Major differences in inflammatory dendritic cells and their products distinguish atopic dermatitis from psoriasis

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Background: Atopic dermatitis (AD) and psoriasis represent contrasting poles of the T_H1 versus T_H2 paradigm. Both diseases have been associated with increased numbers of dendritic cells (DCs) in the skin, but the similarities and differences in DC populations need to be established.
Objective: We aimed to characterize the specific DC subsets, as well as chemokine and cytokine environment in chronic AD compared with psoriasis.
Methods: Skin biopsies were obtained from patients with acute exacerbation of chronic AD (n = 18), psoriasis (n = 15), and healthy volunteers (n = 15) for microarray analysis, RT-PCR, immunohistochemistry, and double-label immunofluorescence.
Results: Myeloid DCs upregulate CCL17 and CCL18 in AD, as opposed to TNF-α and inducible nitric oxide synthase (iNOS) in psoriasis. In our study, we identified cells phenotypically identical to the inflammatory dendritic epidermal cells in the dermis in both diseases, although to a lesser extent in psoriasis. We found substantially higher numbers of dermal CCL22 producing plasmacytoid DCs in AD. The thymic stromal lymphopoietin receptor showed significantly higher expression in AD, whereas the thymic stromal lymphopoietin ligand was upregulated more in psoriasis.
Conclusion: There are major differences in myeloid and plasmacytoid subsets of cutaneous DCs and the chemokine/cytokine environment between AD and psoriasis. Distinct subsets within the $CD11c^+$ population may influence polarization through the production of regulatory mediators, including iNOS, TNF, CCL17, and CCL18. Plasmacytoid DCs may also influence T_H2 polarization, having a more important role in AD than previously appreciated.
Clinical implications: Dermal inflammatory dendritic cells in AD and TNF and iNOS–producing DCs in psoriasis, and/or their regulatory products, may be potential targets for future therapeutic interventions. (J Allergy Clin Immunol 2007;119:1210-7.)

***Key words:** Atopic dermatitis, psoriasis, myeloid DCs, inflammatory dendritic epidermal cells, plasmacytoid DCs, TIP-DCs*

Psoriasis and atopic dermatitis (AD) are common inflammatory skin diseases, accounting for the largest group of human diseases likely to be T-cell–mediated or autoimmune diseases in human beings.[1-4] Chronic AD and psoriasis vulgaris share many pathologic features in skin lesions, including the presence of marked T-cell infiltrates, hyperplasia/altered differentiation of keratinocytes, and infiltration by a group of $CD11c^+/CD1a^+$ dendritic cells (DCs) that have been termed *inflammatory dendritic epidermal cells* (IDECs).[5-7] Whereas the original methods for definition of this DC subset were based on flow-cytometric techniques and examination of DCs in cell suspensions of the epidermis (which led to classification of the cells as epidermal),[6-8] more recent work has identified a significant population of $CD1a^+$ DCs within the dermis of normal skin.[9] The overall number and distribution of IDECs within the epidermis and dermis of normal skin and inflammatory skin disorders are presently unknown, although this is potentially a key issue in the activation of T cells located in the epidermis versus dermis of inflammatory skin diseases.

An increased frequency of another DC subset, plasmacytoid DCs ($CD11c^-$ DCs that express blood dendritic cell antigen (BDCA)-2 or CD123), has been noted in AD and psoriasis.[10-12] Recent work in psoriasis has also identified skin infiltration by a group of $CD11c^+$ DCs that synthesize TNF-α and inducible nitric oxide synthase (iNOS), termed *TNF and iNOS-producing DCs* (TIP-DCs). These cells are abundant in the dermis, approximately equal in number to T cells in the skin lesions.[13] Atopic lesions have not yet been investigated for the presence of TIP-DCs. Because TNF-α and iNOS likely contribute to the inflammation of psoriasis, it would be important to compare psoriasis and AD in terms of the types of inflammatory DCs.

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Abbreviations used

AD: Atopic dermatitis
BDCA: Blood dendritic cell antigen
DC: Dendritic cell
DC-SIGN: Dendritic cell–specific intercellular adhesion molecule 3–grabbing nonintegrin
FC: Fold change
hARP: Human acidic ribosomal protein
IDEC: Inflammatory dendritic epidermal cell
iNOS: Inducible nitric oxide synthase
PDC: Plasmacytoid dendritic cell
TIP-DC: TNF and iNOS-producing dendritic cell
TSLP: Thymic stromal lymphopoietin
TSLPR: Thymic stromal lymphopoietin receptor

