Published in final edited form as:

J Clin Immunol. 2009 May ; 29(3): 247–256. doi:10.1007/s10875-009-9278-8.

Cytokine-producing dendritic cells in the pathogenesis of inflammatory skin diseases

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Abstract

Inflammatory skin diseases can be examined from many viewpoints. In this review, we consider three distinct cutaneous inflammatory diseases from the point of view of their major lesional dendritic cell (DC) subpopulations. The DC populations considered are Langerhans cells, myeloid DCs, and plasmacytoid DCs (pDCs), with specific attention to the presence and role of the inflammatory counterparts of these cells. From such a “dendritic cell-centric” focus, psoriasis, atopic dermatitis (AD), and cutaneous lupus erythematosus (CLE) are explored. In psoriasis, there is a specific population of myeloid “inflammatory” DCs that appears to play an important pathogenic role, while pDCs have been recently implicated in the initiation of psoriatic lesions. In AD, Langerhans cells may be important during initiation, while “inflammatory dendritic epidermal cells” (IDECs) appear to be abundant in lesional epidermis and dermis and contribute to maintenance of AD. These IDECs may actually be analogous to the myeloid inflammatory DCs found in the epidermal and dermal compartments of the skin in psoriasis, although they express distinct surface markers and induce different T cell polarities as a result of different cytokine milieu in which they develop. CLE has been recently characterized as a type I IFN-mediated disease, and pDCs are integral to the pathogenesis of this disease. Thus these DC subpopulations and their products will be reviewed in the context of these three cutaneous diseases, to provide clinico-pathophysiological correlations between the lesional DC, their products, and the skin diseases.

Keywords

Dendritic cell; cytokine; skin; inflammation; psoriasis; atopic dermatitis

Introduction

The accessibility of the skin for biopsies has facilitated research into the complex immune pathways that initiate and maintain autoimmune and inflammatory diseases. Our laboratory has focused on the role of DCs in steady state skin and in cutaneous inflammation, as well as their interactions with T cells. Cutaneous DCs have been distinguished based on the expression of a number of surface molecules. In normal skin, four main populations have been identified: epidermal Langerhans cells (Langerin⁺, CD1a⁺), resident dermal myeloid DCs (CD11c⁺, CD1c⁺), pDCs (BDCA-2⁺, CD123⁺), and a recently identified dermal population of CD14⁺ CD11c⁺ DCs [1,2]. Langerhans cells are the predominant DC population in the epidermis and are thus the first line of defense against antigens that penetrate the skin [3]. Their main role is

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The authors do not have any financial interest related to this work.

to take up and process antigens, migrate to local skin-draining lymph nodes, where they present to antigen-specific T cells. In the normal dermis, myeloid CD11c⁺ DCs are relatively immature and have a moderate T cell stimulatory capacity, which can be enhanced by maturation stimuli [4]. Myeloid DCs have a similar migratory capacity for antigen presentation. pDCs are the major DC subtype that responds to viral infection, and although dermal pDCs can also present antigens to T cells, they are primarily characterized by their ability to produce type I interferons (IFN- α/β) [5].

Here, we review the contributions of these “resident” DC populations, and additional “inflammatory” DC subtypes to three prototypical inflammatory skin diseases, psoriasis, AD, and CLE. A characteristic feature of inflammatory skin diseases is the presence of additional populations of DCs, giving each disease a particular DC profile. For example, the inflammatory infiltrate in psoriatic and AD lesions contains a considerable number of myeloid CD11c⁺ DCs [6,7]. In psoriasis, myeloid CD11c⁺ DCs can be further subdivided based on expression of CD1c; steady state skin has a predominance of CD11c⁺ CD1c⁺ resident DCs while during inflammation, a population of CD11c⁺ CD1c⁻ DCs, which we termed myeloid “inflammatory” DCs is also seen [4]. Investigation of the DC populations in CLE revealed the numbers of pDCs in lesional skin were dramatically increased compared to normal skin [8–10]. All in all, these studies demonstrate that different pathological outcomes of skin inflammation may be associated with the presence of different DC subtypes.

