production [50].

Fig. 1. Distribution of human dendritic cells, monocytes and macrophages in skin, blood and lymph nodes. Changes during inflammation are indicated in red text. pDC = plasmacytoid DCs, Mac = macrophage, mono = monocytes, mo-Mac = monocyte-derived macrophage, inf DC = inflammatory DCs, IDEC = inflammatory dendritic epidermal cell, TipDC = TNFα and iNOS producing DC.
In AD skin, CD1a⁺CD11b⁺CD1c⁺ myeloid DCs and pDCs [51,54–56] have been observed. Both subsets express the high affinity IgE receptor, FcER1 [56]. Myeloid DCs isolated from AD epidermal suspensions are called inflammatory dendritic epidermal cells (IDEC) [57]. IDECs are distinct from resident Langerhans cells by their lower expression of CD1a and lack of Birbeck granules, but it is not clear how IDECs relate to dermal resident CD1c⁺ DC, which can co-express CD1a and CD206.

4.2. Origins of inflammatory dendritic cells and their homeostasis in inflammation

Although inflammatory skin lesions contain increased numbers of DC, the precise origin of recruited DCs remains unclear. In animal models, inflammatory DCs derive from the Ly6C⁺ monocytes [47,48,58–60], which are equivalent to CD14 human monocytes [61]. This differentiation is dependent on MyD88, a key regulator of inflammatory cytokine signaling [62]. While GMCSF is used in vitro to model inflammatory DC, its presence in vivo is not essential for monocyte-derived inflammatory DC differentiation [63]. Demonstrating cell ontogeny is more challenging in humans, but transcriptomic analysis showed that inflammatory CD11c⁺HLA-DR⁺CD16⁻CD1c⁺ DCs from synovial and ascitic fluids resemble in vitro mo-DCs [49]. However, convergent genetic reprogramming can occur in both conventional and mo-DC subsets upon microbial stimuli [64]. SLAN⁺TipDCs found in psoriasis have been suggested to originate from blood SLAN⁺ DCs [53]. This conclusion is based on patterns of chemokine receptors, cytokine production and margination of SLAN⁺ cells along dermal capillaries. Analysis of cytokine production in a moDC model of IDECs supports their derivation from CD14 monocytes [65]. The contribution of blood or skin CD1c⁺ DCs, which express FcER1, as precursors of IDECs has not been evaluated. While it is clear that recruited cells are important for the generation of inflammatory DCs, it is difficult to ascertain the precise contribution, if any, of in situ resident DC differentiation to this pool.

During the influx of monocytes to inflamed tissue, steady state mechanisms of DC homeostasis are stressed and may lead to alterations in resident population origin. An excellent example is the differential precursor requirement for LCs in steady state and inflammation. LCs are seeded from embryonic precursors during foetal development and proliferate in quiescent skin to self-renew [32,34]. However, during inflammation, LC may arise from monocytes or bone marrow precursors and have an accelerated turnover, as demonstrated by more rapid transition to donor-derived LC in cutaneous graft versus host disease following bone marrow transplantation [66–68]. In mice, tissue infiltration with monocytes promotes monopoiesis at the expense of other myeloid differentiation [69]. Skewing of myeloid development pathways has not been demonstrated in humans, but may have significant effects in chronic inflammation. Insufficient replacement of resident DCs could contribute to loss of tolerance and secondary infection.

4.3. Functional properties of dendritic cells in inflammation

Inflammatory DCs contribute to beneficial immune responses in murine infectious models. The TipDCs in murine L. monocytogenes infection model have allostimulatory capacity in mixed
leucocyte reactions but are not required for effective CD4 and CD8 T cell priming in vivo. Their beneficial role in clearing bacteria is attributed to TNF and iNOS production [47]. However, inflammatory DC in murine cutaneous Leishmaniasis do prime naïve T cells and contribute to pathogen-clearing Th1 responses in vivo [48]. Protective CD8, and Th2 responses have been demonstrated in influenza, vaccination and sensitization models respectively [59,70,71]. Inflammatory DC may also shape adaptive immunity in situ by activating tissue-resident effector memory T cells [72].

