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Epidermal CCR6⁺ γδ T Cells Are Major Producers of IL-22 and IL-17 in a Murine Model of Psoriasiform Dermatitis

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Cytokine components of Th17 pathway play vital roles in human psoriasis. Although much is known about TCR αβ T cells in psoriasis, the role of unconventional T cells, including γδ T cells, is unclear. In this study, using an IL-23 skin injection model of psoriasiform dermatitis in mice, we demonstrate that IL-22, IL-17A, and the IL-23R were highly enriched in a population of CCR6⁺, TCR γδ-low expressing (GDL) T cells that accumulated in the epidermis after IL-23 injections. GDL cells were distinct from resident TCR γδ-high, Vγ3⁺,CCR6⁻ T cells in the epidermis that did not change appreciably in numbers following IL-23 injection. Large numbers of CCR6⁺ cells were detected at or above the level of the epidermal basement membrane by confocal microscopy 5 d after repeated IL-23 injections at the same time GDL cells increased in numbers in the epidermis. TCR αβ-deficient mice (lacking γδ T cells) exhibited decreased ear swelling and downregulated expression of IL-22 and IL-17A in the epidermis following IL-23 injection. Our data suggest that a subset of γδ T cells play a critical role in IL-23-mediated psoriasiform dermatitis. The Journal of Immunology, 2011, 187: 5026–5031.

The immunopathogenesis of psoriasis has been revealed in much greater depth and complexity as new data implicate the Th17 signaling pathway as a key mediator in the development of psoriasis (1). IL-23, a key upstream player in the Th17 pathway, is an essential cytokine for the maintenance of Th17 cells, and therapeutic agents targeting the shared p40 component of IL-23 have shown remarkable clinical efficacy in psoriasis (2). Current models suggest that IL-23 produced by dendritic cells act to sustain dermal CCR6-expressing Th17 cells, which then produce IL-22 as a major downstream effector of epidermal hyperplasia (3).

Although it is known that CCR6 is essential for the development of a psoriasiform phenotype following injection of IL-23 in mouse skin (4), it is not clear whether other cells of the immune system (besides conventional αβ T cells) produce the critical downstream effector, IL-22, that drives epidermal hyperplasia in psoriasis (5, 6). Moreover, it is unclear whether immune cells present in the dermis or epidermis play the major role of delivering IL-22 to keratinocytes to stimulate hyperplasia.

Recent data reveal that γδ T cells express the IL-23R and respond to IL-23 and IL-1β by secreting IL-17 and IL-22 (7). Moreover, production of IL-17 by skin γδ T cells, as opposed to αβ T cells, was critical for cutaneous defense against Staphylococcus aureus (8). On the basis of these data, we hypothesized that γδ T cells in the skin may be critical for the delivery of IL-22 or other Th17 cytokines to epidermal keratinocytes.

Materials and Methods

Mice and cytokine injections
C57BL/6j wild-type (WT) and TCR δ-deficient mice (B6.129p2-Tcrδtm1Mom) between 8 and 12 wk old were purchased from The Jackson Laboratory. Animal protocols were approved by the Animal Care and Use Committees at the Medical College of Wisconsin. Intradermal injections of 500 ng recombinant mouse IL-23 (eBioscience) in 20 μl PBS were performed into both ears of anesthetized mice every other day for 6 d (unless otherwise indicated) as described previously (4).

Processing of epidermal cells from mouse ears
After recovery of mouse ears, ventral skin sheets were separated from cartilage with forceps and incubated in PBS containing 0.5% trypsin (U.S. Biochemical) for 40 min at 37˚C with dermal side down to separate epidermal sheets from dermal sheets. To obtain cell suspensions, epidermal sheets were treated in DMEM (Invitrogen) containing 0.05% DNase I (Sigma-Aldrich) and 10% FBS as described previously (9). Dermal sheets were incubated in 15 ml RPMI 1640 medium (Invitrogen) containing 40 mg collagenase D (Roche), 0.01% DNase I, and 20% FBS for 45 min at 37˚C as described previously (10). Cells were then filtered through a 70-μm nylon mesh and washed prior to use.

