

Invited Mini Review

The pathophysiological role of dendritic cell subsets in psoriasis

Tae-Gyun Kim^{1,3}, Dae Suk Kim², Hyoung-Pyo Kim^{1,*} & Min-Geol Lee^{2,3}¹Department of Environmental Medical Biology, Institute of Tropical Medicine, Yonsei University College of Medicine,²Department of Dermatology and Cutaneous Biology Research Institute, Yonsei University College of Medicine,³Brain Korea 21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul 120-752, Korea

Psoriasis is a chronic inflammatory disorder characterized by an erythematous scaly plaque of the skin and is occasionally accompanied by systemic complications. In the psoriatic lesions, an increased number of cytokine-producing dendritic cells and activated T cells are observed, which indicate that psoriasis is a prototype of an immune-mediated dermatosis. During the last decade, emerging studies demonstrate novel roles for the dendritic cell subsets in the process of disease initiation and maintenance of psoriasis. In addition, recently discovered anti-psoriatic therapies, which specifically target inflammatory cytokines produced by lesional dendritic cells, bring much better clinical improvement compared to conventional treatments. These new therapies implicate the crucial importance of dendritic cells in psoriasis pathogenesis. This review will summarize and discuss the dendritic cell subsets of the human skin and their pathophysiological involvement in psoriasis based on mouse- and patient-oriented studies. [BMB Reports 2014; 47(2): 60-68]

INTRODUCTION

Psoriasis is a chronic inflammatory disease of the skin that affects 1-2% of the global population (1). Its occurrence is more common in the Western population compared to Asian, and clinical presentations are different among the races, which emphasize the important roles for genetic and environmental factors in psoriasis pathogenesis (2-4). Psoriasis primarily involves the skin; however, it could occasionally affect the articular joints (psoriatic arthritis), which leads to a disabled joint motility. The chronic nature of the psoriatic inflammation could be complicated with systemic inflammatory status (5). Patients with severe psoriasis are associated with a greater risk for systemic comorbidities, including cardiovascular diseases and metabolic syndrome, suggesting that psoriasis is a sys-

temic inflammatory disorder, rather than a sole skin disease (6, 7). Furthermore, psoriatic patients suffer from both physical and psychological distress during social work, due to their characteristic cutaneous marks (8). Thus, continuous efforts to develop the optimal treatment options against psoriasis are truly needed to increase the quality of life outcomes of the patients.

Psoriatic lesions are characterized by thick and erythematous non-pruritic plaques covered by silvery scale on the skin, which could be differentiated from other eczematous inflammatory diseases, such as atopic dermatitis or contact dermatitis (Fig. 1A). Under the microscopic examination, psoriatic plaques reveal a set of typical histological features, including hyperproliferation of keratinocytes in the epidermis (acanthosis) and a huge number of skin-infiltrated inflammatory cells mainly found in the dermis with accompanying increased vasculatures (Fig. 1B). Those cellular infiltrates are comprised of dendritic cells (DCs), macrophages, and T cells. In addition, one can easily detect a group of neutrophils (Munro's microabscess) and scattered T lymphocytes in the epidermal compartment (4). Because psoriatic lesions contain a markedly increased number of inflammatory cells, it has been postulated that psoriasis is a disease caused by an altered immune system of the body (4, 9). Initial studies have focused on the role of T lymphocytes in the pathogenesis of psoriasis because a huge number of T cells are infiltrated in the psoriatic lesions, and the use of calcineurin inhibitors or agents targeting T cells leads to clinical improvement which has demonstrated the cru-

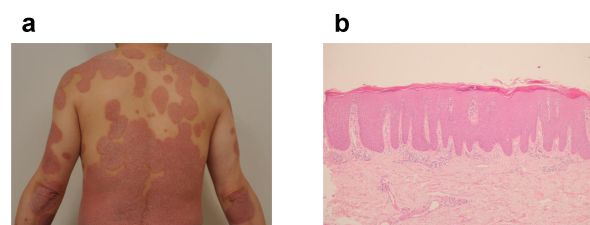


Fig. 1. Clinical and histopathological features of psoriasis. (A) Isolated or confluent sharply demarcated erythematous scaly plaques are typical cutaneous manifestations for chronic psoriasis. (B) Hyperplastic epidermis and a large number of skin-infiltrating inflammatory cells accompanying increased vasculatures are histopathological characteristics of chronic psoriatic lesions.

*Corresponding author. Tel: +82-2-2228-1842; Fax: +82-2-363-8676; E-mail: kimhp@yuhs.ac

<http://dx.doi.org/10.5483/BMBRep.2014.47.2.014>

Received 30 December 2013

Keywords: Dendritic cells, Psoriasis, Skin

ISSN: 1976-670X (electronic edition)

Copyright © 2014 by the The Korean Society for Biochemistry and Molecular Biology

© This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

cial pathogenic role for T cells (10). Among the T cells, IFN- γ -producing T cells had been specifically investigated by researchers, because the psoriatic skins characteristically express type 1 immune signatures, compared to atopic dermatitis skins which are associated with an increased type 2 immune molecules (11, 12). However, recent clinical and genome-oriented, population-based studies have elucidated the chief involvement of IL-17A-producing helper T cells (Th17) in the pathogenesis of psoriasis (13, 14). IL-17A could activate epidermal keratinocytes or other epithelial cells to produce the inflammatory molecules that mediate Th17-associated inflammations (15-17). Psoriatic lesions exhibit a highly elevated *IL17a* message level, and lesion-infiltrating T cells actively produce IL-17 cytokine upon *in vitro* stimulation (18, 19). More importantly, emerging clinical trials have shown a good therapeutic efficacy for the use of anti-IL-17A or anti-IL-17 receptor. A monoclonal antibodies in the treatment of severe psoriasis, which also emphasizes the pivotal involvement of IL-17A-producing T cells in psoriasis (20, 21). Although lesional T cells present an activated and memory phenotype *in situ*, the cellular mechanisms for controlling their pathologic activation so far remain elusive (22, 23). Thus, it would be noteworthy to clarify the upstream cellular sources or molecules that participate in the process of T cell activation for the development of new therapeutic modalities for psoriasis treatment.

DCs are bone-marrow-derived, professional antigen-presenting leukocytes that link innate and adaptive immunity (24). They finely orchestrate the magnitude and direction of adaptive immune responses against pathogens, via priming and activating T lymphocytes according to the particular environmental circumstances (25). DCs are composed of heterogeneous subsets classified by surface markers, anatomical locations, and functional specificities. DCs are found in the blood, lymphoid tissues, and almost all peripheral organs, including skin, which implicate the important position of DCs in immune surveillance (26). Owing to their distinctive ability to regulate T cell immune responses, DCs have long been recognized as playing a central role for the development of multiple inflammatory disorders, such as psoriasis (25). Recent advances have provided a bunch of evidence that DCs actively participate in the pathogenesis of psoriatic inflammation (27). The aim of this review is to present a recent understanding of the DC network in the normal human skin, and how cutaneous DCs play a role in the pathogenesis of psoriasis to provide the concept that DCs are promising therapeutic target for anti-psoriasis treatment.