An additional pathogenic factor in AD is thymic stromal lymphopoietin (TSLP). TSLP is an IL-7–like cytokine produced by AD keratinocytes.[14-16] It binds to a heterodimeric receptor composed of the IL-7R and TSLP receptor (TSLPR). TSLP matures myeloid DCs to produce T_H2-attracting chemokines, such as CCL17 (thymus and activation-regulated chemokine) and CCL22 (macrophage-derived chemokine),[4,14-16] and to differentiate T cells to become inflammatory T_H2 cells producing TNF-α, IL-4, IL-5, and IL-13. This reveals a potential functional link among epithelial cells, DCs, and T-cell–mediated immune responses.[14-16]

To define similarities and differences between AD and psoriasis further, we characterized the specific DC subsets and chemokine and cytokine environment in patients with chronic AD. First, we noted an abundance of myeloid DCs in both AD and psoriasis, but in AD, these DCs expressed chemokines that attract T_H2 cells, and the AD DCs lacked iNOS. Second, IDECs were found predominantly in the dermis of both diseases, although they were significantly increased in AD compared to psoriasis. Third, there were significantly more plasmacytoid DCs (PDCs) in AD than psoriasis. Finally, whereas TSLP was expressed more in psoriasis, the TSLPR showed significantly higher expression in AD. Thus, there are major differences in the myeloid and plasmacytoid subsets of cutaneous DCs and chemokine/cytokine environment between these 2 important inflammatory skin diseases.

METHODS

Study design and skin samples

Skin biopsies were collected from 18 patients with atopic dermatitis (12 male subjects, 6 female subjects; age, 17-66 years; median, 37 years), 15 patients with psoriasis (lesional and nonlesional skin; 11 men, 4 women; age, 28-59 years; median, 48 years), and 15 healthy volunteers (7 men, 8 women; age, 24-69 years; median, 41 years) under a Rockefeller University Institutional Review Board–approved protocol. Patients with moderate to severe psoriasis (psoriasis involvement of > 10% body surface area) and with an acute exacerbation of chronic AD (Scoring Atopic Dermatitis Index between 20 and 70, all with elevated IgE) who did not receive any therapy for > 4 weeks were included.

Sample preparation for gene chip analysis

The microarrays used for this study were U95A-set GeneChip probe arrays (Affymetrix Inc, Santa Clara, Calif) containing probe sets of approximately 12,000 genes. The labeled target was fragmented and hybridized to probe arrays as previously described.[17] A description of RNA extraction and chip processing is provided in the Methods in this article's Online Repository at www.jacionline.org. On each chip, the human housekeeping genes β-actin and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) served as controls for normalization of expression values. Chips with 3′ to 5′ ratios for GAPDH less than 3 and scaling factors within 3-fold of each other were compared for the study.

DNA microarray analysis

Data were analyzed with Affymetrix Microarray Suite 5.0 software (Affymetrix Inc) and GeneSpring 7.0 software (Silicon Genetics, Redwood City, Calif). Detailed protocols for data analysis were previously described.[18]

Gene expression analysis. Using GeneSpring 7.0, the Robust Multi-Chip Average algorithm was applied for normalizing and summarizing probe-level intensity measurements, as described elsewhere.[18]

Hierarchical clustering and heatmaps. Hierarchical clustering was performed by using GeneSpring 7.0. Genes with a similar pattern of expression were grouped as hierarchical clusters and presented as heatmaps. The gene tree was computed on the basis of a full data set, and distances between samples were computed by using Pearson correlations as similarity measures. Each line in the heatmap represents genes with relative upregulated *(red)* or downregulated *(green)* expression values in fold changes.

Statistical comparisons. Data were analyzed by unpaired 2-tailed *t* test or 1-way ANOVA. We considered genes that passed the Benjamini and Hochberg correction as the most relevant for skin inflammation. An associated probability of <.05 was considered significant.

Description of relevant functions of genes. GeneOntology annotations of differentially expressed genes were collected from LocusLink (http://www.ncbi.nlm.nih.gov/LocusLink).

Real-time PCR analysis. Primers and probes for TaqMan RT-PCR (Applied Biosystems, Foster City, Calif) assays were generated with the Primer Express algorithm (Applied Biosystems), version 1.0, by using published genetic sequences (National Center for Biotechnology Information-PubMed) for each gene. Sequences are published in the Methods in this article's Online Repository at www.jacionline.org. The data were analyzed and quantified by the software provided with the Applied Biosystems PRISM 7700 (Sequence Detection Systems, version 1.7). Statistical comparisons of mRNA expression levels were performed by using a 2-tailed Student *t* test, with a probability of $P < .05$ considered significant.