DCs can contribute to inflammatory processes through the activation of antigen-specific T cells. Both the type of DC and the inflammatory environment in which DCs become activated can influence the type of T cell response they elicit. Psoriasis lesions have increased frequencies of IFN- γ -producing Th1 and Th17 cells producing IL-17 and IL-22 [11]. Recently, a population of CD8⁺ T cells producing IL-17 has been described in the epidermis of psoriasis lesions [12]. In comparison, acute AD lesions have predominantly IL-4-producing Th2 cells, and chronic AD lesions are mainly Th2 polarized but some Th1 cells are also activated. [13]. Depending on the type of lupus erythematosus, outlined further below, cutaneous lesions can contain predominantly Th1 cells (discoid LE [14]) or both Th1 and Th2 cells (systemic LE and acute CLE [15,16]). Thus, understanding the immune pathways that control the differentiation, recruitment, and maintenance of polarized helper T cells is of great relevance. Here, we review the types of DCs in the skin with particular focus on the cytokines and chemokines they produce and how they help to shape the immune response during skin inflammation.

Psoriasis

Psoriasis vulgaris, the most common type of psoriasis, is a chronic inflammatory skin disease characterized by red scaly patches. These lesions may be confined to commonly affected areas such as the elbows, knees and scalp, or may be scattered over the whole body area. Psoriasis affects 1–2% of the population of North America, representing approximately 3–6 million people.

The histological appearance of normal skin (Figure 1A) will be briefly described so that the changes that occur in the skin during inflammation can be appreciated. The skin can be divided into an upper outer layer of constantly reproducing keratinocyte cells called the epidermis. Within the epidermis, there are also melanocytes, cells that make pigment, and Langerhans cells, antigen presenting cells of the epidermis. The dermis is a supporting layer beneath the epidermis, containing fibroblasts producing collagen and elastin, as well as resident leukocytes such as myeloid DCs and T cells.

There is a characteristic histopathology in psoriasis (Figure 1B). The epidermis is greatly thickened (termed acanthosis) with elongation of the rete ridges that protrude down into the thickened papillary dermis. This epidermal thickening is due to a dramatic increase in the

proliferation of psoriatic keratinocytes at the base of the epidermis. This leads to reduced maturation of the cells as they journey outward, and retention of keratinocyte nuclei, which can be seen in the scaly layer (the stratum corneum) as parakeratosis. Collections of neutrophils can also be seen in the epidermis and stratum corneum. These histological features give rise to the characteristic clinical observation of “silvery scale” shown by almost all psoriasis lesions. In the dermis, there is elongation and dilation of the dermal blood vessels that protrude up between the rete ridges, giving rise to the red color of psoriasis lesions. These dermal blood vessels and surrounding upper dermal spaces are filled with leukocytes, including DCs, T cells, and neutrophils.

An interesting feature of psoriasis skin lesions is that successful treatment may clear lesions without any residual clinical changes. This is in contrast to other skin diseases such as CLE where there may be atrophy or scarring. The return of normal-appearing skin after resolution of psoriatic lesions may be due to the preservation of the dermo-epidermal junction, a fine structure between the epidermis and dermis, composed of many specialized proteins responsible for keeping the epidermis attached to the dermis.

Myeloid “inflammatory” DCs

In psoriasis lesions, the dermal inflammatory infiltrate is composed of roughly equivalent numbers of DCs and T cells, representing an almost 30-fold increase in CD11c⁺ DCs compared to normal skin [6]. This increase in myeloid DCs is in the “inflammatory” CD1c⁺ population, not the CD1c⁺ DCs found in normal skin [4]. A large proportion of these DCs express tumor necrosis factor (TNF) and the enzyme inducible nitric oxide synthase (iNOS) [17]. These DCs have been proposed to be equivalent to TIP-DCs (TNF- and iNOS-producing DCs), cells that are important in bacterial clearance in mice [18]. Using immunofluorescence, our group has demonstrated that most of the psoriatic TIP-DCs are contained within the “inflammatory” CD1c⁺ DC population [4].