DC SUBSETS IN THE NORMAL HUMAN SKIN

Heterogeneous DC populations are located in the quiescent human skin. Although much effort has been conducted to clarify the precise taxonomy for cutaneous DCs, the current classification for DC subsets in the skin is still somewhat complicated, due to a great number of surface antigens to be used for

identifying DCs and functional modification during the tissue preparation for *ex vivo* experiments. Nevertheless, recent elegant studies have established the discrete resident subsets of DCs in the steady-state human skin: 1) epidermal Langerhans cells (LCs), 2) dermal myeloid DCs (mDCs), and 3) plasmacytoid DCs (pDCs) (28, 29).

LCs are distinct subset of DCs that reside in the suprabasal epidermis where they organize a lacelike network (30). LCs are characterized by the expression of C-type lectin Langerin (CD207) and a major histocompatibility complex I-like molecule CD1a, which could act as molecular receptors that recognize and endocytose carbohydrate structures of the pathogens and microbial lipids, respectively (31). LCs have a unique intracellular ultrastructure called Birbeck granule, visible by electron microscope, which is associated with the internalized Langerin (32, 33). The homeostasis of LCs differ from that of other DC subsets, in that LCs are believed to sustain their epidermal pool by self-renewal throughout the life (34). The role of LCs in cutaneous immunity has not been conclusive so far (30). Currently, we have understood that LCs represent bidirectional functions in cutaneous immune responses in different contexts (i.e. immune-stimulatory or immune-regulatory) that have still been a matter of controversy (35). Recently it has been shown that LCs could induce IL-22 production by a subset of CD1a-autoreactive T cells through CD1a molecule to support the epithelial immunologic barrier of the skin (36, 37). Seneschal *et al.* reported sophisticated study that LCs are basically programmed to primarily induce the proliferation of skin resident regulatory T cells; however, foreign pathogen-activated LCs have converted their characteristics to activate and proliferate skin resident effector memory T cells, suggesting the dual role for LCs in cutaneous immunity depending on the presence or absence of infectious challenge (38).

Dermal mDCs are a classic type of DCs that are mainly located in the upper part of the dermis (28, 39). The best surface antigen known for the identification of dermal mDCs is a myeloid marker CD11c. Historically, dermal mDCs had been called "dermal dendrocytes" according to their dendritic appearance. Early studies had recognized dermal dendrocytes by the expression of Factor XIIIa antigen (40, 41). However, recent double immunofluorescence-based *in situ* study has clearly shown that most CD11c⁺ dermal mDCs characteristically co-express CD1c (BDCA-1) but not Factor XIIIa, while the positivity for Factor XIIIa denotes another cellular population, namely, dermal macrophages (39). Purified CD1c⁺ mDCs show a relatively immature phenotype with poor immunostimulatory activity; however, the addition of maturation stimuli for DCs greatly increases their ability to induce T cell proliferation (39). CD1c⁺ dermal mDCs are shown to have a capacity for priming and activating CD4⁺ T cells *ex vivo*; however, the amount and direction of T cell responses mounted by dermal mDCs has been reported to be somewhat discrepant among the research groups, possibly depending on the mDC isolation techniques (42-45).

There is another population of dermal mDCs recognized by the expression of CD141 (BDCA-3) in the normal human skin, comprising a relatively small fraction of mDCs (approximately 10%) (28, 39, 46). These CD141⁺ mDCs have initially been identified in the blood, and shown to be less immunostimulatory compared to CD1c⁺ mDC subset (47). Recent investigations on CD141⁺ human mDCs have provided the evidence for the important role of CD141⁺ mDCs in cross-presenting exogenous antigens to CD8⁺ T cells, a process that is crucial for anti-viral, anti-tumoral, and vaccination immunity (48-50). In the mouse system, CD8 α ⁺ DC subset possesses cross-presenting ability, which represents mouse CD8 α ⁺ DCs as a counterpart to human CD141⁺ mDCs (51). Human CD141⁺ mDCs are also characterized by CLEC9A and XCR1 expression discovered by recent comparative biology approaches (52, 53). Haniffa et al. have recently explored a wide range of human peripheral tissue CD141⁺ mDCs which harbor cross-presenting ability with functional similarity to mouse CD103⁺ nonlymphoid DCs (46). These results indicate that human peripheral CD141⁺ mDCs could be a promising target for mounting vaccination immunity against viral infections or multiple tumors through the relatively simple peripheral routes, including skin.

pDCs are a unique DC subset initially described by their similar morphology with plasma cells (54). Immunophenotypically, pDCs are distinguishable from classic mDCs by their lack of myeloid markers CD11c or CD11b, while expressing CD123, CD303 (BDCA-2), and CD304 (BDCA-4) (55). They are generally poor stimulators for T cell priming and activation compared to mDCs; however, pDCs are specifically equipped for rapidly producing type I interferon in response to toll-like receptor 7 (TLR7) or TLR9 engagement by viral or self-nucleic acids (55, 56). This particular characteristic designates pDCs as a central defender against viral infections. Recent evidences have suggested that pDCs located in peripheral tissues are directly associated with the induction of tolerance via regulating regulatory T cells, indicating that pDCs actually play a dual role for immune responses depending on the circumstances (57). In the normal human skin, pDCs are rarely detectable and their precise function remains to be determined (39, 58).

DC SUBSETS IN THE PSORIATIC SKIN AND THEIR ROLE FOR PSORIASIS PATHOGENESIS

Psoriatic skin contains a highly increased number of CD11c⁺ mDCs in the dermis, suggesting the important role of mDCs in the psoriasis pathogenesis (59) (Fig. 2). Psoriatic mDCs are comprised of both immature and mature phenotypes, and mature mDCs are characterized by dendritic cell-lysosomal-associated membrane protein (DC-LAMP) or CD83 expression. Typically, those mature mDCs present as dense cellular clusters, frequently aggregated with lesional infiltrating T cells, which resemble the lymphoid-clusters of secondary lymphoid organs or inflamed peripheral tissues (59-62). Because a ma-

ajority of lesional-infiltrating T lymphocytes present proliferating status and activated memory phenotype, it has been postulated that cluster-forming mature mDCs could act as the cellular nidus, which contribute to the disease progression by autoantigen presentation and activation of T cells *in situ* (22, 23, 63-65). Thus, the way for inhibiting T cell activation via interfering with DC/T cell interaction has been considered to be an effective therapeutic strategy for psoriasis. Currently, two biological regimens have been assessed to repress psoriatic inflammation by targeting co-stimulatory activating signals on T cells generated by cellular contact with antigen-presenting DCs. Alefacept is a human lymphocyte function-associated antigen-3 (LFA-3) fusion protein that binds to CD2 molecules, and it blocks the interaction between co-stimulatory molecule LFA-3 and CD2 expressed on DCs and T cells, respectively (9, 66). The administration of alefacept in psoriatic patients revealed a good clinical therapeutic efficacy, accompanied with the decreased number of lesion-infiltrating DCs and T cells (59, 67, 68). Efalizumab is a chimeric monoclonal anti-CD11a (alpha chain of LFA-1) antibody that blocks LFA-1 of T cells, the molecule that binds with intercellular adhesion molecule 1 (ICAM-1) expressed by endothelial cells and DCs (9). It inhibits