Immunohistochemistry and immunofluorescence. Tissue sections were stained with hematoxylin and eosin. mAbs used for immunohistochemistry are listed in the Methods in this article's Online Repository at www.jacionline.org. Biotin-labeled horse antimouse antibody was amplified and developed as previously described.[13] Positive cells were counted by using computer-assisted image analysis, National Institutes of Health software (NIH IMAGE 6.1), which captures an image of a 1-mm length of epidermis (and approximately 1 mm depth of dermis below this length). Cells were counted per 1-mm epidermal length in both epidermis and dermis. The counts were analyzed by using the Mann-Whitney test, comparing epidermis and dermis of normal, psoriatic, and AD skin. A probability of $P < .05$

was accepted as significant. For immunofluorescence, skin sections were fixed with acetone and then blocked in 10% normal goat serum (Vector Laboratories, Burlingame, Calif). Primary antibodies were incubated overnight at 4°C. Sections were stained with an anti-isotype antibody conjugated to a fluorochrome and then blocked with 10% mouse serum. A second primary was applied to the section and detected with an anti-isotype antibody conjugated to an alternate fluorochrome. Images were acquired by a Zeiss Axioplan 2I upright microscope (Zeiss, Thornwood, NY) with attached Zeiss 5 Fluar/0.25 and 10 Fluar/0.05 lenses and appropriate filters.

RESULTS

In this study, we characterized DCs and inflammatory products in patients with untreated active psoriasis or atopic dermatitis. The extent of epidermal reaction was similar by histologic and genomic measures, as shown in this article's Fig E1 in the Online Repository at www.jacionline.org.

Quantification and distribution of T cells and major DC lineages in normal skin, psoriasis, and AD lesions

We analyzed biopsies for the number and distribution of T cells and the 3 main DC lineages: Langerhans cells, $CD11c^+$ DCs (marking dermal and interstitial DCs),[19] and PDCs. We also included a number of other markers that may distinguish functional DC subsets within these classes. Results are shown in Fig 1 and this article's Fig E2 in the Online Repository at www.jacionline.org.

T cells. We measured the number of T cells and DCs in biopsies of normal skin, psoriasis, and AD (Fig 1). Although AD and psoriasis had similar numbers of $CD3^+$ T cells in the dermis, the number of T cells in the epidermis was significantly higher in psoriasis (a mean of 109 and 53 T cells per millimeter in psoriatic and AD epidermis, respectively; $P = .01$). Normal skin had minimal T-cell infiltrates.

Langerhans cells. We identified Langerhans cells using both langerin and CD1a. In normal and psoriatic skin, there was a similar number and distribution of epidermal $langerin^+$ and $CD1a^+$ cells (Fig 1), and these markers were consistently coexpressed in Langerhans cells (Fig 2, *B*). However, in AD, there was significantly increased CD1a distribution in both the epidermis and dermis, but the increase in $CD1a^+$ cells in the dermis was particularly notable ($P = .004$ psoriatic vs AD dermis). Langerin and CD1a were coexpressed on epidermal but not on dermal cells in AD (Fig 2, *C*), which might indicate a dermal $CD1a^+$ IDEC population that is langerin-negative.

$CD11c^+$DCs. Compared with normal skin, both psoriasis and AD have consistent increases in $CD11c^+$ DCs, in a similar pattern (30/123 $CD11c^+$ cells per millimeter epidermis/dermis in psoriasis; 38/158 $CD11c^+$ cells per millimeter epidermis/dermis in AD; and 11/72 $CD11c^+$ cells per millimeter epidermis/dermis in normal skin). AD showed increased $CD11c^+$ cells in the dermis compared with psoriasis ($P = .046$). However, as will be discussed, the products of $CD11c^+$ DCs were markedly different in these 2 diseases.

PDCs. We found a significantly higher number of $BDCA2^+$ cells in the dermis of AD compared with both psoriatic and normal skin. The mean number of $BDCA2^+$ cells was < 10 cells per millimeter in normal and psoriatic dermis and 52 cells per millimeter in AD ($P = .002$ for AD dermis compared with psoriatic dermis, and $P = .009$ for AD compared with normal dermis).

IDECs. IDECs are defined as $HLA\text{-}DR^+Lin^-$ $CD11c^+CD1a^+CD123^-/BDCA2^-$ DCs that coexpress CD206/macrophage mannose receptor (MMR), CD36, FcεRI, IgE, CD1b/c, and CD11b.[6,7] Given the increased expression of $CD1a^+$ in dermal cells in AD, we further analyzed additional markers of IDECs, including CD36 (thrombospondin receptor), CD206 (MMR), FcεRI, and CD1b/c.

Based on cell counts (Fig 1), the number of $CD36^+$, $CD206^+$, and $Fc\varepsilon RI^+$ cells was higher in the dermis of AD lesions compared with normal skin ($P < .05$ for all antigens). $CD206^+$ cell numbers were also higher in AD epidermis and dermis compared with psoriasis ($P = .0003$, .0007, respectively). The distribution pattern of CD36 and CD206 markers was similar in all skin samples, suggesting they identified the same cell type. FcεRI, considered a hallmark of IDECs, was similarly distributed in AD and psoriasis, displaying a relatively more restrictive staining pattern than CD206 and CD36. FcεRI staining was mainly dermal in all skin lesions (Fig 1; see this article's Fig E2 in the Online Repository at www.jacionline.org). CD1b/c displayed a significantly higher dermal distribution in AD (a mean number of 39 vs 89 cells per millimeter in the dermis in psoriasis vs AD, respectively; $P = .02$). The majority of $CD1b/c^+$ DCs in AD, like the $CD1a^+$ DCs, were dermal residents.

