Dermal dendritic cells in psoriasis, nummular dermatitis, and normal-appearing skin

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Background: The reason psoriasis (PSO) favors extensor skin is unknown. We hypothesized that PSO may involve extensor skin preferentially because of differences in the number or type of dermal dendritic cells (dDCs) between flexural and extensor skin.

Objective: We sought to compare dDC type and distribution in normal-appearing flexural and extensor skin, PSO, and nummular dermatitis (ND).

Methods: Using immunohistochemical markers, the number, distribution, and type of Langerhans cells, myeloid dendritic cells (DCs), and plasmacytoid DCs was compared in normal-appearing skin, PSO, and ND.

Results: Significant differences in dDC density were not identified between flexural and extensor skin, although extensor skin contained fewer $CD11a^+$ and $CD11c^+$ cells. Compared with normal-appearing skin, cells expressing CD11a, CD11c, CD123, CD303, and CD207 were increased in PSO. ND lesions showed similar increases. No significant difference between PSO and ND was evident with the exception of decreased $S100A6^+$ cells in PSO.

Limitations: We did not study seasonal variation in DC density or assess nonlesional skin from patients with PSO.

Conclusions: The data did not support the hypothesis that PSO favors extensor skin because of differences in DC localization. However, dDCs were significantly increased in PSO by comparison with normal-appearing skin, supporting existing evidence that they are involved in the overall pathogenesis of PSO. (J Am Acad Dermatol 2012;66:98-105.)

Key words: CD11; CD123; CD207; CD303; dendritic cells; psoriasis.

Great advances in the understanding of psoriasis (PSO) have occurred in recent years. In addition to lymphocytes and other inflammatory cells, it is now evident that psoriatic plaques also contain dendritic cells (DCs).[1] DCs are cells that take up antigen, migrate to local lymph nodes, and present that antigen in association with major histocompatibility complex molecules to T lymphocytes and B lymphocytes.[2-4] They also produce cytokines and inflammatory mediators that stimulate and regulate T lymphocytes and other DCs. DCs originate in the bone marrow, enter the systemic circulation, and eventually migrate into peripheral tissues. Although they are related to macrophages and resemble them morphologically,

Abbreviations used:

DC:	dendritic cell
dDC:	dermal dendritic cell
IFN:	interferon
IL:	interleukin
LC:	Langerhans cell
mDCs:	myeloid dendritic cells
pDCs:	plasmacytoid dendritic cells
ND:	nummular dermatitis
PSO:	psoriasis

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macrophages lack the complex antigen processing and presenting capabilities of DCs.

Until recently, the Langerhans cells (LCs) of the epidermis were widely regarded as the only cutaneous antigen-presenting cells. Now, however, it appears that DCs residing within the dermis (dermal DCs [dDCs]) are actually of equal or greater importance in the pathogenesis of many skin inflammatory diseases. Depending on the methods used to identify them and the criteria by which they are classified, as many as 5 different subtypes of cutaneous dDCs have been described.[5] For purposes of simplification, however, they may be broadly categorized into one of 3 general subsets: (1) epidermal LCs; (2) dermal myeloid DCs (mDCs); and (3) dermal plasmacytoid DCs (pDCs)[6] (Fig 1). During inflammatory states, a population of inflammatory mDCs can also be detected,[7] but it is not clear whether these are a distinct cell type derived from progenitor cells within the systemic circulation or simply mDCs in an activated state.

CAPSULE SUMMARY

- Dermal dendritic cells (dDCs) may play a role in psoriasis (PSO) pathogenesis. We hypothesized that differences in dDCs might account for the preference of PSO for extensor skin.
- No significant differences in dDCs between normal-appearing flexural and extensor skin were found using immunohistochemical markers for dDCs. However, PSO and nummular dermatitis contained increased dDCs, including both myeloid and plasmacytoid subtypes. The changes were not site specific.
- The results support other data suggesting dDCs are involved in PSO, but their quantity does not appear to account for the predilection of PSO for extensor skin.

Several studies have implicated dDCs in PSO. A marked increase in dDCs expressing $CD11c^+$ occurs in psoriatic plaques.[8,9] These cells are also increased in nonlesional skin of patients with PSO, and they are thought to play a role in the subsequent development of plaques[9] in part by stimulating T-lymphocyte development and proliferation.[10] This is likely accomplished by their production of cytokines, several of which have been previously implicated in the pathogenesis of PSO, including tumor necrosis factor-alfa, interferon (IFN)-α, interleukin (IL)-23, and IL-15.

The success of antipsoriatic therapies seems to support a role for dDCs in PSO pathogenesis.[11] Psoralen plus ultraviolet A decreases dDCs and epidermal T lymphocytes in association with clearing of chronic plaque PSO. Efalizumab, a human monoclonal antibody directed against lymphocyte function associated antigen-1 that is efficacious in PSO (although it is no longer available because of an unacceptably high risk of progressive multifocal leukoencephalopathy), blocks the interaction between lymphocyte function associated antigen-1 on T cells and intracelluar adhesion molecule-2 on DCs and reduces the density of $CD11c^+$ dDCs.[12] Tumor necrosis factor inhibitors have also been shown to decrease dDCs.

Studies of dDCs are dependent on markers that allow their reliable identification. In the late 1980s and early 1990s, markers such as factor XIIIa were found to label dermal cells with dendritic morphology that were referred to as "dermal dendrocytes."[13] The specificity of these antibodies for antigen-presenting cells is doubtful, however, because they are usually expressed by macrophages as well. Numerous other markers are known to label dermal cells with dendritic morphology, including CD34, CD68, and S100. Like factor XIIIa, however, they are by no means specific for antigen-presenting cells.

Fortunately, markers with increased specificity have since emerged. Although some are suitable only for flow cytometric analysis, many are now available for immunohistochemistry as well. CD1a, an antibody directed against an major histocompatibility complex-like molecule involved in antigen presentation, is highly specific for LCs and has been used in routine diagnostic work for years.[14,15] CD207/Langerin, a recently identified LC marker, is a membranous C-type lectin that recognizes mannosylated ligands found on the surface of viruses, bacteria, and other pathogens.[16] Although it is found on epidermal LCs, it is also expressed by a subset of DCs that appear to be distinct from their epidermal counterparts.[17-20] CD11c, an integrin expressed by dDCs in normal-appearing/steady-state skin and also by inflammatory DCs,[7] is relatively specific for the myeloid subset of DCs (mDCs). CD11a composes part of the heterodimeric lymphocyte function associated antigen-1 molecule (CD11a/CD18). Although it is generally expressed primarily by T lymphocytes rather than DCs, CD11a binds intracellular adhesion molecules on DCs and plays a key role in lymphocyte trafficking, antigen presentation, and T-cell costimulation. In contrast to mDCs, pDCs are negative for CD11c. Instead, they are recognized by their expression of CD123 and CD303/blood dendritic cell antigen-2.[21]