2,4-Dinitro-1-fluorobenzene treatment
We treated the ventral side of WT mouse ears with 10 μl acetone containing 0.5% 2,4-dinitro-fluorobenzene (Sigma-Aldrich) and 20% olive oil for 2 d prior to analysis.

Real-time PCR
The extraction of RNA from epidermal or dermal cell suspensions was performed using an RNeasy Kit, according to the manufacturer’s instructions (Qiagen). RT-PCR was performed via StepOnePlus Real-Time PCR System (Applied Biosystems).

Flow cytometry
mAbs against mouse γδ TCR (catalog number 553177), Vγ3 TCR, and CD3e were purchased from BD Biosciences. Abs against IL-22, IL-17A, and CCR6 were purchased from R&D Systems and BioLegend. Intracellular staining for IL-22 was done after incubating cells for 2 h with GolgiStop (BD Biosciences). Cells were then fixed and permeabilized using the BD Cytofix/Cytoperm Plus Kit (BD Biosciences). Flow cytometric data were analyzed using FlowJo version 7.5.5 software (Tree Star).

Histopathological analysis and immunofluorescence microscopy
Frozen 5-μm sections of whole mouse ears were stained with H&E. Staining for CCR6 and Laminin332 was done using frozen 8-μm sections

Department of Dermatology, Medical College of Wisconsin, Milwaukee, WI 53226
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Address correspondence and reprint requests to Dr. Sam T. Hwang, Department of Dermatology, Medical College of Wisconsin, FEC 4100, 9200 West Wisconsin Avenue, Milwaukee, WI 53226. E-mail address: sthwang@mcw.edu
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Abbreviations used in this article: DETC, dendritic epidermal T cell; GDH, γδ-high expressing; GDL, γδ-low expressing; GDN, γδ-negative; WT, wild-type.
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of whole mouse ears. Sections were air dried after 20 min fixation in cold acetone, blocked for 1 h at 20°C with 5% goat serum, Fc blocker (2.4G2; BioXCell), and goat anti-rabbit IgG-HRP (Santa Cruz Biotechnology) in PBS containing 3% skim milk. After the sections were washed in PBS, they were incubated with anti-mouse CCR6 mAb or rat IgG (R&D Systems) overnight at 4°C. Following a brief washing step with PBS, sections were then incubated with anti-Laminin332 Ab (11) or rabbit IgG (R&D Systems) overnight at 4°C. After washing in PBS, the sections were incubated with goat anti-Ki67 polyclonal Ab (Santa Cruz Biotechnology) or goat IgG (R&D Systems) overnight at 4°C. After they were washed in PBS, the sections were incubated with anti-Laminin332 Ab (11) or rabbit IgG (R&D Systems) for overnight at 4°C. After they were washed in PBS, the sections were incubated for 30 min at 20°C with Alexa 568-conjugated donkey anti-rabbit IgG (Invitrogen), then washed in PBS and mounted using ProLong Gold anti-fade reagent with DAPI nuclear stain (Invitrogen). Images were acquired using the Carl Zeiss LSM510 confocal microscope with axio-observer microscope and LSM510 version 4.2 software.

Staining for Ki67 and Laminin332 was done using frozen 8-μm sections of whole mouse ears. Sections were air-dried after 10 min fixation in PBS containing 4% paraformaldehyde, blocked for 1 h at room temperature with 5% donkey serum, Fc blocker (2.4G2; BioXCell), and donkey anti-goat IgG-HRP (Santa Cruz Biotechnology) in PBS containing 3% skim milk. After they were washed in PBS, the sections were incubated with goat anti-Ki67 polyclonal Ab (Santa Cruz Biotechnology) or goat IgG (R&D Systems) overnight at 4°C. After they were washed in PBS, the sections were incubated with anti-Laminin332 Ab (11) or rabbit IgG (R&D Systems) for overnight at 4°C. After they were washed in PBS, the sections were incubated for 30 min at 20°C with Alexa 568-conjugated donkey anti-goat IgG (Invitrogen) and Alexa 488-conjugated donkey anti-rabbit IgG (Invitrogen) and then washed in PBS and mounted using ProLong Gold anti-fade reagent with DAPI nuclear stain (Invitrogen). Images were acquired using the Carl Zeiss LSM510 confocal microscope with axio-observer microscope and LSM510 version 4.2 software (Lumenera).