The receptors for TNF, TNFR1 and TNFR2, are expressed on a wide range of cells, including keratinocytes, and are upregulated in psoriasis [19]. The proinflammatory nature of TNF- α in psoriasis and other inflammatory diseases has been well established (reviewed in [20]). TNF- α induces expression of intracellular adhesion molecule-1 (ICAM-1) on keratinocytes, facilitating the adhesion of circulating leukocytes [21]. Moreover, TNF- α can stimulate keratinocytes and dermal fibroblasts to produce IL-8, a potent neutrophil chemoattractant, as well as proinflammatory cytokines, IL-6 and IL-1 [22,23], key players in the generation and maintenance of Th17 cells [24]. Th17 cells produce IL-17, which induces many chemokines including IL-8 (a neutrophil chemoattractant) and CCL20 (a chemotactic factor for DCs and T cells). IL-22, also a Th17 cell product, appears to be important for epidermal thickening [25]. Consequently, treatment with etanercept, a soluble human recombinant TNFR2 receptor that blocks binding of TNF to its receptors, successfully diminished the IL-23/IL-17 response [6] highlighting the importance of TNF in the inflammatory cascade in psoriasis.

Additionally, inflammatory DCs express inducible nitric oxide synthase (iNOS), which is not usually found in normal resting cells, but is induced in response to inflammatory stimuli [26]. It is the enzyme responsible for the generation of nitric oxide (NO) from L-arginine. In the skin, NO may play many roles, including vasodilation, inflammation, and an antimicrobial effect. Consequently, NO may account for the vasodilation of dermal blood vessels in the skin in psoriasis, and explain the red color of lesions. Interestingly, NO inhibitors such as statins may have a beneficial effect on psoriasis [27], although this has not been well studied in a randomized prospective manner. Along with TNF- α and iNOS, “inflammatory” DCs produce other pathogenic cytokines (Figure 2), such as IL-20, which enhances keratinocyte activation and proliferation [28], and IL-23 [6,29], which aids in differentiation, proliferation, and

survival of IL-17-secreting T cells (Th17) that have been recently identified in psoriasis [11, 12].

The centrality of IL-23 in autoimmune inflammation is becoming increasingly evident. It has been implicated in the pathogenesis of the autoimmune disorders, Crohn's disease and colitis [30,31], and is a very effective target for psoriasis therapy [32]. Moreover, polymorphisms in the genes encoding the receptor for IL-23 (*IL23R*) and the IL-12/23p40 subunit (*IL12B*) have been linked to psoriasis, either contributing to susceptibility or providing a protective advantage [33–35]. However, it is still unclear why certain variations predispose patients to develop psoriasis, while others confer protection. Due to their ability to secrete multiple proinflammatory mediators including IL-23, we proposed that these CD1c⁺ inflammatory DCs are central to the pathogenesis of psoriasis [36].

Plasmacytoid DCs

In addition to inflammatory DCs, a new line of research has focused on the contributions of pDCs to psoriatic inflammation. In some studies, the frequency and activation status of pDCs is increased in psoriatic lesional skin compared to normal skin [37]. Further flow cytometric analysis of dermal single cell suspensions revealed that lesional pDCs produced IFN- α [37]. Type I IFNs (IFN- α/β) have been established as a potential pathogenic cytokine in psoriasis with several studies demonstrating an activated IFN- α signaling pathway, as evidenced by increased expression of IFN- α -regulated genes [37–41]. Additionally, treatment of non-psoriatic conditions (e.g. viral infections) with IFN- α can exacerbate psoriasis [42,43]. The importance of IFN- α in disease pathogenesis was further strengthened by xenograft transplantation studies where non-lesional psoriatic skin is grafted onto immunodeficient mice. In this model, the engraftment of skin alone is sufficient to induce psoriasis [44]. Intravenous administration of either α IFN- α/β receptor blocking antibodies or α BDCA-2 antibodies, which specifically inhibit IFN- α production by pDCs, was sufficient to prevent the development of psoriasis [37]. Taken together, these data indicate that pDC production of IFN- α may be central to the initiation of psoriasis.

Much effort has been devoted to understanding the pathways that stimulate IFN- α production by pDCs. pDCs play a crucial role in the control of viral infections; viral nucleic acids activate pDCs through TLR9 and induce large amounts of IFN- α [45,46]. However, pDCs must be able to distinguish between viral DNA and self-DNA, which is abundantly released during apoptosis, to prevent inappropriate activation by self-antigens. Several control mechanisms are in place to prevent activation of pDCs by self-DNA. The abundant DNase enzymes rapidly degrade DNA released from dying cells. Furthermore, self-DNA is unable to spontaneously enter cells and is thus unable to engage endosomal TLR9. However, in the case of psoriasis, tolerance to self-DNA can be broken. Recently, Lande *et al.*, demonstrated that self-DNA forms aggregates with LL37 (cathelicidin), an antimicrobial peptide that normally acts as a natural “antibiotic” to prevent microbial infection [47]. Complexing of self-DNA with LL37 not only prevents DNA degradation by nucleases, but also allows for endocytosis by pDCs and sustained interactions of self-DNA with intracellular TLR9. As a consequence, pDCs become activated to produce high levels of IFN- α , thus initiating the inflammatory cascade.