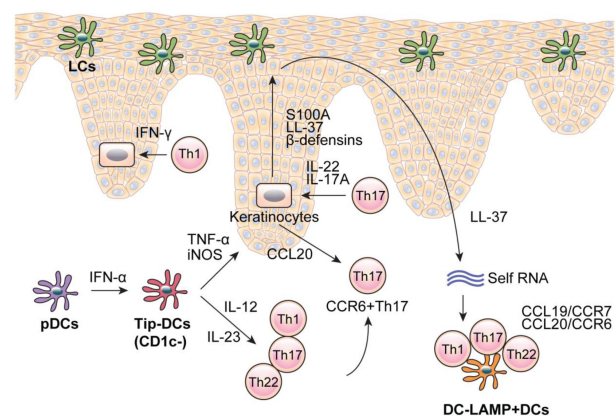


Fig. 2. A schematic model for the central role of dendritic cell (DC) subsets in psoriasis. Psoriatic plasmacytoid DCs (pDCs) produce type I interferon, including IFN- α , and participate in the initiation phase of psoriatic inflammation. TNF- α and inducible nitric oxide synthase-producing DCs (Tip-DCs) are inflammatory DC subset found in the psoriatic skins. They actively produce proinflammatory molecules, TNF- α and iNOS, to enhance the psoriatic inflammation. IL-12 and IL-23 are also expressed by Tip-DCs, and are crucial for Th1 and Th17 development and expansion, respectively. Th17-driven IL-17A and IL-22 act on keratinocytes to induce CC chemokine 20 (CCL20) and anti-microbial peptides. Highly increased epidermal CCL20 attracts CCR6-bearing Th17 cells, and recruited Th17 cells further activate keratinocytes to produce CCL20 in a positive feedback manner. Lesional self-RNA and anti-microbial peptide LL-37 could be combined to generate self-RNA/LL-37 complex, which activates resident immature DCs to be mature DCs (DC-LAMP⁺). Those DC-LAMP⁺ mature DCs frequently aggregate with lesional T cells possibly via certain chemokine systems, including CCL19/CCR7 or CCL20/CCR6.

the cell-to-cell adhesion between T cells and DCs thereby reducing the T cell activation (69). Although efalizumab has been withdrawn from the market due to its severe side effect, initial clinical studies using efalizumab revealed a good therapeutic effect on the treatment of psoriasis (70).

Chemokine systems play a central role for tissue trafficking of diverse leukocytes, including DCs and T cells (71). Although a number of chemokine pairs are expressed in the psoriatic plaques (72, 73), the precise chemokines that contribute to the recruitment and formation of dermal DC/T cell clusters have been poorly understood yet. Mitsui *et al.* have reported that dermal clusters of the psoriatic skin express lymphoid-organizing CCL19 ligand and its receptor CCR7 (74). Apart from the results by Mitsui *et al.*, we have recently demonstrated *in situ* evidence for the association of CCL20/CCR6 chemokine system with psoriatic dermal aggregates (75). Lesional aggregating DC-LAMP⁺ mature mDCs and T cells expressed CCR6 and, interestingly, psoriatic DCs and T cells were the prominent cellular sources for CCR6 ligand, CCL20. Importantly, the number of dermal DC-LAMP⁺ mature DCs was significantly higher in chronic psoriasis compared to other acute inflammatory skin lesions, and correlated to disease severity, indicating possible pathologic involvement of mature mDCs in the chronic nature of psoriasis. In line with our data, Ganguly *et al.* reported that self-RNA/LL-37 complexes were able to activate mDCs via TLR8-dependent manner, and the positive correlation between DC-LAMP⁺ mature mDCs and the amount of lesional self-RNA/LL-37 complexes was observed in chronic psoriatic plaques (76). Thus, a blockade of the formation of dermal DC/T cell immunological aggregates may be a promising therapeutic target for alleviating chronic psoriasis, especially via targeting specific chemokine pairs, including CCL19/CCR7 and CCL20/CCR6.

The composition of DC subsets found in the psoriatic plaques is quite different from those in cases of quiescent skin. Emerging studies have allowed us to understand the re-established DC network present in the psoriasis and their pathologic engagement with psoriatic inflammation (27).

pDCs as an initiator of the psoriatic inflammation

In contrast to normal skin, an increased number of pDCs was detected in psoriatic skin (77, 78). Clinically, topical application of TLR7 agonist imiquimod aggravated psoriasis, with increased number of pDCs in the dermal infiltrating cells (78). These findings were in accordance with a previous study, which revealed an evident IFN- α signature in psoriatic skin lesions (79). In addition, during the last decade, decent studies have shown a role for pDCs during the initiation phase of psoriasis. Nestle *et al.*, with their xenograft mouse model of human psoriasis, demonstrated that the development of psoriasis can be prevented by blocking IFN- α . Furthermore, sequential analysis of psoriasis development in xenograft model revealed that IFN- α signaling signature is actually present in developing psoriasis, and precedes the characteristic psoriatic

phenotype (79-81). However, the exact mechanism of pDCs activation in psoriatic skin remained unknown. Subsequent elegant studies had shown that the cathelicidin LL-37, which is upregulated endogenous antimicrobial peptide in psoriatic skin, binds to self-DNA and self-RNA released from stressed or dying cells and activates pDCs via TLR9 and TLR7, respectively, and induces type I IFN production (76, 80). Since pDCs are tolerant to self-DNA/RNA during homeostasis, LL-37 is necessary to break this innate tolerance. Therefore, LL-37 mediates recognition of self-DNA and self-RNA, probably released from injured or stressed epidermal cells, by pDCs, and activates them to initiate psoriasis development. However, the exact source and characteristics of self-DNA/RNA in psoriasis are not fully identified. Moreover, whether pDCs from psoriasis patient are more prone to LL-37 mediated activation needs to be studied in the near future.

TNF- α and inducible nitric oxide synthase (iNOS)-producing myeloid DCs are pathologic inflammatory DCs in psoriasis

As mentioned above, a markedly increased number of CD11c⁺ mDCs is observed in the psoriatic dermis (~30 times higher compared to the normal skin) (28, 59, 82). An initial functional study conducted by Nestle *et al.* showed that psoriatic dermal DCs are capable of stimulating autologous T cells, with the induction of IL-2 and IFN- γ cytokine production (65). Because psoriatic skin expressed high level of iNOS and TNF- α , which are potent inflammatory mediators (83, 84), Lowes *et al.* investigated the *in situ* local expression of those molecules in the psoriatic plaques. Notably, CD11c⁺ mDCs are unique cellular sources for iNOS and TNF- α in psoriatic dermis (59). Previously TNF- α - and iNOS-producing DC subset (called Tip-DCs) have been identified in the spleens of *Listeria* monocytogenes-infected mice, and they play a crucial role for eradicating intracellular *Listeria* (85). Interestingly, these Tip-DCs-like mDC subsets have been found in the human psoriatic dermis by Lowes *et al.*, and an initial large scale clinical study showed that a blockade of TNF- α using etanercept led to a significant reduction in the severity of psoriasis (86). These results indicate that TNF- α cytokine-producing inflammatory mDCs are critically involved in the pathogenesis of psoriasis. Moreover, local gene expression profiles within psoriatic skins before and after treatment with etanercept revealed that TNF- α suppression was significantly associated with the downregulation of Th17-associated genes, and etanercept-treated *in vitro*-generated DCs were poor stimulators for T cell proliferation responses, indicating that TNF- α directly regulates DC functions in an autocrine and/or paracrine manner (60). In addition to etanercept, other TNF- α -blocking biologic agents, such as adalimumab and infliximab, have been shown to have a significant therapeutic effect for alleviating psoriasis (87). IL-23 is a key cytokine that promotes the expansion of the IL-17-producing Th17 cells (88). DCs are known as one of the cellular sources for IL-23 production, and IL-12/23p40 and IL-23p19 mRNA were highly expressed in the

