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Th17 Cells Carrying TCR Recognizing Epidermal Autoantigen Induce Psoriasis-like Skin Inflammation

Shuhei Nishimoto,*,† Hitoshi Kotani,*, Sanae Tsuruta,*, Nana Shimizu,*, Minako Ito,*, Takashi Shichita,*, Rimpei Morita,*, Hayato Takahashi,† Masayuki Amagai,† and Akihiko Yoshimura*‡

Psoriasis is considered a Th17-type autoimmune skin inflammatory disease; however, involvement of an autoantigen-specific TCR has not been established. In this study, we show that psoriasis-like skin inflammation can be induced by autoreactive Th17 cells. We previously developed the desmoglein 3–specific TCR-transgenic (Dsg3H1) mouse, in which CD4+ T cells recognize physiological epidermal autoantigen. T cells from Dsg3H1 mice were polarized into Th17 cells in vitro and then adoptively transferred into Rag2–/– mice. Dsg3H1-Th17 cells induced severe psoriasis-like skin inflammation within 2 wk after transfer in the tissues in which desmoglein 3 is expressed. Such pathology was not observed when wild-type Th17 cells or Th1-skewed Dsg3H1 T cells were transferred, and it was strongly suppressed by anti–IL-12/23 and anti–IL-17 Abs. Although IFN-γ–deficient Dsg3H1-Th17 cells were fully pathogenic. These results demonstrate that cutaneous psoriasis-like immunopathology can be developed by epidermis-specific recognition of Th17 cells, which is strictly dependent on IL-17 but not IFN-γ.

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merging data in mice and humans reveal a critical contribution of Th17-associated cytokines, particularly IL-23 and IL-17, in the pathogenesis of psoriasis (1). Examples of murine models for psoriasis-like skin inflammation are the adoptive transfer of human CD4+CD45Rbhigh T cells into immunodeficient scid/scid recipient mice (2), injection of rIL-17F (3) or rIL-23 (4, 5) into murine ear tissue, application of 12-O-tetradecanoylphorbol-12-acetate to K5.Stat3C (6) or K14/VEGF (7) transgenic (tg) mice, and the topical application of imiquimod (8). IL-17A, IL-22, IL-17F, IL-23p19, and IL-12/IL-23p40 were shown to be elevated in mice with psoriasis-like lesions induced by 12-O-tetradecanoylphorbol-12-acetate, imiquimod, or rIL-23 and in human psoriatic lesions (4, 7, 9), and IL-17–producing CD3+ T cells were increased in IL-23–induced dermatitis (7, 9, 10). Immunocompromised mice transplanted with grafts from humans with psoriasis develop typical features over several weeks (11, 12), and the development of psoriasis is dependent on the injection of CD4+ T cells (13). A recent study showed that anti-human IL-23 Ab blocked the development of psoriasiform lesions in xenotransplanted mice (14).

Furthermore, human IL-17–specific mAbs were effective in inhibiting psoriatic lesions in human patients (15, 16). Collectively, these disease models and clinical trials suggest that the IL-23–IL-17 pathway plays essential roles in the development of psoriasis.

Psoriasis is considered an autoimmune disease. The association of psoriasis with HLA-C*06 strongly suggests the involvement of T cells in its development (17, 18). Essential roles for autoreactive CD4+ T cells in psoriasis were demonstrated in human psoriasis xenograft mouse models (19, 20) and in a naive CD4+ T cell transfer model (21). However, CD4+ T cells were shown to be an important source of IL-17 in skin inflammation models (22, 23). In this sense, there are no definitive animal models of autoimmune psoriasis because autoreactive T cells or TCR that react with skin autoantigen have not been identified.