Thus current evidence supports an integral role for myeloid DCs in the pathogenesis of psoriasis. However, the role of pDCs is less well understood. Further studies are necessary to determine the relationship between these two DC subpopulations in psoriasis, and their relative contributions to different phases of lesion development.

Atopic dermatitis

AD is another common skin disease, often considered to be the polar opposite of psoriasis. There is no pathognomonic clinical appearance of AD, although it often involves specific areas such as the flexures and face, and first occurs in young children. The clinical changes seen in the skin are considered to be a consequence of scratching and rubbing of the skin. The skin appears red and thickened (lichenification), and there may be scratch marks. Some lesions may also have a yellowish crust indicating cutaneous infection by *Staphylococcus aureus* (impetigo), a common problem among AD patients that has been attributed to the defective upregulation of antimicrobial peptides, the “natural antibiotics” in the skin (reviewed in [48]).

The histological appearances of AD are also not pathognomonic. Any acute dermatitis may produce epidermal edema which breaks apart the epidermal connections (spongiosis), as shown in Figure 1C. The epidermis becomes acanthotic with scratching, and there is a variable dermal infiltrate consisting of T cells, DCs, macrophages, eosinophils and mast cells.

The pathogenesis of AD is still not well understood, but there is evidence of potential contributions from both the innate and adaptive immune systems, as well as the epidermis itself, and recently identified genetic mutations. It is likely that several of these components play a role in the development of the clinical phenotype of AD lesions. For example, genetic mutations in filaggrin have recently been reported in some patients with AD [49]. Filaggrin is an important protein in the maintenance of epidermal integrity, and abnormal filaggrin may lead to a dysfunctional skin barrier, allowing allergens to penetrate the skin and gain access to immune cells. Two populations of DCs have been identified in atopic skin lesions: resident Langerhans cells and infiltrating myeloid inflammatory DCs. Both of these cell types may play important, but diverse roles in the initiation and maintenance of AD. While the acute phase of AD is characterized by Th2-polarization, during the chronic phase, a population of Th1 cells emerge into this Th2-dominant environment [13]. This biphasic nature of AD may be attributable to the type of DC that becomes activated, Langerhans cells and then myeloid inflammatory DCs, respectively.

Langerhans cells

LCs may have an important role in the initiation of AD. LCs express two receptors, high affinity IgE receptors (FcεRI), and thymic stromal lymphopoietin receptor (TSLPR), which have been implicated in AD pathogenesis. The overall effect of activation of LCs by these two receptors is stimulation of antigen-specific T cells to produce a Th2 cytokine environment. The specific effects of stimulation of LCs via FcεRI and TSLPRs are discussed below.

FcεRI-expressing LCs are able to bind to and internalize allergens specific for these IgE molecules [50,51]. By presenting IgE-bound auto-antigens or allergens, LCs are thought to hyperstimulate a Th2 cell response [52,53] either in the local skin-draining lymph nodes, or possibly *in situ* in the skin [2]. The cytokines produced by FcεRI ligation are difficult to determine *in vivo*, but *in vitro* stimulation of “Langerhans-like” cells via FcεRI induces secretion of pro-inflammatory cytokines: IL-8, monocyte chemokine MCP-1/CCL2, and IL-16. Moreover, the supernatant of these stimulated cells induces T cell and monocyte chemotaxis [54]. T cells engaged by these FcεRI-activated DCs produce a Th2 pattern of cytokines, namely IL-4, IL-5, IL-13 and IL-31 [54,55]. The stimulation of FcεRI-bearing Langerhans cells and resulting Th2 cytokine production creates an amplification loop in which further IgE production is induced [50,56] to perpetuate the inflammatory cycle.