Sorting γδ T cells for RT-PCR  γδ TCR-high, γδ TCR-low, and γδ TCR-negative populations were sorted from epidermal cell suspensions using a FACS Aria System flow cytometer (BD Biosciences). To recover sufficient RNA for RT-PCR analysis, identical numbers of these different cell populations were added to a 10-fold excess of B16 murine melanoma cells prior to recovery of RNA.

Statistics  All quantitative data were shown as the mean ± SEM unless otherwise indicated. Simple comparisons of means and SEM of data were made by using Student t test, and post hoc multiple comparisons were made by using Tukey’s test.

Results  Epidermal cells contribute a significant proportion of IL-22 and IL-17A mRNA production in the IL-23 injection model of psoriasiform dermatitis  Previously, we demonstrated that IL-23 induced significant ear swelling in WT, but not CCR6-deficient, mice (4). We replicated and expanded this observation in WT C57BL/6 mice (Fig. 1). To study early events in the inflammatory process, we focused on day 5 following initiation of IL-23 treatment. Although epidermal hyperplasia at day 5 is not as robust as that observed at day 15, changes in epidermal hyperplasia, leukocyte infiltration, and ear swelling are still quite evident (Supplemental Fig. 1A). Enhanced proliferation in IL-23–treated ears was noted through the presence of increased Ki67 staining in IL-23–treated versus PBS-treated ears (Supplemental Fig. 1B). Ear swelling (a useful measure of inflammation in the ear in the IL-23 injection model (4, 5)) steadily increased with every other day IL-23 injections (versus PBS) and then washed in PBS and mounted using ProLong Gold anti-fade reagent with DAPI nuclear stain (Invitrogen). Images were acquired using the Carl Zeiss LSM510 confocal microscope with axio-observer microscope and LSM510 version 4.2 software.

FIGURE 1. Epidermis is a major source of IL-22 and IL-17A in an IL-23–mediated model of psoriasiform dermatitis. A, Mouse ears were injected with IL-23 or PBS every other day for 15 d. *p < 0.01 versus PBS-injected group. B, At day 5 following IL-23 or PBS injection, ears were harvested, and the epidermal sheets were separated from dermal sheets by established methods. Epidermal and dermal cell suspensions were used for real-time RT-PCR to measure expression of IL-22 and IL-17A. **p < 0.05. These experiments were repeated four times with similar results.

A novel population of non-Vγ3, CCR6-expressing, γδ-low T cells is recruited to murine epidermis upon treatment with IL-23  To determine whether γδ T cells were the source of IL-22, we stained epidermal suspensions from IL-23–injected ears with mAb against the γδ TCR and assessed numbers of γδ T cells in the epidermis. Of note, two populations of γδ TCR-positive cells were seen (Fig. 2A). A γδ TCR-high (hereafter, γδ-high expressing [GDH]) population was present in resting or PBS-injected ear skin at a frequency of ∼2–3%. Following IL-23 injection, however, CD3ε-low and γδ TCR-low (hereafter, γδ-low expressing [GDL]) cells accumulated within the epidermis (arrow, Fig. 2A). GDH cells uniformly expressed Vγ3 (Fig. 2B), indicating that they were Vγ3-positive [or Vγ5, depending on nomenclature (12)] skin-resident dendritic epidermal T cells (DETC). By contrast, GDL cells were uniformly Vγ3 negative (Fig. 2B). This finding also made it highly unlikely that GDL T cells were derived from resident GDH T cells given the lack of Vγ3 expression in former population. GDL T cells from IL-23–treated mice produced more IL-22 than GDH T cells as determined by flow cytometry (Fig. 2C). Compared with PBS-injected mice (Supplemental Fig. 2C), GDL T cells were present in the epidermis of IL-23–treated mice (Fig. 2C) at higher frequencies and with higher expression of IL-22. Last, CCR6 was much more highly expressed in the GDL (versus GDH) population (Fig. 2C).