Previously, we reported a unique system evaluating the in vivo pathogenicity of desmoglein 3 (Dsg3)-reactive T cells at a clonal level in a mouse model for pemphigus vulgaris, an autoimmune blistering disease induced by anti-Dsg3 autoantibodies (24, 25). Dsg3-reactive CD4+ T cell lines generated in vitro were adoptively transferred into Rag-2–/– mice with primed B cells derived from Dsg3-immunized Dsg3–/– mice. Seventy of twenty T cell lines induced IgG anti-Dsg3 Ab production and acantholytic blister, a characteristic histological feature, in recipient mice. Th2-type differentiation was required for pathogenic Dsg3-reactive T cell lines to promote IgG anti-Dsg3 Ab production by primed B cells (25). Furthermore, we showed that interface dermatitis was developed in mice that were adoptively transferred with Dsg3-specific CD4+ T cells from Dsg3-specific TCR-tg mice or CD4+ T cells carrying retrovirotransduced Dsg3-specific TCR (26). The use of retrovirotransduced Dsg3-specific T cells revealed that interface dermatitis occurred in an IFN-γ–dependent manner. Thus, Th1 cells carrying skin-specific autoantigen could induce interface dermatitis, indicating that effector Th1/Th2 phenotypes, in addition to autoreactive TCR, may determine the pathological feature of autoreactive T cells (26). However, it is not known whether psoriasis, the most prevalent Th17-type autoimmune disease, develops if autoreactive T cells are skewed into Th17.
In this study, we show that Th17-skewed autoreactive T cells can induce psoriasis-like skin inflammation. We isolated CD4+ T cells from Dsg3-specific TCR-tg mice and polarized them into Th17 cells with IL-6, IL-23, and TGF-β in vitro. When they were adoptively transferred into Rag2−/− mice, the mice that received a transfer of Th17-skewed T cells developed skin inflammation resembling the histopathology and inflammatory molecular patterns of psoriasis. These pathologies were not observed when Th1-skewed T cells or non-Tg Th17 cells were transferred. Although IFN-γ/IL-17 double-positive T cells were drastically increased in the skin lesions after transfer, IFN-γ was not required for the pathogenesis, whereas anti–IL-17 Ab or IL-12/23 p40-blocking Ab reduced the pathology, indicating that Th17-type cytokines were essential for the development of psoriasis-like disease. These results demonstrated that cutaneous psoriasis-like immunopathology can be caused by epidermis-specific recognition of Th17 cells, and our system provides a useful tool for analyzing and treating human psoriasis.

Materials and Methods

Mice

Dsg3-specific–tg mice (Dsg3H1) were produced as previously described (26). C57BL/6 Rag2−/− mice were purchased from the Central Institute for Experimental Animals (Tokyo, Japan). Ifng−/− mice were purchased from The Jackson Laboratory. Dsg3H1 mice (C57BL/6 background) were bred with Ifng−/− mice (C57BL/6 background) to generate IFN-γ-deficient Dsg3H1 mice. The Keio University Ethics Committee for Animal Experiments approved all experiments in this study.

CD4 T cell preparation and in vitro differentiation

Th1 and Th17 differentiation was carried out as described (27). LN was collected, single-cell suspensions from either mouse spleens or lymph nodes (LNs) were positively selected using CD4-conjugated magnetic MicroBeads (Miltenyi Biotec) at a 1:10 dilution for 20 min on ice. The CD4+ T cells (8 × 10^6 cells/well) were cultured at 37 °C (5% CO2) in RPMI 1640 (Invi- trogen Life Technologies). The medium was supplemented with 10% FCS, 100 U/ml penicillin, 100 μg/ml streptomycin, and 50 μM 2-ME. The cells were stimulated with plate-bound anti-CD3 Ab (5 μg/ml; clone 145-2C11) and soluble anti-CD28 Ab (1 μg/ml; eBioscience). For Th1 differentiation, the cells were cultured with 10 ng/ml mouse anti-IFN-γ, 20 ng/ml mouse IL-12, 20 ng/ml mouse IL-23, 10 μg/ml mouse anti–TGF-β, 1 μg/ml mouse anti–IL-4 Ab, and 1 μg/ml anti–IL-2 Ab. For Th17 differentiation, the cells were cultured with 20 ng/ml mouse anti-IFN-γ, 10 ng/ml mouse IL-6, 10 ng/ml mouse IL-23, 10 μg/ml mouse anti–TGF-β, 1 μg/ml mouse anti–IL-4 Ab, and 1 μg/ml anti–IL-2 Ab. Differentiated CD4+ T cells (1 × 10^6) were injected i.v. into Rag2−/− mice, as described previously (28). For Ab treatment of transferred mice, Abs (0.1 mg/mouse) were injected i.p. on days 0 and 7. Anti-p40 Ab (C17.8) was produced in-house, and mouse anti–IL-17A Ab and IgG2A isotype control were purchased from R&D Systems.