In normal skin, CD1a and CD11c were mainly epidermal and dermal, respectively, and not coexpressed (Fig 2, *A*), whereas langerin and CD1a were expressed on the same cell and located in the epidermis (Fig 2, *B*). In AD, langerin was mainly epidermal, but CD1a also has a dermal distribution (Fig 2, *C and D*), with minimal coexpression of these 2 markers in the dermis (Fig 2, *C*). In contrast with normal skin, IDECs in AD (defined by coexpression of $CD11c^+/CD1a^+$, $CD11c^+/Fc\varepsilon RI^+$, and $CD11c^+/CD206^+$) were mainly located in the dermis (Fig 2, *D-F*), although a few $CD11c^+/CD1a^+$ cells appear to be migrating into the epidermis (Fig 2, *D*). The expression of DC-specific intercellular adhesion molecule 3–grabbing nonintegrin (DC-SIGN/CD209), although not a known IDEC marker, was found to parallel other IDEC markers (Fig 1). Double immunofluorescence labeling showed that DC-SIGN–positive cells are also CD206-positive (see this article's Fig E3 in the Online Repository at www.jacionline.org). The combination of single IDEC markers shown in Fig 1 and double-label markers shown in Fig 2 establishes a predominantly dermal location for IDEC-like DCs.

TIP-DCs. TIP-DCs are a new type of myeloid $CD11c^+$ DCs that are increased in psoriasis compared with normal skin.[13] These cells show an intense distribution of iNOS, as well as TNF in psoriasis. In AD, however, as well as