In triple staining experiments, >90% of IL-22+ or IL-17A+ GDL T cells expressed the CCR6 receptor (Supplemental Fig. 2),
a marker for Th17 conventional T cells and specific γδ T cell populations (13–15). The small numbers of IL-22+ GDH T cells, representing <0.1% of the combined GDH and GDL populations (Supplemental Fig. 2) showed no specific CCR6 staining, suggesting that the CCR6+ cells were restricted to the GDL population. Interestingly, not all forms of inflammatory stimuli elicited the recruitment of GDH T cells because application of 2,4-dinitro-1-fluorobenzene, a well-described skin contact sensitizer, did not result in accumulation of GDL T cells (Fig. 2E). Thus, a CCR6+, IL-22–producing population of GDH T cells (distinct from resident Vyγ3+ GDH cells/DETC) accumulates in the murine epidermis following IL-23 treatment.

FIGURE 2. IL-23–injected ears show increased numbers of IL-22+, CCR6+ γδ low-expressing cells compared with PBS-injected ears. Five days after initial IL-23 injection, epidermal suspensions of cells were analyzed by flow cytometry. A, Staining with anti-γδ TCR mAb showed a large increase in γδ low-to-intermediate–expressing (GDL) T cells following IL-23 injection (bold arrow). B, GDL T cells (bold arrow in A) in IL-23–injected mice are distinct from resident Vyγ3 (also known as Vy5)-expressing GDH T cells. GDL T cells (bold arrow in A) in IL-23–injected mice expressed higher levels of IL-22 (C) by intracellular flow cytometry and CCR6 (D) by surface staining relative to GDH T cells. The numbers represent the percentage of cells in the solid square compared with the dashed square, respectively. These experiments were repeated more than four times with similar results. E, Mouse ears were topically treated daily with 10 μl acetone containing 0.5% 2,4-dinitro-1-fluorobenzene (DNFB) in 20% olive oil for 2 d prior to analysis as in A. Similar results were obtained in two independent experiments.

FIGURE 3. Time course of GDL cell recruitment to epidermis following IL-23 injection. A, Following treatment with PBS or IL-23 for the indicated time period, mice were euthanized, and epidermal cell suspensions were prepared for flow cytometric analysis with a pan-γδ TCR mAb. B and C, Ears were stained with anti-CCR6 mAb (green) and anti-Laminin332 mAb (basement membrane in red), revealing larger numbers of CCR6+ cells in the epidermis (above the basement membrane) at day 5 in IL-23–, but not PBS-injected, mice. Isotype control staining showed no staining with either IL-23 or PBS-injected ears (data not shown). Similar results were obtained in two independent experiments. Original magnification ×200 (B) and ×400 (C).
Trafficking of GDL cells to epidermis correlates with entry of CCR6+ cells into the epidermis

To examine the time course of recruitment of GDL T cells to the epidermis, we quantified numbers of GDL T cells by flow cytometry at days 1, 3, and 5 following IL-23 treatment. Small numbers of GDL T cells were detected as early as day 1 following IL-23 injection. Larger numbers of GDL T cells (an increase of ~4-fold over day 1) were generally present in the epidermis at day 5 following IL-23 injection, whereas virtually no GDL T cells accumulated in the epidermis following PBS injection throughout the 5-d course of the experiment (Fig. 3A). Interestingly, at day 5, we also observed increased numbers of CCR6+ cells in the epidermis of IL-23–injected, but not PBS-injected, skin when we used immunofluorescence microscopy to localize these cells (Fig. 3B). Close inspection at the level of the basement membrane (revealed by anti-Laminin332 Abs, red) showed many CCR6+ cells either at or immediately adjacent to the basement membrane, suggesting that these cells were trafficking into the epidermis (Fig. 3C). Thus, GDL T cells (as well as CCR6+ cells) appear to increase substantially in the epidermis at day 5 following an IL-23 injection, although smaller numbers are present in the epidermis as early as day 1 after injection.