Real-time RT-PCR

Total RNA was extracted from the whole skin, as described (29). Skin samples were pooled to obtain a sufficient amount of mRNA for analysis. The RNA was extracted using an RNeasy Micro Kit (QIAGEN), according to the manufacturer’s instructions. RNA was reverse transcribed to cDNA with random primers and a high-capacity cDNA reverse transcription kit (Applied Biosystems, Carlsbad, CA), in accordance with the manufacturer’s instructions. Gene expression was examined using a CFX384 real-time PCR detection system (Bio-Rad, Foster City, CA) and a Kapa SYBR FAST qPCR kit (Kapa Biosystems, Boston, MA). The results were normalized to β-actin levels. The primers used were as follows: 5’-GCTCCAGAAGGCCCCTCAG-3’ and 5’-CTTTCCCTCGCATTGACA-3’ for IL-17A; 5’-GCCARGGATTACACATCCTAC-3’ and 5’-CAGTGGCGCCATGGAC-3’ for IFN-γ; 5’-GGGCGAGCCTTGCAGATAACA-3’ and 5’-GGTTCGACTTCCCTACCC-3’ for S100a9; 5’-CACTGAGGACAGCATGGA-3’ and 5’-GATCGTGGATATTTGCAGCTAC-3’ for Ggtg-3’ for Cxcl5; 5’-ATGTTGTCGCTGGACGATGA-3’ and 5’-CATCCGCTGTTGTTGTTGAGACG-3’ for Ggtg-3’. All data are expressed as the mean ± SE and were analyzed statistically using the Dunnett test and the independent-samples t test. The p values < 0.05 were considered statistically significant.

Results

Th17-skewed CD4+ Dsg3H1 T cells induce psoriasis-like skin inflammation in Rag2−/− mice

To obtain polarized autoreactive CD4+ T cells against epidermal autoantigen, we used the Dsg3-specific TCR-tg (Dsg3H1) mouse (26). Dsg3H1 mice developed interface dermatitis after >10 wk of age, and CD4+ T cells from Dsg3H1 mice responded to Dsg3 in vitro and induced more severe interface dermatitis after transfer of Dsg3H1 T cells into Rag2−/− mice. Thus, Dsg3-specific T cells must be present in Dsg3H1 mice, and we addressed whether Th1 or Th17 skewing of Dsg3H1 T cells induced different types of autoimmune diseases after they were transferred into Rag2−/− mice. As shown in Fig. 1A, Th1 or Th17 cell differentiation was successfully induced using Dsg3H1 T cells in vitro. Th17 cells were induced by anti–CD3 and anti–CD28 stimulation in the presence of IL-6, IL-23, and TGF-β, whereas induction of Th1 cells occurred in the presence of IL-12. The proportion of Th17...
cells in Dsg3H1 CD4+ T cells was ~15–20%, which was similar to that in wild-type (WT) CD4+ T cells (Fig. 1A). We observed only a few IFN-γ+IL-17+ double-positive cells after in vitro Th17 cell differentiation. Approximately 40% of CD4+ Dsg3H1 T cells possessed Vβ6 after differentiation, which was similar to that for naïve Dsg3H1 CD4+ T cells (18) (data not shown), indicating that TCR specificity was not altered by in vitro differentiation.