Food allergy, anaphylaxis, dermatology, and drug allergy

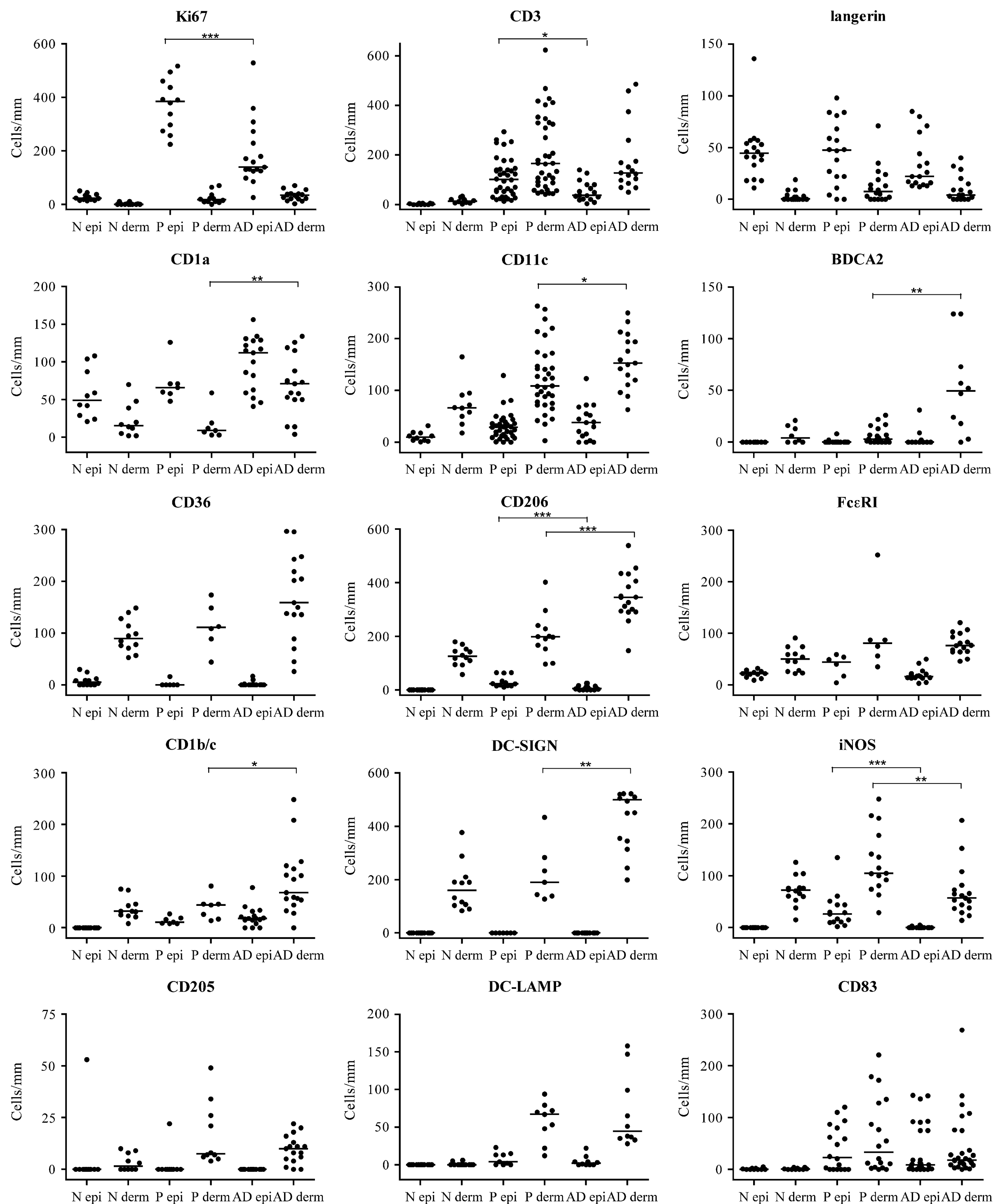

FIG 1. Quantification of the cellular microenvironment in normal skin, psoriasis, and AD. Cell counts/mm and means in normal epidermis *(N epi)*, normal dermis *(N derm)*, psoriatic epidermis *(P epi)*, psoriatic dermis *(P derm)*, AD epidermis *(AD epi)*, and AD dermis *(AD derm)*. $*P < .05$, $**P < .01$, $***P < .001$.

in normal skin, we found less intense staining for iNOS (see this article's Fig E2 in the Online Repository at www.jacionline.org) and significantly fewer iNOS$^+$ cells (Fig 1). The mean number of iNOS$^+$ cells was 0 and 71 cells per millimeter in normal skin, 33 and 126 cells per millimeter in psoriatic epidermis and dermis, respectively, and 0 and 68 cells per millimeter in AD ($P < .0001$, and $P = .003$ in AD vs psoriasis epidermis and dermis,