TSLP, an IL-7-like cytokine, is highly expressed by keratinocytes in AD, and its receptor TSLPR, is highly expressed on dermal DCs in atopic skin lesions [7,57]. *In situ* TSLP expression in AD skin correlated with a loss of epidermal Langerin⁺ cells with a concurrent

increase in mature (DC-LAMP⁺) Langerin⁺ cells in the dermis, suggesting that TSLPR⁺ DCs in the dermis may be mature LCs [57]. Again, it is difficult to determine the effect of TSLP binding to TSLPR on DCs *in vivo*, but *in vitro* studies indicate that TSLP induces production of IL-15, IL-8, and chemokines CCL17, CCL22 and CCL24, main attractants for Th2 cells (reviewed in [58]). TSLP conditions DCs to promote Th2 cells, which produce typical Th2 cytokines, IL-4, IL-5, IL-13, but very little IL-10. TSLP-DCs polarize Th2 cells that also produce high levels of TNF- α that have been described as “inflammatory” Th2 cells [57,59, 60]. Subsequent studies demonstrated that TSLP-stimulated DCs induce TNF- α -producing Th2 cells via OX40L interactions, a process which depends on the absence of IL-12 [61]. Indeed, IL-12 expression is dampened in AD [29], thus providing a microenvironment permissive to the generation of these “inflammatory” Th2 cells.

Myeloid inflammatory dendritic cells

IDECS are a subpopulation of myeloid DCs that were first described using flow cytometric analysis of epidermal single cell suspensions of AD lesions, and were thus considered predominantly epidermal in location [62]. They were first defined by the surface phenotype of CD11c⁺, HLA-DR⁺, Lin⁻, CD1a⁺, CD206/macrophage mannose receptor⁺, CD36⁺, Fc ϵ RI^{high}, IgE⁺, CD1b/c⁺, CD11b⁺, and CD209/DC-SIGN⁺ [62–64]. However, the majority of “IDECS”, defined as DCs with this range of markers, are also located in the dermis of AD lesions [7], and are thus better called myeloid inflammatory DCs. There are some differences compared to the myeloid inflammatory DCs found in psoriasis, namely there is no iNOS signature, nor much TNF produced by these DCs in AD [7] (Figure 2).

As these myeloid inflammatory DCs express Fc ϵ RI, they may also respond to specific allergens, although the outcome appears to be different than the stimulation of LCs described above. *In vitro* stimulated “IDEC-like” cells produced IL-1, MIP-1 α , IL-16, and Th1 polarizing cytokines IL-12p70 and IL-18 [54]. Additionally, in contrast to LCs which induce a Th2 response upon Fc ϵ RI ligation, *in vitro* IDEC-like cells promoted Th1 polarization and IFN- γ production [54]. Thus stimulation of these DCs by allergens via Fc ϵ RI may be primarily responsible for the later more chronic maintenance phase of AD, in which there is a more pronounced Th1 cytokine profile. TSLP may also activate myeloid DCs *in vitro*, causing maturation of DCs in an antigen-independent manner with the induction of regulatory T cells [58].

Plasmacytoid DCs

Alterations in pDC function have been observed in atopic dermatitis. There are few pDCs in lesional skin of AD patients [65], and thus most studies have assessed the phenotype of peripheral blood pDCs. PDCs isolated from the blood of AD patients express the high affinity IgE receptor, Fc ϵ RI, and activation via Fc ϵ RI induces IL-10 production [66]. Moreover, when compared to normal pDCs, Fc ϵ RI-stimulated pDCs from AD patients produce much less IFN- α [66]. These observations may explain the increased susceptibility of AD patients to viral infections, such as herpes simplex.

Taken together, these studies suggest that during AD, LCs may initially polarize a Th2 response, while also promoting chemotaxis of additional DC precursors (most likely monocytes), which mature into myeloid inflammatory DCs that may be responsible for the eventual appearance of a Th1 response.

Cutaneous lupus erythematosus

Lupus erythematosus is an autoimmune disease forming a spectrum from a chronic cutaneous form (discoid lupus erythematosus), through a more active cutaneous form (subacute lupus

erythematosus), to a severe multi-system disease systemic lupus erythematosus (SLE). Some patients only develop skin disease, while approximately half the patients with systemic disease develop skin lesions. Antibodies to DNA subunits have been well characterized in this disease, although the pathogenic process that leads to skin disease is not well understood.

The pathognomonic histological feature of CLE is involvement of the dermo-epidermal junction (Figure 1D). Lymphocytes line up and can obscure this region in a “lichenoid” histological pattern. In an acute presentation, there is edema associated with this region and as the reaction becomes more prolonged, the epidermis can flatten and become atrophic. There is a mixed dermal infiltrate associated with this process including lymphocytes and DCs, which may be patchy or surround vessels and appendages.