Current understanding of psoriasis reveals multiple contributions by DCs in disease pathogenesis. INFαx produced by pDCs during initial plaque formation [52] leads to IL-23 and IL-17 upregulation in the skin. IL-23 polarizes Th17 cell differentiation and also potentiates IL-17 production by a variety of immune cells [73]. The genetic association with the IL-23/Th17 pathway and the clinical reports show that anti-TNFα therapy targets the disease pathogenesis. IFNαx situ by activating tissue-resident effector memory T cells[72]. It also potentiates IL-17 production by a variety of immune cells[73]. The genetic association with the IL-23/Th17 pathway and the clinical reports show that anti-TNFα therapy targets the disease pathogenesis. IFNαx situ by activating tissue-resident effector memory T cells[72]. It also potentiates IL-17 production by a variety of immune cells[73].

The human skin has a rich network of DCs which are heterogeneous and functionally specialized. Recent progress in distinguishing DC subsets from resident macrophages and the characterization of the dynamic populations in inflammatory states has begun to shed light on their role in skin homeostasis and pathology. An enhanced understanding of skin DCs origin, homeostasis, function and pathogenic role in disease will provide novel avenues to be exploited for clinical therapy.

5. Conclusion

The human skin has a rich network of DCs which are heterogeneous and functionally specialized. Recent progress in distinguishing DC subsets from resident macrophages and the characterization of the dynamic populations in inflammatory states has begun to shed light on their role in skin homeostasis and pathology. An enhanced understanding of skin DCs origin, homeostasis, function and pathogenic role in disease will provide novel avenues to be exploited for clinical therapy.

Funding

We acknowledge funding from The Wellcome Trust, UK (WT088555; M.H. and WT097941; LJ); British Skin Foundation (M.H. and M.G.); and AXA Research Fund (M.G.).

Acknowledgments

We thank Nick Reynolds, Newcastle University for critical reading of the manuscript and Katja Fink, Singapore Immunology Network for assistance with illustration.