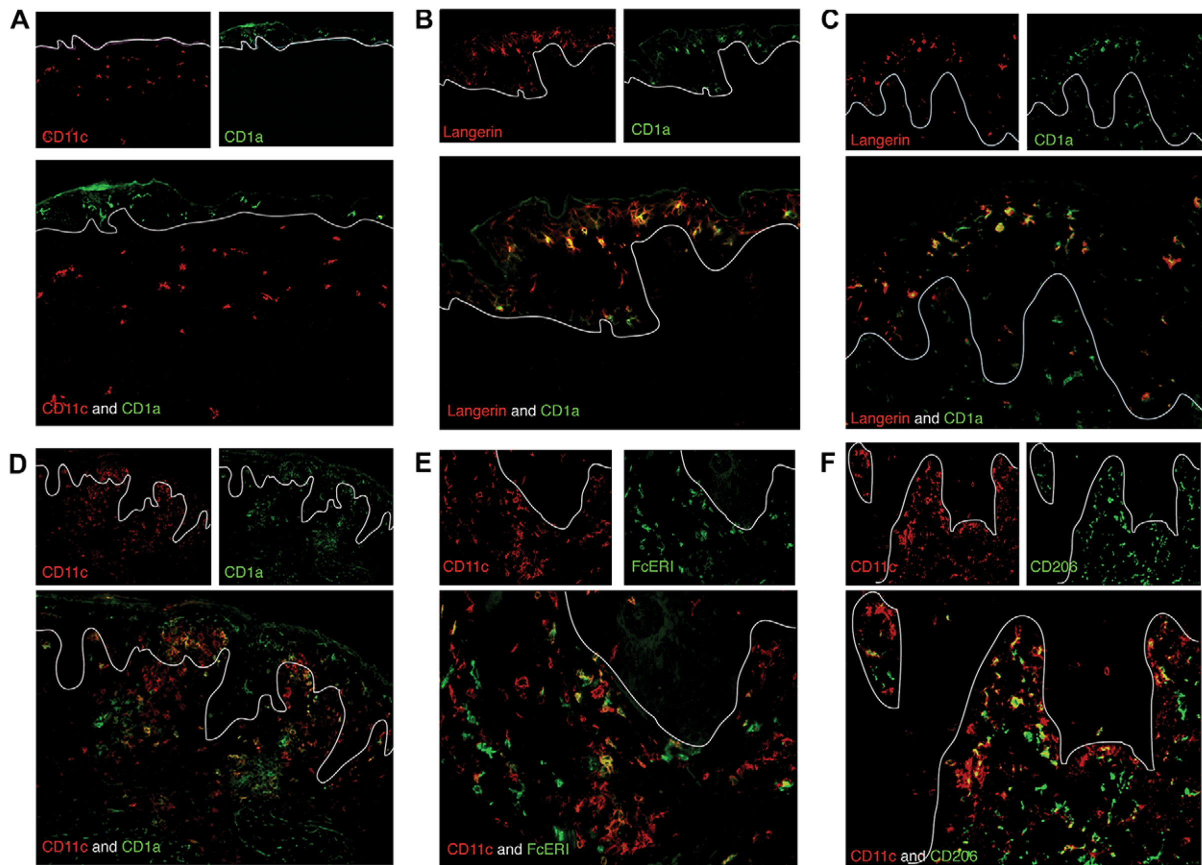

FIG 2. Double-label immunofluorescence confirmed the dermal presence of $CD1a^+$ cells in AD and the lack of complete overlap with langerin, in contrast with normal skin. **A and B,** Normal skin; **C-F,** AD. CD11c and CD1a were not coexpressed *(A)*, whereas langerin and $CD1a^+$ were nearly completely coexpressed *(B)* in normal skin. In AD, there was only partial coexpression of $CD1a^+$ and langerin, with substantial dermal localization of $CD1a^+$ cells *(C)*, and partial coexpression of $CD11c^+$ and $CD1a^+$ cells *(D)* in both epidermis and dermis. In AD, $CD11c^+$ cells colocalized with FcεRI and CD206 markers in the upper dermis *(E and F)*.

respectively; Fig 1). In addition, there was reduced iNOS mRNA in AD versus psoriasis ($P < .0001$; Fig 3). Hence, TIP-DCs appear to characterize psoriasis but not AD.

DCs with markers of maturation and strong antigen-presenting potential. Markers of highly immunogenic DCs include CD1b/c, CD205, DC-lysosomal-associated membrane protein (LAMP), and CD83, with the last 2 also identifying mature DCs. All these markers were increased in AD versus normal skin ($P < .05$ for all comparisons; Fig 1; see this article's Fig E2 in the Online Repository at www.jacionline.org). CD83 was minimally distributed in normal skin and increased in AD and psoriasis ($P <$ .001 for psoriasis and AD vs normal skin). CD205 (DEC-205), a member of the family of C-type lectin endocytic receptors, is a DC antigen uptake/processing receptor. There was little CD205 staining in normal skin, but clear expression in AD and psoriasis (Fig 1; see this article's Fig E2 in the Online Repository at www.jacionline.org). DC-$LAMP^+$, $CD83^+$, and $CD205^+$ cells were often organized in discrete dermal clusters in both AD and psoriasis (see this article's Fig E2 in the Online Repository at www.jacionline.org). These clusters also contain many T cells intermixed with DCs (data not shown).

Expression of T_H2-type inflammatory genes in AD versus psoriasis

We verified high-quality mRNA, based on the control gene human acidic ribosomal protein (hARP), a high level of keratin16 expression in both psoriasis and AD, and also a high level of expression of several epidermal activation genes using Affymetrix U95 gene arrays (Affymetrix, Santa Clara, Calif) (Fig 3, *A*; see this article's Fig E1 in the Online Repository at www.jacionline.org), which were confirmed by RT-PCR. As expected, AD was characterized by a T_H2 profile, with abundant IL-5, IL-10, and IL-13, and reduced expression of IFN-γ (Fig 3, *A*). In contrast, psoriasis showed a T_H1 pattern, with elevated IFN-γ and low levels of expression of IL-5, IL-10, and IL-13. In addition, IL-8 and IL-1β were increased in psoriasis. We therefore analyzed a set of cytokines, chemokines, and receptors that are associated with polarization by DCs toward cell populations that stimulate T_H1 versus T_H2 cell responses.