GDL cells are enriched in expression of IL-22, IL-17A, IL-23R, and CCR6 mRNA compared with other epidermal cell populations

To determine whether GDL T cells were a major source of IL-22 in IL-23–treated epidermis, we used flow cytometry to segregate GDL, GDH, and γδ-negative (hereafter, GDN) T cells from epidermal suspensions following IL-23 treatment for closer analysis. GDN cells had no expression of the γδ TCR and represented all other epidermal cells. Because recovery of the γδ TCR populations were low after sorting, we mixed identical numbers of the three cell populations with a 10-fold excess of B16 murine melanoma cells (as carriers) to recover sufficient RNA. Of note, GDL T cells were highly enriched in expression of IL-22, IL-17A, and CCR6 mRNA transcripts compared with the other populations tested as well as to epidermal cells from PBS-treated mice (Fig. 4). GDL T cells were also highly enriched for expression of the IL-23R, suggesting they were one of a minority of cells in the epidermis that was capable of being stimulated by IL-23 (Fig. 4). Thus, GDL T cells represent major sources of key cytokines, particularly IL-22, which play critical roles in epidermal proliferation and dermal inflammation in the IL-23 injection model.

γδ T cells play a functional role in dermal inflammation in the IL-23 injection model of psoriasiform dermatitis

To determine whether γδ T cells played a critical functional role in our model, we subjected TCR δ-deficient mice (lacking γδ T cells) to our IL-23 skin injection protocol. WT mice injected with IL-23 as controls displayed the usual ear swelling, whereas TCR δ-deficient and WT mice injected with PBS failed to show any significant increase in ear swelling (Fig. 5A). TCR δ-deficient mice, however, showed a marked decrease in ear swelling when compared with WT mice in the first 5–8 d following IL-23 injection, but these mice showed ear swelling that was similar to that of WT control mice on day 10 and later (Fig. 5A). At day 12, the skin of IL-23–injected skin in WT and TCRδ-deficient mice...
appeared histologically identical and was equivalently increased in mean epidermal thickness compared with PBS-injected skin (Supplemental Fig. 3A, 3B). Interestingly, at day 12, the number of GDL cells in epidermis as determined by flow cytometry was somewhat diminished in number (0.01% of epidermal cells) compared with day 5 (contrast with Fig. 3A), suggesting that GDL cells may leave the epidermis at that time or that proliferation is enhanced in keratinocytes to the point that GDL represent a smaller fraction of epidermal cells. A modest reduction in mean epidermal thickness was also noted in the TCR δ-deficient versus WT mice at day 5 but not day 15 (Fig. 5B). At day 5, RT-PCR analysis revealed that epidermal cells from TCR δ-deficient mice showed reduction in the expression of IL-22, IL-17a, and CCR6 compared with WT mice following IL-23 injection (Fig. 5C), suggesting that γδ T cells were a major, but not exclusive, source of IL-22 and IL-17A in the epidermis. By day 12, epidermal mRNA expression of IL-17a and IL-22 continued to be moderately decreased in TCR δ-deficient mice injected with IL-23 (Supplemental Fig. 3C). Interestingly, we could not detect IL-22 in epidermal γδ T cells in TCR δ-deficient mice following IL-23 injection, suggesting they were not the source of residual IL-22 expression (Supplemental Fig. 3D). Thus, γδ T cells play a functional role in producing IL-22 and IL-17A and in the development of early ear inflammation in this model. Although this experiment could not rule out the functional participation of the resident GDH T cell population, the relative absence of IL-22 and IL-17A expression in GDH T cells in IL-23–injected WT mice (Fig. 4) reduced the likelihood that they played significant roles in ear inflammation in this model.

Discussion

The role of γδ, or unconventional, T cells in psoriasis is virtually unknown, although γδ T cells from the synovial fluid of patients (16) or from psoriatic skin can be isolated (17). Moreover, γδ T cells, including those expressing the cutaneous lymphocyte-associated Ag, have been reported to be present in greater numbers in guttate and plaque psoriasis lesions (18, 19). Interestingly, peripheral γδ T cells express high levels of IL-23R and respond to IL-1β and IL-23 by producing IL-17 and IL-22 (7).

In mouse skin, there are at least two distinct populations of γδ T cells (20). Those expressing high levels of the γδ receptor are generally present in larger relative numbers even in unperturbed skin, show dendritic morphology (have been termed DETC), and express canonical TCRs (Vγ3 or 5, depending on the nomenclature used (12)). In certain strains of mice (but not C57BL/6 used in our studies), the lack of resident γδ T cells predisposes mice to spontaneous dermatitis and likely contributes to surveillance of skin cancer (20).