References

[1] Stingl G, Wolff-Schreiner EC, Pichler WJ, Gochnait F, Knapp W, Wolff K. Epidermal Langerhans cells bear Fc and C3 receptors. Nature 1977;268: 245–236.
[2] Rowden G, Lewis MG, Sullivan AK. La antigen expression on human epidermal Langerhans cells. Nature 1977;268:247–8.
[3] Klareksos L, Tjernlund U, Forsum U, Peterson PA. Epidermal Langerhans cells express la antigens. Nature 1977;268:248–50.
[4] Schuler G, Steinman RM. Murine epidermal Langerhans cells mature into potent immunostimulatory dendritic cells in vitro. J. Exp. Med. 1985;161: 526–46.
[5] Cerio R, Griffiths CE, Cooper KD, Nickoloff BJ, Headington JT. Characterization of factor XllA positive dermal dendritic cells in normal and inflamed skin. Br. J. Dermatol. 1985;121:421–31.
[6] Lenz A, Heine M, Schuler G, Romani N. Human and murine dermis contain dendritic cells. Isolation by means of a novel method and phenotypical and functional characterization. J. Clin Invest 1993;92:2587–96.
[7] Nestle FO, Zheng XC, Thompson CB, Turka LA, Nickoloff BJ. Characterization of dermal dendritic cells obtained from normal human skin reveals phenotypic and functionally distinctive subsets. J. Immunol. 1993;151:6535–45.
[8] Zaba LC, Fuentes-Duculan J, Steinman RM, Krueger JG, Lowes MW. Normal dermal dermal dendritic cells contain distinct populations of CD11c+CD207+ dendritic cells and CD163+CD1a+ macrophages. J. Exp. Invest. 2007;117:2517–25.
[9] Haniffa M, Ginhoux F, Wang XN, Bigley V, Abel M, Dimmick J, et al. Differential regulation of human dendritic cell and macrophages during hematopoietic stem cell transplantation. J. Exp. Med. 2009;206:371–85.
[10] Haniffa M, Shin A, Bigley V, McGovern N, Teo P, See P, et al. Human tissues contain CD141(hi) cross-presenting dendritic cells with functional homology to mouse CD103(+)/nonlymphoid dendritic cells. Immunity 2012;37: 60–73.
[11] Chu C-C, Ali N, Karagiannis P, Di Miglio P, Skowera A, Napolitano L, et al. Resident CD141+ (BDCA3)+ dendritic cells in human skin produce IL-10 and induce regulatory T cells that suppress skin inflammation. J. Exp Med 2012; 209:935–45.
[12] Wang XN, McGovern N, Gunawan M, Richardson C, Windebank M, Siah TW, et al. A three-dimensional atlas of human dermal leukocytes, lymphatics, and blood vessels. J. Invest. Dermatol. 2014;134:965–74.
[13] Haniffa M, Collin M, Ginhoux F. Ontogeny and functional specialization of dendritic cells in human and mouse. Adv. Immunol. 2013;120:1–49.
[14] McGovern N, Schlitzer A, Gunawan M, Jardine L, Shin A, Poyner E, et al. Human Dermal CD14(+) Cells are a Transient Population of Monocyte-Derived Macrophages. Immunity 2004;41(3):465–77.
[15] Nestle FO, Conrad C, Tun-Kyi A, Honey B, Gombert V, Boymann O, et al. Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. J. Exp. Med. 2005;202:135–43.
[16] Albanesi C, Scarponi C, Pallotta S, Daniele R, Bosisio D, Madonna S, et al. Chemerin expression marks early psoriatic skin lesions and correlates with plasmacytoid dendritic cell recruitment. J. Exp. Med. 2009;206:249–58.
[17] Grouard G, Russoa MC, Filgueira I, Durand J, Ranchereau J, Liu YJ. The enigmatic plasmacytoid T cells develop into dendritic cells with interleukin (IL)-3 and CD40-ligand. J. Exp. Med. 1997;185:1101–11.
[18] Boenning K, North M, Burke M, Singh H, Renslton S, Aqual N, et al. Plasmacytoid dendritic cells (PDC) are the major DC subset innately producing cytokines in human lymph nodes. J. Leukoc. Biol. 2005;78:1142–52.
[19] Caux C, Vanbervliet B, Massacrier C, Dezutter-Dambuyant C, de Saint-Viss B, Jaoulet C, et al. CD34+ hematopoietic progenitors from human cord blood differentiate along two independent dendritic cell pathways in response to GM-CSF+ TNF alpha. J. Exp. Med. 1996;184:695–706.
[20] Klechevsky E, Morita R, Liu M, Cao Y, Coquery S, Thompson-Snipes L, et al. Functional specializations of human epidermal Langerhans cells and CD14(+) dermal dendritic cells. Immunity 2008;29:497–510.
[21] Morelli AE, Rubin JP, Erdos G, Tkacheva OA, Mathers AR, Zahorachak AF, et al. Arlregina AT: CD4(+) T Cell responses elicited by different subsets of human skin migratory dendritic cells. J. Immunol. 2005;175:7905–15.
[22] de Grujil TD, Sombroek CC, Lougheed SM, Oosterhoff D, Bater J, van den Eertwegh AJ, et al. A postmigrational switch among skin-derived dendritic cells to a macrophage–like phenotype is predetermined by the intracutaneous cytokine balance. J. Immunol. 2006;176:7232–42.
[23] Angel CE, George E, Brooks AE, Ostrovsky LL, Brown TL, Dunbar PR. Cutting edge: CD14+ antigen-presenting cells in human dendritic cells respond rapidly to Con A signals. J Immunol. 2000;164:2730–4.

[24] Polak NE, Newell L, Tabaray V, Pickard C, Healy E, Friedmann PS, et al. CD70–CD27 interaction augments CD8+ T-cell activation by human epidermal Langerhans cells. J Invest Dermatol. 2012;132:1636–44.

[25] Lindenmaier J, Oosterhoff D, Sonnekoo C, Lougen MM, Hoehg J, Stamm AG, et al. IL-10 conditioning of human skin affects the distribution of migratory dendritic cell subsets and functional T cell differentiation. PLoS One 2013;8:e68327.

[26] Larregina AT, Morelli AE, Spencer LA, Logar AJ, Watkins SC, Thomson AW, et al. Dermal-resident CD14+ cells differentiate into Langerhan cells. Nat. Immunol. 2001;2:1151–8.

[27] Maraskovsky E, LaBrec R, Tepee E, Maliszewski CR, Hoej K, et al. In vivo generation of human dendritic cell subsets by Fr3 ligand. Blood 2000;96:878–84.

[28] McKenna HJ, Stocking KL, Miller RE, Brasel K, De Smedt T, Maraskovsky E, et al. IRF8 mutations and human dendritic cell immunodeficiency. N. Engl. J. Med. 2011.