We then adoptively transferred 1 × 10^5 in vitro–differentiated Dsg3H1-Th17 cells into Rag2^-/- mice, and we observed a high degree of weight loss within 1–2 wk (Fig. 1B, H1 Th17). Such rapid weight loss was not observed when WT-Th17 cells or WT-Th1 cells were transferred (data not shown). Adoptive transfer of Dsg3H1-Th1 cells did not cause any body weight loss within 4 wk (Fig. 1B); however, skin inflammation was observed 4 wk after transfer.

FIGURE 1. Th17-skewed Dsg3H1 T cells induce inflammatory dermatitis. (A) IL-17A and IFN-γ staining of Dsg3H1 CD4+ T cells and WT CD4+ T cells cultured under Th1 or Th17 conditions in vitro. After 5 d in culture, cytokine staining for IL-17A and IFN-γ was performed after stimulation of T cells with PMA/ionomycin for 5 h and brefeldin A for 4 h. H1 Th1, Th1-skewed T cells from Dsg3H1-tg mice; H1 Th17, Th17-skewed T cells from Dsg3H1-tg mice; WT Th17, Th17-skewed Th17 cells from WT mice. (B) Weight change in recipient mice after adoptive transfer of Dsg3H1-Th1 cells (H1 Th1) or Dsg3H1-Th17 cells (H1 Th17) (n = 7). (C) Appearance of ear and tail of Rag2^-/- mice 2 wk after transfer of the indicated cells. (D) Appearance of skin of Rag2^-/- mice 4 wk after transfer of Th17-Dsg3H1 T cells. (E) Histopathology of the ear 2 wk after transfer of the indicated T cells (original magnification ×200). (F) Skin lesions from mice that received Dsg3H1-Th17 cells (original magnification ×400). (G) Histology of indicated tissues from mice that received Dsg3H1-Th17 cells or H1 Th1 cells (original magnification ×200). Results examined by histology after HE staining (E–G). Representative data from at least three independent experiments are shown in (A) and (C–G). *p < 0.05.
Transfer of Dsg3H1-Th1 cells did not induce gross abnormalities within 2 wk (Fig. 1C, H1 Th1). However, histological examination revealed interface dermatitis in the skin and hard palate (Fig. 1E, I1, H1 Th1), which became more severe 4 wk after transfer, as reported previously (26). We found that interface dermatitis was more severe in the hard palate compared with the ear. Histologically, infiltration of lymphocytes at the dermal–epidermal junction and keratinocyte apoptosis, characteristics of interface dermatitis, were evident.

Because IL-23 is important for the pathogenicity of Th17 cells, Dsg3H1-Th17 was induced by the Th17 culture condition, with or without IL-23, to clarify the role of IL-23 in vitro. There was no difference in the proportion of IL-17A–producing cells in vitro (Supplemental Fig. 1A), weight loss, or histological skin inflammation after transfer into Rag2−/− mice (Supplemental Fig. 1B, 1C). These data indicate that, during in vitro differentiation, IL-23 is not necessary to induce pathogenic Th17 cells.

Th17-Dsg3H1 T cells induce psoriasis-like pathological events in Rag2−/− mice

We then analyzed infiltration of mononuclear cells into the skin lesions. As shown in Fig. 2A, IFN-γ production was retained on day 14 in Dsg3H1-Th1 cells in the LN of Rag2−/− mice, whereas IL-17 production was reduced and IFN-γ production appeared in Dsg3H1-Th17 cells after transfer. Interestingly, IFN-γ and IL-17 double-positive (Th1/17) cells were consistently observed in Dsg3H1-Th17 cells after transfer. Such Th1/17 cells were often observed in the inflammatory regions in experimental autoimmune encephalomyelitis models (31, 32) and inflammatory bowel disease models (33), and they are thought to be pathogenic Th17 cells (33, 34). Therefore, it is highly possible that Th17-skewed Dsg3H1 T cells further converted to pathogenic Th1/17 cells in vivo.