By contrast, the physiologic role of the smaller numbers of T cells with diminished levels of the γδ receptor in skin is unknown, although they do not downregulate cutaneous inflammation as resident γδ T cells do (20). A new study described a motile population of dermal γδ T cells that express low–intermediate levels of the γδ TCR (compared with DETC), CCR6 and CXCR6, and IL-17 (21). Importantly, these thymically derived cells did not have features of DETC, but the role(s) of these cells in inflammatory skin disease, including psoriasis, were not explored (21). It is conceivable that the GDL T cells we observe to be recruited to epidermis after IL-23 injection represent transepidermal migration of dermal γδ T cells described by Gray et al. (21). Indeed, we detected GDL T cells in the dermis in both PBS- and IL-23–injected skin at similar frequencies (Supplemental Fig. 4). Interestingly, at baseline these dermal GDL T cells expressed IL-22, which did not increase with IL-23 treatment. Our results (Fig. 3) suggest that up to 5 d of repeated IL-23 injections are required to recruit larger numbers of GDL T cells to the epidermis from dermis and/or peripheral blood.

Recently, CCR6 was shown to be a marker of peripheral IL-17A–expressing γδ T cells (13, 22). We now demonstrate migration of CCR6+ cells in the epidermis or at the dermal–epidermal junction after 5 d of IL-23 injection (Fig. 3) at the same time point when larger numbers of GDL cells are detected in the epidermis by flow cytometry (Fig. 3). The GDL T cells we observed following IL-23 injection are highly enriched in IL-17A, IL-22, and IL-23R compared with GDH T cells but do not express IFN-γ as detected by RT-PCR and intracellular flow cytometry (data not shown), suggesting they bear similarities to peripheral IL-17A–expressing γδ T cells that have been suggested to have roles in several autoimmune disease models (23–25).

**FIGURE 5.** TCR δ-deficient mice show reduced ear swelling in response to IL-23 injection. A, WT and TCR δ-chain-deficient mice that lack γδ T cells were injected with IL-23 or PBS per protocol with measurement of ear swelling throughout the treatment period. *p < 0.01 versus all other groups, **p < 0.01 versus PBS-injected groups, ***p < 0.05 versus PBS-injected groups. This experiment was performed three times with similar results. B, At days 5 and 15 following IL-23 or PBS injection, ears were harvested, and the epidermal thickness was measured by imaging software from paraffin-embedded, H&E-stained tissues. C, IL-22, IL-17A, and CCR6 mRNA expression was assessed in treated mice by quantitative RT-PCR on day 5. Similar results were obtained in two independent experiments.
IL-22 is a key activator of epidermal hyperplasia in human psoriasis (6). Our data reveal that a discrete epidermal population of CCR6+ GDL T cells is highly enriched for IL-22 after IL-23 injection. Although we could not rule out that the cumulative expression of IL-22 or IL-17A by GDN cells might have been biologically relevant, the reduced ability of TCR δ-deficient mice to respond to IL-23 injection (Fig. 5A) argues that γδ T cells play a role in mediating the effects of IL-23 injection until day 10 when other sources for Th17 cytokines then likely come into play. Even without γδ T cells, ~20–40% of mRNA expression for IL-17A and IL-22 are maintained, suggesting that other sources of these cytokines are present in the epidermis (Fig. 5C).

By virtue of their epidermal location, GDL T cells are ideally placed to deliver high levels of IL-22 and/or IL-17A directly to keratinocytes. That the GDL T cells were CCR6 positive is interesting in light of our previous finding that CCR6 is required for development of IL-23-mediated psoriasis-like dermatitis (4). GDL T cells may represent a source of IL-22 and IL-17A that contributes to the pathogenesis of psoriasis or to other skin conditions, suggesting that therapy directed at these cells (or their specific receptors such as CCR6 (26)) may be useful for the treatment of several autoimmune inflammatory conditions, including psoriasis.

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Disclosures

The authors have no financial conflicts of interest.

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