[29] Bigley V, Haniffa M, Doutlovat S, Wang XN, Dickson R, McGovern N, et al. The human dendritic cell homologues CD8alpha+ and CD11c+ are monocytes and monocyte-derived dendritic cells, respectively. Blood 2000;100:4512–20.

[30] Hoeffel G, Wang Y, Greter M, See P, Teo P, Mallaret B, et al. Adult Langerhans cell role in the differentiation of epidermal dendritic cell subset. J. Exp. Med. 2011;208:1109–20.

[31] Schulz C, Gomez Perdiguero E, Chorro L, Szabo-Rogers H, Cagnard N, Kierdorf K, et al. CD27 interaction augments CD8+ T-cell activation by human epidermal dendritic cell precursors. J. Exp. Med. 2011;208:3089–100.

[32] Van Voorhis WC, Hair LS, Steinman RM, Kaplan G. Human dendritic cells. Enrichment and characterization from peripheral blood. J. Exp. Med. 1982;155:1172–87.

[33] O'Doherty U, Peng M, Gezelter S, Swiggard WJ, Betjes M, Bhardwaj N, et al. Human blood contains two subsets of dendritic cells, one immunologically mature and the other immature. Immunology 1994;82:487–93.

[34] Macdonald KP, Munster DJ, Clark DJ, Dzioenek A, Schmitz J, Hart DN, Charmandy L. Human blood dendritic cell subsets. Blood 2002;100:6412–20.

[35] Schakel K, von Ketelzell M, Haukes A, Ebling A, Schulze L, Escher M, et al. Human 6-sulfo LacNAc-expressing dendritic cells are principal producers of early innate immune defense against bacterial infection. Immunity 2003;19:59–70.

[36] Gunther C, Starke J, Zimmermann N, Schakel K, et al. Human 6-sulfo LacNAc (slan) dendritic cells are inflammatory dermal dendritic cells for immune T cell areas. Cell 2010;143:416–29.

[37] Greter M, Helft J, Cho J, Illig T, Angeli V, Bogunovic M, et al. GM-CSF controlling dendritic cell maturation. Immunity 2013;38:322–35.

[38] Plantinga M, Guilliams M, Vanheerswynghels M, Deswarte K, Vanhaecke F, Baert J, et al. Chemokine receptor 1 is a conserved selective marker of mammalian cells of the monocyte/macrophage lineage. J. Immunol. 2005;175:1939–46.

[39] Plantinga M, Guilliams M, Vanheerswynghels M, Deswarte K, Vanhaecke F, Baert J, et al. Plasmacytoid dendritic cells: a new cutaneous dendritic cell subset with distinct role in inflammatory skin diseases. J. Invest Dermatol. 2002;119:1096–102.

[40] Berrie T, Kraft S, Geiger E, Wollenberg A, Koch S, Novak N, Fe (correction of Ef) epsilon RI expressing dendritic cells: the missing link in the pathobiology of atopic dermatitis? J. Dermatol. 2000;27:698–9.

[41] Stary G, Bangert C, Stingl G, Kopp T. Dendritic cells in atopic dermatitis: expression of FcepsilonRI supports distinct immunomodulation-associated subsets. Int. Arch. Allergy Immunol. 2005;138:278–90.

[42] Wollenberg A, Kraft S, Hanau D, Bieber T. Immunomorphological and ultrastructural characterization of Langerhan cells and a novel, inflammatory dendritic epidermal cell population in lesional skin of atopic eczema. J. Invest Dermatol. 1996;106:446–53.

[43] Cheong C, Matsi I, Choi JH, Dandamudi DB, Shrestha E, Longhi MP, et al. Microbial stimulation fully differentiates monocytes to DC-SIGN/CD209+ (>90%) dendritic cells for immune T cell areas. Cell 2010;143:416–29.

[44] Stuehr DJ, Plevy SE, Hektor M, Brisse M, Costello P, Canfield S, et al. Expression and function of the mannose receptor CD206 on epidermal dendritic cells. J. Invest. Dermatol. 2011;131:2334–44.

[45] Acosta-Rodriguez EV, Rivino L, Geginat J, Jarrossay D, Gattorno M, Lanzavecchia A, et al. Human Langerhans cells in hematopoietic stem cell transplantation. J. Exp. Med. 2011;208:227–34.

[46] Segura E, Touzot M, Bohineust A, Cappuccio A, Chiocchia G, Hosmalin A, et al. Human inflammatory dendritic cells mediate innate immune defense against bacterial infection. Immunity 2003;19:59–70.