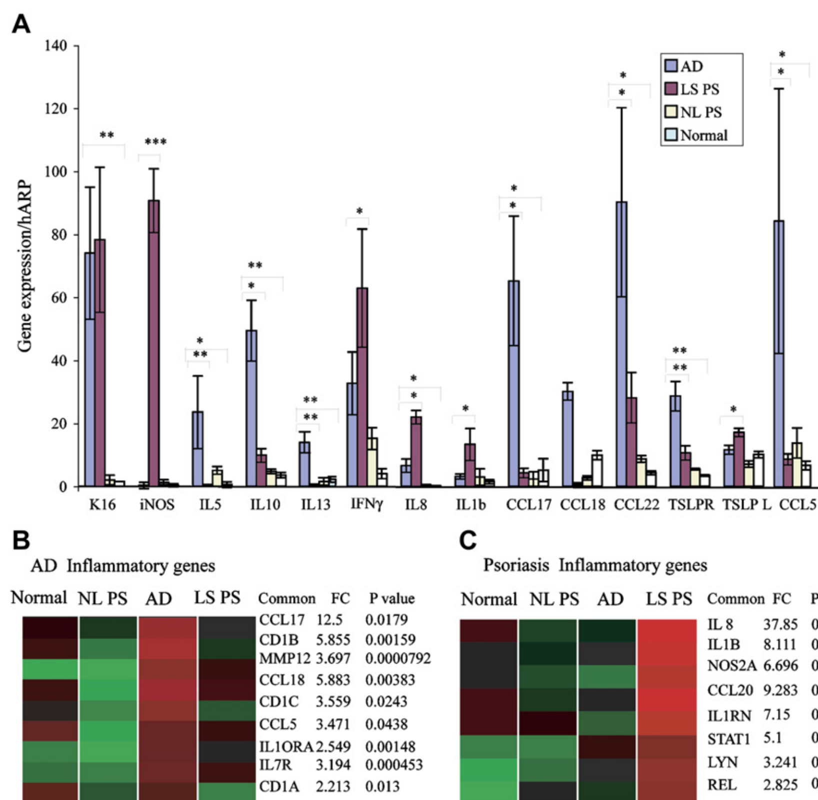

FIG 3. Genomic expression differences in AD compared to psoriasis. **A,** RT-PCR analysis of selected genes in AD, lesional psoriasis *(LS PS)*, nonlesional psoriasis *(NL PS)*, and normal skin. Mean gene expression values/hARP are shown (SEM), with statistical analyses indicated. **B and C,** Heat maps showing the differences in expression of proinflammatory DC products between AD and psoriasis, upregulated genes in AD *(B)*, and psoriasis *(C)*. FC and *P* values represent AD versus psoriasis.

Differential expression of chemokines and cytokines that may regulate T_H2 versus T_H1 polarization in AD versus psoriasis

Chemokines produced by DCs polarizing T_H2 responses include CCL17, CCL18 (pulmonary and activation-regulated chemokine), and CCL22. We found significantly increased CCL17 and CCL22 mRNA expression in AD skin lesions compared with psoriasis and normal skin ($P < .01$; Fig 3, *A*). TSLP, thought to be critical for activating $CD11c^+$ DCs to polarize T cells toward proallergic effectors, and TSLPR were also analyzed. Although we expected TSLP to be higher in AD, this was not the case, with increased TSLP mRNA expression in psoriasis ($P < .05$; Fig 3, *A*). In contrast, TSLPR mRNA expression was significantly greater in AD compared with both psoriatic and normal skin ($P < .001$ for both comparisons). TSLPR immunostaining was also more intense and diffuse in AD skin lesions compared with psoriasis lesions and normal skin (see this article's Fig E2 in the Online Repository at www.jacionline.org), suggesting that receptor expression may be more important in regulating TSLP activity rather than TSLP expression. mRNA expression of CCL5/RANTES, a T_H2 chemokine which attracts eosinophils, was significantly increased in AD compared with psoriasis and normal skin ($P < .04$; Fig 3, *A*).

In AD we found an inflammatory T_H2 gene signature with a significantly higher expression of the following products compared with psoriasis: CCL17 (fold change [FC] of 12.5; $P < .02$), CCL18 (5.88 FC; $P < .004$), CCL5/RANTES (3.471 FC; $P < .04$), IL-10 receptor antagonist (2.5 FC; $P < .001$), IL-7 receptor (part of TSLPR; 3.15 FC; $P < .0004$), CD1a, CD1b, and CD1c. Matrix metalloproteinase 12 was also significantly upregulated in AD (3.7 FC; $P < .00007$; Fig 3, *B*). In contrast, psoriatic skin exhibited significantly increased expression of proinflammatory mediators, including IL-8, IL-1β, signal transducer and activator of transcription 1, and nitric oxide synthase 2A (NOS2A, gene for iNOS; Fig 3, *C*). Among T_H1 chemokines, macrophage inflammatory protein 3α (CCL20) was highly expressed in psoriasis (9.3 FC; $P < .0005$; Fig 3, *C*).

T_H2 polarizing chemokines were produced by DCs in AD

To determine the cell types that produced these polarizing chemokines, we localized protein expression to DC

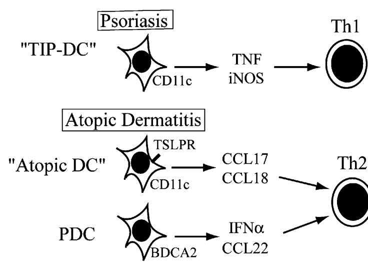

FIG 4. A proposed alternate model of dermal DC plasticity during cutaneous inflammation. Depending on environmental triggers, as well as intrinsic or genetic differences, dermal $CD11c^+$ DCs differentiate to an inflammatory DC. These IDEC-like interstitial DCs encompass both the proposed atopic DC in AD and TIP-DC in psoriasis.

subtypes. CCL17, CCL18, and CCL22 all showed increased dermal protein in AD compared with psoriasis (see this article's Fig E4, *A,* in the Online Repository at www.jacionline.org). $CD11c^+$ myeloid DCs produced CCL17 and CCL18 (see this article's Fig E4, *B,* in the Online Repository at www.jacionline.org). PDCs appeared to be the predominant source of CCL22, because CCL22 was mostly expressed within $BDCA\text{-}2^+$ DCs (see this article's Fig E4, *B,* in the Online Repository at www.jacionline.org), whereas we observed minimal coexpression with $CD11c^+$ DCs (data not shown).