psoriatic skins (60). In the mouse study, intradermal injection of IL-23 induced a Th17-dependent psoriasis-like cutaneous inflammation (89, 90). Psoriatic mDCs have been demonstrated to produce IL-23, and functionally they were capable of proliferating and activating CD4⁺ T cells to produce IL-17A upon mixed leukocyte reactions (18, 82, 91, 92). Those mouse- and human-based studies essentially implicate the crucial role of IL-23 in the pathogenesis of psoriasis. Ustekinumab is an anti-IL-12p40 monoclonal antibody that binds to the p40 subunit of human IL-12 and IL-23, and prevents its interaction with IL-12Rβ1 (9, 93). The use of ustekinumab shows a significant efficacy for the treatment of psoriasis, and was recently approved by the FDA for biological therapeutics for psoriasis (94-96). Collectively, cytokine-producing mDCs of psoriasis are a central target for anti-psoriatic strategies, and recent clinical trials have provided a new avenue for the psoriasis treatments.

Although the phenotypic characteristics and functional properties of the psoriatic inflammatory mDCs have been extensively investigated, their precise cellular origins have not yet been elucidated. Zaba *et al.* have reported that those inflammatory Tip-DCs in the psoriatic dermis express CD11c myeloid marker, but are devoid of CD1c, that is, Tip-DCs are phenotypically CD11c⁺CD1c⁻ (82). This result indicates that psoriatic inflammatory DCs are different from CD1c⁺ resident dermal mDCs, in part due to a differential surface antigens expression. Zaba *et al.* also showed that TNF-related apoptosis-inducing ligand (TRAIL) was a marker for CD11c⁺CD1c⁻ inflammatory DCs, distinguishing them from CD1c⁺ resident mDCs identified using a transcriptome-based approach (97). However, principal component analysis revealed the close genomic similarity between psoriatic CD1c⁻ inflammatory and CD1c⁺ resident DCs, suggesting the possible progression of psoriatic inflammatory DCs from the skin-resident or blood-driven CD1c⁺ mDCs. Some researchers have demonstrated that 6-sulfo LacNAc DCs (slanDCs) are prominent cellular sources for TNF-α, iNOS, and IL-23 in the psoriatic dermis, and could induce the production of IL-17A from the CD4⁺ T cells after DC/T cell co-culture (98). In addition, treatment with anti-TNF-α antagonist infliximab led to the down-regulation of proinflammatory cytokines produced by slanDCs and suppressed their T cell-activating ability, indicating that slanDCs are a promising cellular target for anti-TNF-α therapies (99). Although the surface phenotype of slanDCs is similar to those of inflammatory DCs of psoriasis (i.e. CD11c⁺CD1c⁻), they characteristically express CD16, which is also detected on the human non-classical monocytes subsets (100). In addition, gene expression of CD16⁺ monocytes is comparable to mouse Gr-1 low monocytes, suggesting that CD16⁺ cells, including slanDCs, are actually monocytes rather than DCs (101). Thus, further investigations are needed to shed light on the cellular identity of the psoriatic inflammatory DCs.

LCs: a bystander?

Currently, the exact role of LCs in the pathogenesis of psoriatic inflammation has not been elucidated. Although the cellular number and morphology of LCs were comparable between the uninvolved skin of psoriasis and normal skin of healthy subjects, LCs residing in the uninvolved skin of the psoriatic patients revealed a defective migratory property in response to the various LC mobilization-inducing stimuli, including intradermal injection of IL-1β or TNF-α (102). Interestingly, according to the ages of onset for psoriasis, LCs in the uninvolved skin of early-onset psoriasis could respond to IL-1β; but those of late-onset psoriasis could not, indicating the important differences in LC function between early- and late-onset psoriasis (103). However, functional relevance for the migratory defects in psoriatic LCs remains to be determined.

CONCLUSION

Emerging studies have established the cutaneous DC networks, and highlighted their specific role for the skin immune homeostasis. Furthermore, there are expanding evidence regarding the pathophysiological role of cutaneous DC subsets in the psoriasis pathogenesis clarified by the recent elegant efforts. It is now clear that cutaneous DCs are specifically involved in the cascade of psoriatic inflammation, and they are attractive targets for the current psoriasis treatment. Future studies should focus on the elucidation of cellular origin, recruitment mechanisms, and other uncharacterized functions of the DC subsets present in psoriasis to develop new therapeutic modalities against chronic psoriasis.

ACKNOWLEDGEMENTS

This work was supported by a grant of the Korea Health technology R&D Project, Ministry of Health & Welfare, Republic of Korea (A121795 to M.-G. Lee) and the National Research Foundation of Korea (NRF) grants funded by the Korea government (MSIP) (numbers; NRF-2011K1A3A1A08665090 to M.-G. Lee; NRF-2011-0030086, 2012M3A9B4028272, and NRF-2013R1A1A2008812 to H.-P. Kim). The authors thank Dong-Su Jang for his excellent support with medical illustration.

REFERENCES

1. Christophers, E. (2001) Psoriasis—epidemiology and clinical spectrum. *Clin. Exp. Dermatol.* **26**, 314-320.
2. Lew, W., Lee, E. and Krueger, J. G. (2004) Psoriasis genomics: analysis of proinflammatory (type 1) gene expression in large plaque (Western) and small plaque (Asian) psoriasis vulgaris. *Br. J. Dermatol.* **150**, 668-676.
3. Tsai, T. F., Wang, T. S., Hung, S. T., Tsai, P. I., Schenkel, B., Zhang, M. and Tang, C. H. (2011) Epidemiology and comorbidities of psoriasis patients in a national database in Taiwan. *J. Dermatol. Sci.* **63**, 40-46.
4. Lowes, M. A., Bowcock, A. M. and Krueger, J. G. (2007)