Plasmacytoid DCs

pDCs represent a distinct subset of DCs, whose main role is to secrete type I IFN in response to viral and bacterial stimuli, although they also function as antigen-presenting cells [67]. The role of pDCs in SLE was actually postulated following elegant studies demonstrating that SLE was characterized by elevated type I IFN (IFN α/β) [68–71]. Since pDCs are the main cell type producing type I IFNs, pDCs were implicated in disease pathogenesis. Indeed, there is a higher frequency of pDCs in skin compared to the blood of patients with SLE, suggesting that pDCs migrate from the circulation into the skin [10,65]. Immune complexes of anti-DNA antibodies and self-DNA may be deposited at the dermo-epidermal junction and stimulate local cutaneous pDCs to secrete IFN α [10,72,73], thus initiating lupus lesions in the skin. Accordingly, the accumulation of pDCs in cutaneous lesions correlates well with the expression of myxovirus protein A (MxA), an IFN- α induced gene [10,74], which is consistent with local production of type I IFNs.

Since many cutaneous cells express the type I IFN receptor (IFN- α/β R), production of IFNs in the skin can have widespread consequences. Notably, IFN- α can amplify cutaneous inflammation via the induction of chemokines that recruit potentially auto-reactive T cells into the skin. For example, IFN- α induces the production of chemokines, CXCL9, CXCL10, and CXCL11, which recruit chemokine receptor CXCR3 expressing lymphocytes [8,74], including Th1 cells and CD8⁺ T cells, from peripheral blood into inflamed skin. Along these lines, histological analysis illustrated that the expression pattern of IFN-inducible MxA reflected the distribution of CXCR3⁺ CD3⁺ T cells [75]. Additionally, pDCs, which also express CXCR3, migrate into inflamed skin, where local IFN- α can stimulate them to produce more IFN [8], thus perpetuating the inflammatory process. Thus pDCs may contribute directly to T cell infiltration and the lichenoid tissue reaction characteristic of cutaneous lupus [76,77].

In addition to eliciting chemotactic factors, IFN- α also acts directly on other immune cells. For example, serum from patients with SLE induces the *in vitro* differentiation of monocytes into mature DCs in an IFN- α -dependent manner [68]. These cells are able to capture antigens from apoptotic cells and stimulate auto-reactive T cell responses [68]. Consistent with these observations, DCs isolated directly from the blood of lupus patients have a more mature phenotype and are able to stimulate greater naïve T cell proliferation and activation, presumably through the effects of systemic IFN- α [78]. IFN- α has also been shown to act directly on T cells, to enhance both IFN- γ production and survival [79]. It may also activate Th1 cells to cooperate in B cell maturation, amplifying autoantibody production [79]. Thus, the central role of pDCs and type I IFN in the initiation and maintenance of cutaneous LE appears well established.

Concluding remarks and future directions

This review summarizes the current literature on the roles of DCs in psoriasis, AD and CLE. However, many questions remain unanswered. First, what is the origin of the inflammatory DCs in psoriasis and AD? Our working hypothesis is that they differentiate from monocytes that are recruited during the early stages of inflammation (Figure 3). Once monocytes infiltrate the skin, the cytokine milieu drives DC differentiation. The early cutaneous microenvironment is different in psoriasis and AD, resulting in DCs that produce diverse cytokines and T cell polarities. Thus these DCs may be conditioned by the skin microenvironment to produce a specific array of inflammatory cytokines and chemokines, which can have potent effects on surrounding immune cells, driving either psoriasis, AD or CLE.

Second, is there a similar sequential role for DCs in cutaneous inflammation in the initiation and maintenance of lesions? Specifically, it is possible that the temporal development and the initiation and maintenance phases of psoriasis, AD and CLE are dependant on different subpopulations of DCs. It has been hypothesized that pDCs initiate psoriasis, and myeloid inflammatory DCs maintain lesions. In AD, the respective DC populations may be LCs and myeloid inflammatory DCs. In CLE, the pDCs may be capable of both initiation and maintenance of lesions.