[47] Leon B, Lopez-Bravo M, Ardavin C. Monocyte-derived dendritic cells formed at the infection site control the induction of protective T helper 1 responses against Leishmania. Immunity 2007;26:519–31.

[48] Segura E, Touzot M, Bohineust A, Cappuccio A, Chiocchia G, Hosmalin A, et al. Human inflammatory dendritic cells induce th17 cell differentiation. Immunity 2013;38:346–58.

[49] Sere K, Baek JH, Ober-Blobaum J, Muller-Newen G, Tacke F, Yokota Y, et al. Two subsets of human Langerhans cells with distinct functions. J. Immunol. 2003;170:7678–85.

[50] Novak N, Kraft S, Hackbarst J, Geiger E, Allam P, Bieber T. A reducing microenvironment leads to the generation of FcepsilonRIhigh inflammatory Langerhans cells. J. Immunol. 2002;169:1096–102.

[51] Acosta-Rodriguez EV, Rivino L, Geginat J, Jarrossay D, Gattorno M, Lanzavecchia A, et al. Human slan (6-sulfo LacNAc) dendritic cells are inflammatory dermal dendritic cells in psoriasis and drive strong TH1/TH17 T-cell responses. J. Allergy Clin. Immunol. 2011;127:787–94. e1-9.

[52] Willenberg A, Wagner M, Gunther S, Towarowski A, Tuma E, Moderer M, et al. Plasmacytoid dendritic cells: a new cutaneous dendritic cell subset with distinct role in inflammatory skin diseases. J. Invest Dermatol. 2002;119:1096–102.

[53] Nestle FO, Conrad C, Tun-Kyi A, Hombuch R, Boyman O, et al. Distinct type of Langerhans cells populate the skin during steady state and inflammation. J. Invest Dermatol. 2002;119:1096–102.
Novak N, Allam JP, Hagemann T, Jenneck C, Laffer S, Valenta R, et al. Characterization of epidermal hyperplasia by TNF inhibition is associated with reduced TH17 responses. J. Exp. Med. 2007;204:3183–94.

Lee E, Trepicchio WL, Oestreicher JL, Pittman D, Wang F, Chaman F, et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. J. Exp. Med. 2004;199:125–30.

Cragg MS, Walshe CA, Ivanov AO, Glenneis MJ. The biology of CD20 and its potential as a target for mAb therapy. Curr. Dir. Autoimmun. 2005;8:140–74.

Fujita H, Shemer A, Suarez-Farinaz M, Johnson-Huang LM, Tintle S, Cardinale I, et al. Lesional dendritic cells in patients with chronic atopic dermatitis and psoriasis exhibit parallel ability to activate T-cell subsets. J. Allergy Clin. Immunol. 2011;128:574–82 (e1–12).

Boylan O, Hefi HP, Conrad C, Nickoloff BJ, Suter M, Nestle FO. Spontaneous development of psoriasis in a new animal model shows an essential role for resident T cells and tumor necrosis factor-alpha. J. Exp. Med. 2004;199:731–6.

Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat. Genet. 2006;38:441–6.

Kabashima K. New concept of the pathogenesis of atopic dermatitis: interplay among the barrier, allergy, and pruritus as a trinity. J. Dermatol. Sci. 2013;70:3–11.

Souenlis V, Reche PA, Kanzler H, Yuan W, Edward G, Homey B, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. Nat. Immunol. 2002;3:673–80.

Nogroales KE, Zaba LC, Shemer A, Fuentes-Duculan I, Iizuki T, et al. IL-22-producing T22 cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 cells. J. Allergy Clin. Immunol. 2009;123:1244–52 e2.

Duhem T, Geiger R, Jarrossay D, Lanzavecchia A, Sallusto F. Production of interleukin 22 but not interleukin 17 by a subset of human skin-homing memory T cells. Nat. Immunol. 2009;10:857–63.

Novak N, Allam JP, Hagemann T, Jenneck C, Laffer S, Valenta R, et al. Characterization of FcepsilonRI-bearing CD123 blood dendritic cell antigen-2 plasmacytoid dendritic cells in atopic dermatitis. J. Allergy Clin. Immunol. 2004;114:364–70.

Romani N, Brunner PM, Stingl G. Changing views of the role of Langerhans cells. J. Investig Dermatol 2012;132(3 Pt 2):872–81.