- Pathogenesis and therapy of psoriasis. *Nature* **445**, 866-873.
- Davidovici, B. B., Sattar, N., Prinz, J., Puig, L., Emery, P., Barker, J. N., van de Kerkhof, P., Stahle, M., Nestle, F. O., Girolomoni, G. and Krueger, J. G. (2010) Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. *J. Invest. Dermatol.* **130**, 1785-1796.
 - Gottlieb, A. B. and Dann, F. (2009) Comorbidities in patients with psoriasis. *Am. J. Med.* **122**, 1150 e1151-1159.
 - Kim, N., Thrash, B. and Menter, A. (2010) Comorbidities in psoriasis patients. *Semin. Cutan. Med. Surg.* **29**, 10-15.
 - Ahmed, A., Leon, A., Butler, D. C. and Reichenberg, J. (2013) Quality-of-life effects of common dermatological diseases. *Semin. Cutan. Med. Surg.* **32**, 101-109.
 - Nestle, F. O., Kaplan, D. H. and Barker, J. (2009) Psoriasis. *N. Engl. J. Med.* **361**, 496-509.
 - Ghoreschi, K., Weigert, C. and Rocken, M. (2007) Immunopathogenesis and role of T cells in psoriasis. *Clin. Dermatol.* **25**, 574-580.
 - Lew, W., Bowcock, A. M. and Krueger, J. G. (2004) Psoriasis vulgaris: cutaneous lymphoid tissue supports T-cell activation and "Type 1" inflammatory gene expression. *Trends Immunol.* **25**, 295-305.
 - Biedermann, T., Rocken, M. and Carballido, J. M. (2004) TH1 and TH2 lymphocyte development and regulation of TH cell-mediated immune responses of the skin. *J. Invest. Dermatol. Symp. Proc.* **9**, 5-14.
 - Di Cesare, A., Di Meglio, P. and Nestle, F. O. (2009) The IL-23/Th17 axis in the immunopathogenesis of psoriasis. *J. Invest. Dermatol.* **129**, 1339-1350.
 - Martin, D. A., Towne, J. E., Kricorian, G., Klekotka, P., Gudjonsson, J. E., Krueger, J. G. and Russell, C. B. (2013) The emerging role of IL-17 in the pathogenesis of psoriasis: preclinical and clinical findings. *J. Invest. Dermatol.* **133**, 17-26.
 - Miossec, P., Korn, T. and Kuchroo, V. K. (2009) Interleukin-17 and type 17 helper T cells. *N. Engl. J. Med.* **361**, 888-898.
 - Weaver, C. T., Elson, C. O., Fouser, L. A. and Kolls, J. K. (2013) The Th17 pathway and inflammatory diseases of the intestines, lungs, and skin. *Annu. Rev. Pathol.* **8**, 477-512.
 - Lee, Y. (2013) The role of interleukin-17 in bone metabolism and inflammatory skeletal diseases. *BMB Rep.* **46**, 479-483.
 - Lee, E., Trepicchio, W. L., Oestreicher, J. L., Pittman, D., Wang, F., Chamian, F., Dhodapkar, M. and Krueger, J. G. (2004) Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. *J. Exp. Med.* **199**, 125-130.
 - Lowes, M. A., Kikuchi, T., Fuentes-Duculan, J., Cardinale, I., Zaba, L. C., Haider, A. S., Bowman, E. P. and Krueger, J. G. (2008) Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. *J. Invest. Dermatol.* **128**, 1207-1211.
 - Leonardi, C., Matheson, R., Zachariae, C., Cameron, G., Li, L., Edson-Heredia, E., Braun, D. and Banerjee, S. (2012) Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N. Engl. J. Med.* **366**, 1190-1199.
 - Papp, K. A., Leonardi, C., Menter, A., Ortonne, J. P., Krueger, J. G., Kricorian, G., Aras, G., Li, J., Russell, C. B., Thompson, E. H. and Baumgartner, S. (2012) Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N. Engl. J. Med.* **366**, 1181-1189.
 - Bos, J. D., Hagens, C., Das, P. K., Krieg, S. R., Voorn, W. J. and Kapsenberg, M. L. (1989) Predominance of "memory" T cells (CD4+, CDw29+) over "naive" T cells (CD4+, CD45R+) in both normal and diseased human skin. *Arch. Dermatol. Res.* **281**, 24-30.
 - Chang, E. Y., Hammerberg, C., Fisher, G., Baadsgaard, O., Ellis, C. N., Voorhees, J. J. and Cooper, K. D. (1992) T-cell activation is potentiated by cytokines released by lesional psoriatic, but not normal, epidermis. *Arch. Dermatol.* **128**, 1479-1485.
 - Banchereau, J. and Steinman, R. M. (1998) Dendritic cells and the control of immunity. *Nature* **392**, 245-252.
 - Steinman, R. M. (2012) Decisions about dendritic cells: past, present, and future. *Annu. Rev. Immunol.* **30**, 1-22.
 - Lee, M. Y., Shin, M. C. and Yang, V. C. (2013) Transcutaneous antigen delivery system. *BMB Rep.* **46**, 17-24.
 - Johnson-Huang, L. M., McNutt, N. S., Krueger, J. G. and Lowes, M. A. (2009) Cytokine-producing dendritic cells in the pathogenesis of inflammatory skin diseases. *J. Clin. Immunol.* **29**, 247-256.
 - Zaba, L. C., Krueger, J. G. and Lowes, M. A. (2009) Resident and "inflammatory" dendritic cells in human skin. *J. Invest. Dermatol.* **129**, 302-308.
 - Collin, M., McGovern, N. and Haniffa, M. (2013) Human dendritic cell subsets. *Immunology* **140**, 22-30.
 - Romani, N., Brunner, P. M. and Stingl, G. (2012) Changing views of the role of Langerhans cells. *J. Invest. Dermatol.* **132**, 872-881.
 - Hunger, R. E., Sieling, P. A., Ochoa, M. T., Sugaya, M., Burdick, A. E., Rea, T. H., Brennan, P. J., Belisle, J. T., Blauvelt, A., Porcelli, S. A. and Modlin, R. L. (2004) Langerhans cells utilize CD1a and langerin to efficiently present nonpeptide antigens to T cells. *J. Clin. Invest.* **113**, 701-708.
 - Breathnach, A. S. and Wyllie, L. M. (1965) Electron Microscopy of Melanocytes and Langerhans Cells in Human Fetal Epidermis at Fourteen Weeks. *J. Invest. Dermatol.* **44**, 51-60.
 - Valladeau, J., Ravel, O., Dezutter-Dambuyant, C., Moore, K., Kleijmeer, M., Liu, Y., Duvert-Frances, V., Vincent, C., Schmitt, D., Davoust, J., Caux, C., Lebecque, S. and Saeland, S. (2000) Langerin, a novel C-type lectin specific to Langerhans cells, is an endocytic receptor that induces the formation of Birbeck granules. *Immunity* **12**, 71-81.
 - Merad, M., Manz, M. G., Karsunky, H., Wagers, A., Peters, W., Charo, I., Weissman, I. L., Cyster, J. G. and Engleman, E. G. (2002) Langerhans cells renew in the skin throughout life under steady-state conditions. *Nat. Immunol.* **3**, 1135-1141.
 - Igyarto, B. Z. and Kaplan, D. H. (2010) The evolving function of Langerhans cells in adaptive skin immunity. *Immunol. Cell Biol.* **88**, 361-365.

