Lesional dendritic cells in patients with chronic atopic dermatitis and psoriasis exhibit parallel ability to activate T-cell subsets

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Background: Atopic dermatitis (AD) and psoriasis represent polar immune diseases. AD is a T_H2/T_H22-dominant disease, whereas psoriasis is considered a T_H1/T_H17 disease. Local immune deviation is suggested to be regulated by dendritic cell (DC)–induced T-cell polarization and recruitment of specific T-cell subsets by chemokines. Although the role of chemokines is well documented, the actual contribution of DCs to activate polar T-cell subsets in human subjects is still a matter of speculation.

Objective: We sought to elucidate the significance of each cutaneous DC subset in disease-specific T-cell immune deviation.

Methods: We performed a comprehensive analysis of major cutaneous resident (Langerhans cells and blood dendritic cell antigen 1–positive dermal DCs) and inflammatory (inflammatory dendritic epidermal cells and blood dendritic cell antigen 1–negative dermal DCs) DC subsets directly isolated from the lesional skin of patients with AD and those with psoriasis.

Results: The ability of each DC subset to expand T_H1, T_H2, T_H17, and T_H22 subsets was similar between the 2 diseases, despite the association of both with accumulation of resident and inflammatory DCs. We also confirmed differential upregulation of chemokine expression in patients with AD (CCL17, CCL18, and CCL22) and psoriasis (CXCL1, IL-8, and CCL20). The expression of CCL17 and CCL22 was higher in Langerhans cells from patients with AD than from patients with psoriasis, whereas the opposite was observed for CXCL9 and CXCL10.

Conclusion: Our results suggest that DC polarity does not directly drive differential T-cell subset responses. Alternatively, disease-specific chemokines might recruit specific memory T-cell subsets into the skin, which in turn might be activated and expanded by DCs at the site of inflammation, maintaining differential immune polarity in these diseases. (J Allergy Clin Immunol 2011;128:574-82.)

Key words: *Atopic dermatitis, psoriasis, dendritic cells, T-cell polarity, T_H1, T_H2, T_H17, T_H22, chemokine, skin*

Atopic dermatitis (AD) and psoriasis are the most common inflammatory skin diseases.[1,2] Classically, these diseases have been viewed as polar T_H1 versus T_H2 diseases.[3-5] Chronic AD lesions were shown to have a marked increase in T_H2 T cells and related cytokines compared with psoriatic lesions, although a T_H1 signal was also found during the chronic phase of AD.[1,6,7] Recent works have also shown differences in the frequencies of T_H22 and T_H17 subsets between these diseases.[3,8] Parallel comparison of AD and psoriasis can thus serve as a good model for dissecting disease-specific immune deviation and its underlying mechanisms versus generalized chronic inflammation.[3,6,8-11]

Dendritic cells (DCs), which are composed of diverse cell populations, play an essential role in the generation and regulation of T-cell immune responses.[12,13] Normal human skin contains 2 major subsets of DCs: epidermal Langerhans cells (LCs; $CD1a^+CD207^+$ cells) and dermal myeloid DCs ($CD11c^+$ blood dendritic cell antigen [BDCA] 1^+ cells).[14] In addition, most (>95%) of the skin-homing (cutaneous lymphocyte–associated antigen–positive) resident T cells in steady state are $CD45RO^+$ memory T cells.[15] Chronic lesions from patients with psoriasis and those with AD have marked expansion of DCs, with different characteristics in each disease and differential T-cell subsets.[3,7,16] In addition to resident DCs, inflamed skin also harbors inflammatory DCs both in the epidermis and dermis. Inflammatory dendritic epidermal cells (IDECs; $CD1a^+CD207^-$ cells) were largely represented in the epidermis and potentially the dermis of patients with lesional AD.[6] In patients with psoriasis, a population of inflammatory DCs ($CD11c^+$BDCA-1^- cells) has been demonstrated in lesional skin.[14,17,18] One hypothesis is that disease-specific DC specialization promotes and sustains the polar T-cell responses that characterize each disease.[19,20] Psoriatic skin has a marked population of TNF and iNOS-producing DCs that have been shown to stimulate T_H1- and T_H17-cell expansion.[17,21] In patients with AD, high-level production of thymic stromal lymphopoietin (TSLP) has been detected along with a population of DCs that bear TSLP receptors.[6,22] TSLP-activated DCs have been shown to preferentially activate T_H2 T-cell responses in autologous and allogeneic cultures in an OX40 ligand

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Abbreviations used
AD: Atopic dermatitis
BDCA: Blood dendritic cell antigen
DC: Dendritic cell
FACS: Fluorescence-activated cell sorting
IDEC: Inflammatory dendritic epidermal cell
LC: Langerhans cell
MLR: Mixed leukocyte reaction
OX40L: OX40 ligand
TRAIL: TNF-induced apoptosis-inducing ligand
TSLP: Thymic stromal lymphopoietin

(OX40L)–dependent manner.[23-26] In addition, LCs derived from healthy skin or $CD34^+$ blood precursors have been shown to preferentially activate T_H2 and T_H22 T-cell subsets.[27,28] Thus although specific DC subsets might regulate polar T-cell subset activation in patients with chronic skin diseases, this concept has not been tested in DC subsets isolated directly from skin lesions of patients with AD or psoriasis.