DISCUSSION

Acute AD and psoriasis have been considered opposite poles of the T_H1 versus T_H2 paradigm. AD is initially characterized by a T_H2 profile, with a shift to T_H1 during the chronic phase,[3] whereas psoriasis is considered to be a model T_H1 disease.[1] DC subsets potentially provide different cytokine and chemokine microenvironments that determine this differentiation of T_H1 or T_H2 cells.[20,21] A marked increase in T_H2 and eosinophil-attracting chemokines was demonstrated in AD, whereas psoriasis was associated with an expression of cytokines and chemokines known to attract T_H1 cells and neutrophils, confirming and extending previous reports.[22,23] We found a substantially higher gene expression of CCL5/RANTES in AD in comparison with psoriasis and normal skin, which probably plays a major role in the orchestration and recruitment of eosinophils in ongoing inflammation in AD.[24-26] Our evaluation of DC subsets provides important new information that could help explain T-cell polarization in AD versus psoriasis.

Dendritic cell subsets have been recently expanded to include DCs that are classic antigen presenting cells, and also an inflammatory DC.[27] Although both myeloid ($CD11c^+$) and PDCs have been conceptualized as inflammatory DCs, the potential role of DCs as inflammatory effectors is clearest for TIP-DCs, in which a role in elimination of bacterial infection has been demonstrated.[28] TIP-DCs are also abundant in psoriasis vulgaris skin lesions, where they appear to be the dominant type of myeloid DC, with overall numbers roughly equal to infiltrating T cells.[13] A small fraction of TIP-DCs invades the lower portion of the epidermis in psoriasis, so these cells may in fact be the source of $CD11c^+$ IDECs, which have been defined as being an epidermal population by flow-cytometry–based methods of epidermal single cell suspensions.

Similar to psoriasis, AD lesions contain a rich infiltrate of $CD11c^+$ DCs, with a minority of $CD11c^+$ or $CD1a^+/CD11c^+$ cells infiltrating the lower epidermal layers. On the basis of immunohistochemical or fluorescence detection of the molecules used to classify IDECs as a unique cell type, we detect no difference in phenotype between epidermal and dermal populations of $CD11c^+$ DCs in AD or in psoriasis. Hence, it seems IDECs may actually reflect the larger process by which inflamed skin becomes infiltrated with a population of inflammatory DCs, and these cells span dermal and epidermal tissue compartments, unlike normal skin, in which $CD11c^+$ DCs are located in the dermis.

We propose an updated model of DC behavior during cutaneous inflammation (Fig 4), which encompasses our findings in the context of the recent expansion in the role of DCs. We suggest that dermal $CD11c^+$ myeloid DCs are capable of remarkable plasticity. Depending on environmental triggers, as well as intrinsic or genetic differences, DCs may differentiate to an inflammatory DC. These inflammatory DCs are IDEC-like, and encompass both the proposed ''atopic DC'' in AD and TIP-DC in psoriasis. In AD, stimulation of $CD11c^+$ DCs leads to development of CCL17-producing and CCL18-producing DCs. In conjunction with CCL22 from PDCs, this results in a T_H2-polarizing environment and atopic skin disease. We observed considerable numbers of PDCs in the dermis of AD lesions, far exceeding that of psoriasis lesions and normal skin, supporting an important role for these cells in AD. In contrast, in psoriasis, TIP-DCs produce TNF and iNOS that may have specific roles in stimulating the intense visible cutaneous inflammation of psoriasis.

Another feature of both AD and psoriasis is the presence of mature ($CD83^+$ or $DC\text{-}LAMP^+$) DCs, which are often organized in aggregates intermixed with T cells. In addition, $CD1b/c^+$ cells constitute a large fraction of DCs in both conditions, and previous work has established that this is the most stimulatory type of DC in the peripheral circulation.[29] Hence, T-cell activation could be stimulated directly in skin lesions of both AD and psoriasis by multiple types of DCs, and ongoing T-cell activation is likely to account for the genomic activation of cytokine mRNAs that typify T_H1 versus T_H2 polarity in these diseases.

In summary, in AD and psoriasis, chronic T-cell activation and the polarity of differentiation may be strongly influenced by the mixtures of abundant inflammatory and mature DCs. At this point, more work is required to elucidate distinct factors that allow $CD11c^+$ DCs to differentiate with alternative properties, such as TIP-DCs versus atopic DCs, and also to determine

whether intrinsic differentiation of DCs or T cells is influenced by the complex genetic underpinnings of both diseases.

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