36. Fujita, H., Nograles, K. E., Kikuchi, T., Gonzalez, J., Carucci, J. A. and Krueger, J. G. (2009) Human Langerhans cells induce distinct IL-22-producing CD4+ T cells lacking IL-17 production. *Proc. Natl. Acad. Sci. U. S. A.* **106**, 21795-21800.
37. de Jong, A., Pena-Cruz, V., Cheng, T. Y., Clark, R. A., Van Rhijn, I. and Moody, D. B. (2010) CD1a-auroractive T cells are a normal component of the human alpha-beta T cell repertoire. *Nat. Immunol.* **11**, 1102-1109.
38. Seneschal, J., Clark, R. A., Gehad, A., Baecher-Allan, C. M. and Kupper, T. S. (2012) Human epidermal Langerhans cells maintain immune homeostasis in skin by activating skin resident regulatory T cells. *Immunity* **36**, 873-884.
39. Zaba, L. C., Fuentes-Duculan, J., Steinman, R. M., Krueger, J. G. and Lowes, M. A. (2007) Normal human dermis contains distinct populations of CD11c+BDCA-1+ dendritic cells and CD163+FXIIIa+ macrophages. *J. Clin. Invest.* **117**, 2517-2525.
40. Cerio, R., Griffiths, C. E., Cooper, K. D., Nickoloff, B. J. and Headington, J. T. (1989) Characterization of factor XIIIa positive dermal dendritic cells in normal and inflamed skin. *Br. J. Dermatol.* **121**, 421-431.
41. Meunier, L., Gonzalez-Ramos, A. and Cooper, K. D. (1993) Heterogeneous populations of class II MHC+ cells in human dermal cell suspensions. Identification of a small subset responsible for potent dermal antigen-presenting cell activity with features analogous to Langerhans cells. *J. Immunol.* **151**, 4067-4080.
42. Morelli, A. E., Rubin, J. P., Erdos, G., Tkacheva, O. A., Mathers, A. R., Zahorchak, A. F., Thomson, A. W., Falo, L. D. Jr. and Larregina, A. T. (2005) CD4+ T cell responses elicited by different subsets of human skin migratory dendritic cells. *J. Immunol.* **175**, 7905-7915.
43. Mathers, A. R., Janelins, B. M., Rubin, J. P., Tkacheva, O. A., Shufesky, W. J., Watkins, S. C., Morelli, A. E. and Larregina, A. T. (2009) Differential capability of human cutaneous dendritic cell subsets to initiate Th17 responses. *J. Immunol.* **182**, 921-933.
44. Furio, L., Briotet, I., Joumeaux, A., Billard, H. and Peguet-Navarro, J. (2010) Human langerhans cells are more efficient than CD14(-)CD1c(+) dermal dendritic cells at priming naive CD4(+) T cells. *J. Invest. Dermatol.* **130**, 1345-1354.
45. Penel-Sotirakis, K., Simonazzi, E., Peguet-Navarro, J. and Rozieres, A. (2012) Differential capacity of human skin dendritic cells to polarize CD4+ T cells into IL-17, IL-21 and IL-22 producing cells. *PLoS One* **7**, e45680.
46. Haniffa, M., Shin, A., Bigley, V., McGovern, N., Teo, P., See, P., Wasan, P. S., Wang, X. N., Malinarich, F., Malleret, B., Larbi, A., Tan, P., Zhao, H., Poidinger, M., Pagan, S., Cookson, S., Dickinson, R., Dimmick, I., Jarrett, R. F., Renia, L., Tam, J., Song, C., Connolly, J., Chan, J. K., Gehring, A., Bertoletti, A., Collin, M. and Ginhoux, F. (2012) Human tissues contain CD141hi cross-presenting dendritic cells with functional homology to mouse CD103+ nonlymphoid dendritic cells. *Immunity* **37**, 60-73.
47. MacDonald, K. P., Munster, D. J., Clark, G. J., Dzionek, A., Schmitz, J. and Hart, D. N. (2002) Characterization of human blood dendritic cell subsets. *Blood* **100**, 4512-4520.
48. Bachem, A., Guttler, S., Hartung, E., Ebstein, F., Schaefer, M., Tannert, A., Salama, A., Movassaghi, K., Opitz, C., Mages, H. W., Henn, V., Kloetzel, P. M., Gurka, S. and Kroczeck, R. A. (2010) Superior antigen cross-presentation and XCR1 expression define human CD11c+CD141+ cells as homologues of mouse CD8+ dendritic cells. *J. Exp. Med.* **207**, 1273-1281.
49. Crozat, K., Guiton, R., Contreras, V., Feuillet, V., Dutertre, C. A., Ventre, E., Vu Manh, T. P., Baranek, T., Storset, A. K., Marvel, J., Boudinot, P., Hosmalin, A., Schwartz-Cornil, I. and Dalod, M. (2010) The XC chemokine receptor 1 is a conserved selective marker of mammalian cells homologous to mouse CD8alpha+ dendritic cells. *J. Exp. Med.* **207**, 1283-1292.
50. Jongbloed, S. L., Kassianos, A. J., McDonald, K. J., Clark, G. J., Ju, X., Angel, C. E., Chen, C. J., Dunbar, P. R., Wadley, R. B., Jeet, V., Vulink, A. J., Hart, D. N. and Radford, K. J. (2010) Human CD141+ (BDCA-3)+ dendritic cells (DCs) represent a unique myeloid DC subset that cross-presents necrotic cell antigens. *J. Exp. Med.* **207**, 1247-1260.
51. Shortman, K. and Heath, W. R. (2010) The CD8+ dendritic cell subset. *Immunol. Rev.* **234**, 18-31.
52. Sancho, D., Joffre, O. P., Keller, A. M., Rogers, N. C., Martinez, D., Hernandez-Falcon, P., Rosewell, I. and Reis e Sousa, C. (2009) Identification of a dendritic cell receptor that couples sensing of necrosis to immunity. *Nature* **458**, 899-903.
53. Dorner, B. G., Dorner, M. B., Zhou, X., Opitz, C., Mora, A., Guttler, S., Hutloff, A., Mages, H. W., Ranke, K., Schaefer, M., Jack, R. S., Henn, V. and Kroczeck, R. A. (2009) Selective expression of the chemokine receptor XCR1 on cross-presenting dendritic cells determines co-operation with CD8+ T cells. *Immunity* **31**, 823-833.
54. Corcoran, L., Ferrero, I., Vremec, D., Lucas, K., Waithman, J., O'Keeffe, M., Wu, L., Wilson, A. and Shortman, K. (2003) The lymphoid past of mouse plasmacytoid cells and thymic dendritic cells. *J. Immunol.* **170**, 4926-4932.
55. Reizis, B., Bunin, A., Ghosh, H. S., Lewis, K. L. and Sisirak, V. (2011) Plasmacytoid dendritic cells: recent progress and open questions. *Annu. Rev. Immunol.* **29**, 163-183.
56. Siegal, F. P., Kadowaki, N., Shodell, M., Fitzgerald-Bocarsly, P. A., Shah, K., Ho, S., Antonenko, S. and Liu, Y. J. (1999) The nature of the principal type 1 interferon-producing cells in human blood. *Science* **284**, 1835-1837.
57. Matta, B. M., Castellaneta, A. and Thomson, A. W. (2010) Tolerogenic plasmacytoid DC. *Eur. J. Immunol.* **40**, 2667-2676.
58. Ebner, S., Ehammer, Z., Holzmann, S., Schwingshackl, P., Forstner, M., Stoitzner, P., Huemer, G. M., Fritsch, P. and Romani, N. (2004) Expression of C-type lectin receptors by subsets of dendritic cells in human skin. *Int. Immunol.* **16**, 877-887.
59. Lowes, M. A., Chamian, F., Abello, M. V., Fuentes-Duculan, J., Lin, S. L., Nussbaum, R.,