To test the hypothesis that AD-related DCs induce a T_H2-biased immune response, we performed a comprehensive analysis of resident and inflammatory DC subsets isolated from the lesional skin of patients in the chronic stage of AD and psoriasis. Our results show that resident DC populations and inflammatory DC subsets are potent T-cell stimulators in allogeneic cultures. Each DC subset had the ability to stimulate T_H1, T_H2, T_H17, and T_H22 cells without major differences between DCs isolated from patients with each of the 2 diseases. However, some differences in the chemokines produced by DCs in these patients were detected, and this might lead to the preferential accumulation of T_H2 cells in patients with AD.

METHODS

Skin samples

Skin biopsy specimens were collected from patients with chronic AD (n = 29), patients with psoriasis (n = 28), and healthy volunteers (n = 15; see the Methods section and Tables E1 and E2 in this article's Online Repository at www.jacionline.org for details). For immunohistochemistry, biopsy specimens were frozen in OTC (Sakura, Tokyo, Japan) and stored at −80°C. Epidermal and dermal single-cell suspensions from biopsy specimens of patients with AD and patients with psoriasis were obtained after separation of the epidermis and dermis, as previously described.[27] The study was approved by the Institutional Review Boards of Tel-Hashomer Medical Center and The Rockefeller University. Written informed consent was obtained from all participants.

Fluorescence-activated cell sorting

Fluorescence-activated cell sorting (FACS) of epidermal and dermal single-cell suspensions was performed as previously described with a FACSAria (BD Biosciences, San Jose, Calif; see the Methods section in this article's Online Repository).[27] Antibodies used are outlined in Table E3 (available in this article's Online Repository at www.jacionline.org).

Mixed leukocyte reaction

FACS-sorted epidermal and dermal DCs were cultured with allogeneic total blood T cells or naive $CD4^+$ T cells from a single healthy donor at a DC/T-cell ratio of 1:50 for 7 days, and then T-cell proliferation and the cytokine profile were analyzed as previously described (see the Methods section in this article's Online Repository).[27] Antibodies used are outlined in Table E3.

Intracellular cytokine staining

T cells cultured with allogeneic DCs for 7 days were stimulated for 4 hours with 25 ng/mL phorbol 12-myristate 13-acetate and 2 μg/mL ionomycin in the presence of 10 μg/mL brefeldin A (all from Sigma-Aldrich, St Louis, Mo) at 37°C. Thereafter, intracellular cytokine staining was performed as previously described.[27] Antibodies used are outlined in Table E3. Expression of each molecule was analyzed in activated T cells (high forward scatter, high side scatter).

Microarray hybridization

We used the Human Genome U133 Plus 2.0 arrays (Affymetrix, Santa Clara, Calif). See the Methods in this article's Online Repository for further details.

Immunohistochemistry

Staining of skin sections and cell counts of positive cells were carried out as previously described.[6] Antibodies used are outlined in Table E4 (available in this article's Online Repository at www.jacionline.org).

Statistical analysis

Cell counts were analyzed by using a 2-tailed Student *t* test. The percentage of cytokine-producing cells was compared between patients with AD and psoriasis for each cell type by using repeated-measures ANOVA with between-subjects factors for analysis. *P* values of .05 or less were considered significant. CEL file quality control was assessed by using Harshlight[29] and arrayQualityMetrics packages from R/Bioconductor. Expression measures were obtained with the GeneChip Robust Multiarray Average. Gene-set group differences for T_H1 and T_H2 chemokine gene sets were assessed by using a gene-set analysis approach.[30] Gene-set statistics (the *z* score) were used to calculate the T_H1 and T_H2 score.[31] See the Methods section in this article's Online Repository for further details.

RESULTS

Marked accumulation of DCs in lesional skin characterizes both AD and psoriasis

Biopsy specimens from AD, psoriatic, and healthy skin were evaluated for the presence of DCs by means of immunohistochemistry. We also analyzed several markers that might distinguish functional DC subsets. Representative immunohistochemistry is shown for each marker (Fig 1), and cell counts of all cases are represented in Fig E1 (available in this article's Online Repository at www.jacionline.org). In comparison with healthy skin, skin from patients with AD or psoriasis showed increased numbers of dermal $CD11c^+$ myeloid DCs. A significantly higher number of dermal BDCA-1^+ cells were found in AD skin compared with that seen in psoriatic and healthy skin, indicating an increased population of resident dermal DCs. The numbers of dermal BDCA-1^+ cells in AD and psoriatic skin were lower than $CD11c^+$ counts, reflecting the existence of $CD11c^+$BDCA-1^- dermal inflammatory DC subset in both diseases. CD1a expression, which is common to LCs and IDECs, was increased in the epidermis of patients with both diseases compared with healthy epidermis. CD1a also displayed a dermal distribution in patients with AD only, which corroborated our previous data.[6] FcεRI, which is associated with LCs and IDECs in patients with AD, showed a mainly dermal staining in AD skin, which is also consistent with our previous observations.[6] Because TNF-induced apoptosis-inducing ligand (TRAIL)

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