Third, how can the same initiating cell lead to such different histological and clinical outcomes? PDCs have recently been proposed to initiate both psoriasis and CLE. Perhaps the mechanism of pDC activation—DNA complexed to LL37 in psoriasis, versus complexes of DNA with self-antibodies in CLE—might elicit distinct factors that shape the immune response. PDCs alone may be sufficient to induce a lichenoid, lupus-like reaction, and thus may be the primary pathogenic DC in lupus, fulfilling both initiation and maintenance roles. In psoriasis, myeloid DCs may function in this capacity. Little is known about what actually *initiates* cutaneous inflammation.

In this review, a “DC-centric” focus has been taken to consider three prototypic cutaneous inflammatory diseases. It is clear that DCs can have a profound impact on the state of inflammation in the skin. During inflammation, additional populations are recruited to the skin, including myeloid inflammatory DCs in psoriasis and in AD, and pDCs in CLE. The specific combinations of DC-derived products, as well as factors from other cutaneous cells, are integral to the development and maintenance of inflammatory skin lesions.

Acknowledgments

Research was supported by National Institutes of Health (NIH) grant UL1 RR024143 from the National Center for Research Resources (NCRR). MAL is supported by 1 K23 AR052404-01A1; MAL and LJH are supported by The Doris Duke Charitable Foundation; and NSM is supported by the Milstein Program in Medical Research.

Abbreviations

(DC)	dendritic cells
(IDECs)	inflammatory dendritic epidermal cells
(pDCs)	plasmacytoid dendritic cells
(AD)	atopic dermatitis
(CLE)	cutaneous lupus erythematosus
(TNF)	tumor necrosis factor
(iNOS)	inducible nitric oxide synthase

(NO)	nitric oxide
(TIP-DCs)	TNF and iNOS-producing dendritic cells
(TLSP)	thymic stromal lymphopoietin
(TSLPR)	thymic stromal lymphopoietin receptor
(LCs)	Langerhans cells
(SLE)	systemic lupus erythematosus
(MxA)	myxovirus protein A

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Figure 1. Normal skin, psoriasis, atopic dermatitis, and cutaneous lupus tissue sections by haematoxylin and eosin staining

(A) Normal skin can be divided into the epidermis, the upper outer layer of keratinocyte cells with a “basket weave” stratum corneum, and the dermis, the pale pink layer beneath the epidermis. **(B) Psoriasis** is characterized by a greatly thickened epidermis (acanthosis) with elongation of the rete ridges that protrude down into the dermis. There is retention of keratinocyte nuclei in the outer layers (parakeratosis). Collections of neutrophils can also be seen in the epidermis and stratum corneum. In the dermis, there is elongation and dilatation of the dermal blood vessels that protrude up between the rete ridges. These dermal blood vessels and surrounding upper dermal spaces are filled with predominantly mononuclear leukocytes (including DCs and T cells) and neutrophils. **(C) Dermatitis** may produce epidermal edema, which breaks apart the epidermal connections (spongiosis). The epidermis becomes acanthotic with scratching, and there is a variable dermal infiltrate consisting of T cells, DCs, macrophages, eosinophils and mast cells. **(D) Acute cutaneous lupus** skin lesions demonstrate characteristic involvement of the dermo-epidermal junction that separates the epidermis and dermis. Lymphocytes line up and can obscure this region in a “lichenoid” histological pattern. In an acute presentation, there is edema associated with this region as shown here. There is a mixed dermal infiltrate associated with this process including lymphocytes and DCs, which may be patchy or surround vessels and appendages.

Figure 2. The development and function of myeloid inflammatory DCs in psoriasis and AD

As a result of cytokine production in the cutaneous microenvironment, DC precursors differentiate into inflammatory DCs *in situ*. Depending on the environmental cues, inflammatory DCs produce a distinct set of cytokines. Psoriatic DCs produce TNF- α , nitric oxide, IL-20 and IL-23 and are involved in the development and maintenance of a Th1/Th17 polarized response. In AD, inflammatory DCs neither produce much TNF or IL-23, nor have an iNOS signature, but instead produce chemokines, CCL17 and CCL18, that are involved in ongoing Th2>Th1 cell recruitment.

Figure 3. The putative precursors of inflammatory DCs

It is unclear which cells give rise to inflammatory DCs. It is possible that inflammatory DCs are derived from monocytes infiltrating the skin, or they could differentiate from resident or infiltrating CD1c⁺ DCs.