- Novitskaya, I., Carbonaro, H., Cardinale, I., Kikuchi, T., Gilleaudeau, P., Sullivan-Whalen, M., Wittkowski, K. M., Papp, K., Garovoy, M., Dummer, W., Steinman, R. M. and Krueger, J. G. (2005) Increase in TNF-alpha and inducible nitric oxide synthase-expressing dendritic cells in psoriasis and reduction with efalizumab (anti-CD11a). *Proc. Natl. Acad. Sci. U. S. A.* **102**, 19057-19062.
60. Zaba, L. C., Cardinale, I., Gilleaudeau, P., Sullivan-Whalen, M., Suarez-Farinas, M., Fuentes-Duculan, J., Novitskaya, I., Khatcherian, A., Bluth, M. J., Lowes, M. A. and Krueger, J. G. (2007) Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. *J. Exp. Med.* **204**, 3183-3194.
61. Nograles, K. E., Davidovici, B. and Krueger, J. G. (2010) New insights in the immunologic basis of psoriasis. *Semin. Cutan. Med. Surg.* **29**, 3-9.
62. Carragher, D. M., Rangel-Moreno, J. and Randall, T. D. (2008) Ectopic lymphoid tissues and local immunity. *Semin. Immunol.* **20**, 26-42.
63. Morganroth, G. S., Chan, L. S., Weinstein, G. D., Voorhees, J. J. and Cooper, K. D. (1991) Proliferating cells in psoriatic dermis are comprised primarily of T cells, endothelial cells, and factor XIIIa+ perivascular dendritic cells. *J. Invest. Dermatol.* **96**, 333-340.
64. Guttman-Yassky, E., Nograles, K. E. and Krueger, J. G. (2011) Contrasting pathogenesis of atopic dermatitis and psoriasis—part II: immune cell subsets and therapeutic concepts. *J. Allergy Clin. Immunol.* **127**, 1420-1432.
65. Nestle, F. O., Turka, L. A. and Nickoloff, B. J. (1994) Characterization of dermal dendritic cells in psoriasis. Autostimulation of T lymphocytes and induction of Th1 type cytokines. *J. Clin. Invest.* **94**, 202-209.
66. Miller, G. T., Hochman, P. S., Meier, W., Tizard, R., Bixler, S. A., Rosa, M. D. and Wallner, B. P. (1993) Specific interaction of lymphocyte function-associated antigen 3 with CD2 can inhibit T cell responses. *J. Exp. Med.* **178**, 211-222.
67. Ellis, C. N. and Krueger, G. G. (2001) Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. *N. Engl. J. Med.* **345**, 248-255.
68. Chamian, F., Lowes, M. A., Lin, S. L., Lee, E., Kikuchi, T., Gilleaudeau, P., Sullivan-Whalen, M., Cardinale, I., Khatcherian, A., Novitskaya, I., Wittkowski, K. M. and Krueger, J. G. (2005) Alefacept reduces infiltrating T cells, activated dendritic cells, and inflammatory genes in psoriasis vulgaris. *Proc. Natl. Acad. Sci. U. S. A.* **102**, 2075-2080.
69. Grakoui, A., Bromley, S. K., Sumen, C., Davis, M. M., Shaw, A. S., Allen, P. M. and Dustin, M. L. (1999) The immunological synapse: a molecular machine controlling T cell activation. *Science* **285**, 221-227.
70. Lebwohl, M., Tying, S. K., Hamilton, T. K., Toth, D., Glazer, S., Tawfik, N. H., Walicke, P., Dummer, W., Wang, X., Garovoy, M. R. and Pariser, D. (2003) A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. *N. Engl. J. Med.* **349**, 2004-2013.
71. Sallusto, F., Mackay, C. R. and Lanzavecchia, A. (2000) The role of chemokine receptors in primary, effector, and memory immune responses. *Annu. Rev. Immunol.* **18**, 593-620.
72. Nickoloff, B. J., Xin, H., Nestle, F. O. and Qin, J. Z. (2007) The cytokine and chemokine network in psoriasis. *Clin. Dermatol.* **25**, 568-573.
73. Homey, B. and Meller, S. (2008) Chemokines and other mediators as therapeutic targets in psoriasis vulgaris. *Clin. Dermatol.* **26**, 539-545.
74. Mitsui, H., Suarez-Farinas, M., Belkin, D. A., Levenkova, N., Fuentes-Duculan, J., Coats, I., Fujita, H. and Krueger, J. G. (2012) Combined use of laser capture microdissection and cDNA microarray analysis identifies locally expressed disease-related genes in focal regions of psoriasis vulgaris skin lesions. *J. Invest. Dermatol.* **132**, 1615-1626.
75. Kim, T. G., Jee, H., Fuentes-Duculan, J., Wu, W. H., Byamba, D., Kim, D. S., Kim, D. Y., Lew, D. H., Yang, W. I., Krueger, J. G. and Lee, M. G. (2013) Dermal Clusters of Mature Dendritic Cells and T Cells Are Associated with the CCL20/CCR6 Chemokine System in Chronic Psoriasis. *J. Invest. Dermatol.* 10.1038/jid.2013.534.
76. Ganguly, D., Chamilos, G., Lande, R., Gregorio, J., Meller, S., Facchinetti, V., Homey, B., Barrat, F. J., Zal, T. and Gilliet, M. (2009) Self-RNA-antimicrobial peptide complexes activate human dendritic cells through TLR7 and TLR8. *J. Exp. Med.* **206**, 1983-1994.
77. Wollenberg, A., Wagner, M., Gunther, S., Towarowski, A., Tuma, E., Moderer, M., Rothenfusser, S., Wetzels, S., Endres, S. and Hartmann, G. (2002) Plasmacytoid dendritic cells: a new cutaneous dendritic cell subset with distinct role in inflammatory skin diseases. *J. Invest. Dermatol.* **119**, 1096-1102.
78. Gilliet, M., Conrad, C., Geiges, M., Cozzio, A., Thurlimann, W., Burg, G., Nestle, F. O. and Dummer, R. (2004) Psoriasis triggered by toll-like receptor 7 agonist imiquimod in the presence of dermal plasmacytoid dendritic cell precursors. *Arch. Dermatol.* **140**, 1490-1495.
79. Nestle, F. O., Conrad, C., Tun-Kyi, A., Homey, B., Gombert, M., Boyman, O., Burg, G., Liu, Y. J. and Gilliet, M. (2005) Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. *J. Exp. Med.* **202**, 135-143.
80. Lande, R., Gregorio, J., Facchinetti, V., Chatterjee, B., Wang, Y. H., Homey, B., Cao, W., Wang, Y. H., Su, B., Nestle, F. O., Zal, T., Mellman, I., Schroder, J. M., Liu, Y. J. and Gilliet, M. (2007) Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. *Nature* **449**, 564-569.
81. Chu, C. C., Di Meglio, P. and Nestle, F. O. (2011) Harnessing dendritic cells in inflammatory skin diseases. *Semin. Immunol.* **23**, 28-41.
82. Zaba, L. C., Fuentes-Duculan, J., Eungdamrong, N. J., Abello, M. V., Novitskaya, I., Pierson, K. C., Gonzalez, J., Krueger, J. G. and Lowes, M. A. (2009) Psoriasis is characterized by accumulation of immunostimulatory and Th1/Th17 cell-polarizing myeloid dendritic cells. *J. Invest. Dermatol.* **129**, 79-88.
83. Abrams, J. R., Kelley, S. L., Hayes, E., Kikuchi, T., Brown, M. J., Kang, S., Lebwohl, M. G., Guzzo, C. A., Jegasothy, B. V., Linsley, P. S. and Krueger, J. G. (2000) Blockade of T lymphocyte costimulation with cytotoxic T lymphocyte-associated antigen 4-immunoglobulin

- (CTLA4Ig) reverses the cellular pathology of psoriatic plaques, including the activation of keratinocytes, dendritic cells, and endothelial cells. *J. Exp. Med.* **192**, 681-694.
84. Nickoloff, B. J., Karabin, G. D., Barker, J. N., Griffiths, C. E., Sarma, V., Mitra, R. S., Elder, J. T., Kunkel, S. L. and Dixit, V. M. (1991) Cellular localization of interleukin-8 and its inducer, tumor necrosis factor-alpha in psoriasis. *Am. J. Pathol.* **138**, 129-140.
85. Serbina, N. V., Salazar-Mather, T. P., Biron, C. A., Kuziel, W. A. and Pamer, E. G. (2003) TNF/iNOS-producing dendritic cells mediate innate immune defense against bacterial infection. *Immunity* **19**, 59-70.
86. Leonardi, C. L., Powers, J. L., Matheson, R. T., Goffe, B. S., Zitnik, R., Wang, A., Gottlieb, A. B. and Etanercept Psoriasis Study, G. (2003) Etanercept as monotherapy in patients with psoriasis. *N. Engl. J. Med.* **349**, 2014-2022.
87. Nograles, K. E. and Krueger, J. G. (2011) Anti-cytokine therapies for psoriasis. *Exp. Cell Res.* **317**, 1293-1300.
88. Annunziato, F., Cosmi, L., Santarlasci, V., Maggi, L., Liotta, F., Mazzinghi, B., Parente, E., Fili, L., Ferri, S., Frosali, F., Giudici, F., Romagnani, P., Parronchi, P., Tonelli, F., Maggi, E. and Romagnani, S. (2007) Phenotypic and functional features of human Th17 cells. *J. Exp. Med.* **204**, 1849-1861.
89. Chan, J. R., Blumenschein, W., Murphy, E., Diveu, C., Wiekowski, M., Abbondanzo, S., Lucian, L., Geissler, R., Brodie, S., Kimball, A. B., Gorman, D. M., Smith, K., de Waal Malefyt, R., Kastelein, R. A., McClanahan, T. K. and Bowman, E. P. (2006) IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2-dependent mechanisms with implications for psoriasis pathogenesis. *J. Exp. Med.* **203**, 2577-2587.
90. Zheng, Y., Danilenko, D. M., Valdez, P., Kasman, I., Eastham-Anderson, J., Wu, J. and Ouyang, W. (2007) Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature* **445**, 648-651.
91. Yawalkar, N., Tscherner, G. G., Hunger, R. E. and Hassan, A. S. (2009) Increased expression of IL-12p70 and IL-23 by multiple dendritic cell and macrophage subsets in plaque psoriasis. *J. Dermatol. Sci.* **54**, 99-105.
92. Fujita, H., Shemer, A., Suarez-Farinas, M., Johnson-Huang, L. M., Tintle, S., Cardinale, I., Fuentes-Duculan, J., Novitskaya, I., Carucci, J. A., Krueger, J. G. and Guttman-Yassky, E. (2011) Lesional dendritic cells in patients with chronic atopic dermatitis and psoriasis exhibit parallel ability to activate T-cell subsets. *J. Allergy Clin. Immunol.* **128**, 574-582 e512.
93. Reich, K., Yasothan, U. and Kirkpatrick, P. (2009) Ustekinumab. *Nat. Rev. Drug. Discov.* **8**, 355-356.
94. Leonardi, C. L., Kimball, A. B., Papp, K. A., Yeilding, N., Guzzo, C., Wang, Y., Li, S., Dooley, L. T. and Gordon, K. B. (2008) Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* **371**, 1665-1674.
95. Papp, K. A., Langley, R. G., Lebwohl, M., Krueger, G. G., Szapary, P., Yeilding, N., Guzzo, C., Hsu, M. C., Wang, Y., Li, S., Dooley, L. T., Reich, K. and investigators, P. s. (2008) Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* **371**, 1675-1684.
96. Kim, I. H., West, C. E., Kwatra, S. G., Feldman, S. R. and O'Neill, J. L. (2012) Comparative efficacy of biologics in psoriasis: a review. *Am. J. Clin. Dermatol.* **13**, 365-374.
97. Zaba, L. C., Fuentes-Duculan, J., Eungdamrong, N. J., Johnson-Huang, L. M., Nograles, K. E., White, T. R., Pierson, K. C., Lentini, T., Suarez-Farinas, M., Lowes, M. A. and Krueger, J. G. (2010) Identification of TNF-related apoptosis-inducing ligand and other molecules that distinguish inflammatory from resident dendritic cells in patients with psoriasis. *J. Allergy Clin. Immunol.* **125**, 1261-1268 e1269.
98. Hansel, A., Gunther, C., Ingwersen, J., Starke, J., Schmitz, M., Bachmann, M., Meurer, M., Rieber, E. P. and Schakel, K. (2011) Human slan (6-sulfo LacNAc) dendritic cells are inflammatory dermal dendritic cells in psoriasis and drive strong TH17/TH1 T-cell responses. *J. Allergy Clin. Immunol.* **127**, 787-794 e781-789.
99. Brunner, P. M., Koszik, F., Reininger, B., Kalb, M. L., Bauer, W. and Stingl, G. (2013) Infliximab induces downregulation of the IL-12/IL-23 axis in 6-sulfo-LacNAc (slan)+ dendritic cells and macrophages. *J. Allergy Clin. Immunol.* **132**, 1184-1193 e1188.
100. Ziegler-Heitbrock, L., Ancuta, P., Crowe, S., Dalod, M., Grau, V., Hart, D. N., Leenen, P. J., Liu, Y. J., MacPherson, G., Randolph, G. J., Scherberich, J., Schmitz, J., Shortman, K., Sozzani, S., Strobl, H., Zembala, M., Austyn, J. M. and Lutz, M. B. (2010) Nomenclature of monocytes and dendritic cells in blood. *Blood* **116**, e74-80.
101. Cros, J., Cagnard, N., Woollard, K., Patey, N., Zhang, S. Y., Senechal, B., Puel, A., Biswas, S. K., Moshous, D., Picard, C., Jais, J. P., D'Cruz, D., Casanova, J. L., Trouillet, C. and Geissmann, F. (2010) Human CD14dim monocytes patrol and sense nucleic acids and viruses via TLR7 and TLR8 receptors. *Immunity* **33**, 375-386.
102. Cumberbatch, M., Singh, M., Dearman, R. J., Young, H. S., Kimber, I. and Griffiths, C. E. (2006) Impaired Langerhans cell migration in psoriasis. *J. Exp. Med.* **203**, 953-960.
103. Shaw, F. L., Cumberbatch, M., Kleyn, C. E., Begum, R., Dearman, R. J., Kimber, I. and Griffiths, C. E. (2010) Langerhans cell mobilization distinguishes between early-onset and late-onset psoriasis. *J. Invest. Dermatol.* **130**, 1940-1942.