As shown in Fig. 2B, CD4+ Vß6+ T cells accumulated in the skin lesion in mice that received both Dsg3H1-Th1 and Dsg3H1-Th17 cells; more than 90% of the CD3+ T cells were Vß6+, suggesting that Dsg3-specific T cells accumulated selectively in the epidermis, because the frequency of Vß6+ T cells was <40% before transfer (data not shown). More CD4+ T cells were infiltrated in the skin of mice that received Dsg3H1-Th17 cells compared with Dsg3H1-Th1 cells (41.7% versus 12.2%, Fig. 2B). Consistent with the histological examination (Fig. 1E, 1F), strong neutrophil accumulation in the skin was observed in mice that received Dsg3H1-Th17 cells but not in mice that received Dsg3H1-Th1 cells (Fig. 2B). These infiltrating CD4+ T cells in the skin of mice that received Dsg3H1-Th17 cells expressed higher levels of mRNA of Th17-related cytokines, such as IL-17A, IL-17F, and IL-22, than did those from mice that received Dsg3H1-Th1 cells (Fig. 2C).
The expression of inflammatory factors was compared in the whole-skin lesions of mice that received Dsg3H1-Th1 cells or Dsg3H1-Th17 cells (Fig. 3A). The mRNA of neutrophil-attractive chemokines (CXCL1, CXCL2, CXCL3, CXCL5), psoriasis-related cytokines (IL-1β, TNF-α, IL-23, IL-36), and S100a8 and S100a9, which are characteristically high in psoriatic skin (35, 36), were significantly upregulated in the skin of mice that received Dsg3H1-Th17 cells compared with those that received Dsg3H1-Th1 cells (Fig. 3A). High expression levels of neutrophil-attractive chemokines were consistent with neutrophil accumulation in the skin of mice that received Dsg3H1-Th17 cells (Figs. 1F, 2B). We also observed activation of STAT3 in keratinocytes in the skin lesions of mice that received Dsg3H1-Th17 cells (Fig. 3B), which were often observed in psoriasis models and patients (37, 38). These data support our notion that Dsg3H1-Th17 cells induce psoriasis-like disease in Rag2−/− mice.

FIGURE 3. Expression of Th17-related genes and activation of STAT3 in the skin. (A) Total RNA isolated from the skin of mice that received Dsg3H1-Th1 (H1 Th1) or Dsg3H1-Th17 (H1 Th17) cells and the mRNA levels for the indicated genes were measured using real-time PCR 2 wk after adoptive transfer (n = 5). (B) Immunohisto-staining of pSTAT3 in the skin of mice that received Dsg3H1-Th1 or Dsg3H1-Th17 cells. Original magnification ×400. Representative data of three independent transfer experiments are shown. *p < 0.05, **p < 0.005.
the spleen and LNs were not so different after isotype-control Ab treatment compared with anti-p40 Ab treatment (Supplemental Fig. 1D). These data strongly suggest that, in the absence of IL-23, H1-Th17 cells cannot expand in the skin and/or migrate into the skin. The data suggest a profound effect of IL-12/23 on the emergence of pathogenic Th17 cells in the skin but not in other peripheral lymphoid organs (Fig. 4E, 4F).

To confirm whether IFN-γ from Th1/17-like cells appeared in mice that received Dsg3H1-Th17 cells (Fig. 2A, H1-Th17) had a role in the psoriasis-like skin disease, we obtained CD4+ T cells from IFN-γ−/− Dsg3H1 mice. IFN-γ−/− Dsg3H1 T cells were differentiated into Th17 cells in vitro and then transferred into Rag2−/− mice. To our surprise, similar weight loss was observed after the transfer of IFN-γ−/− sufficient and IFN-γ−/− deficient Dsg3H1-Th17 cells (Fig. 4B). As shown in Fig. 4C and 4D (far right panels), the pathogenicity of IFN-γ−/− Dsg3H1-Th17 cells was as severe as that of IFN-γ+/+ Dsg3H1-Th17 cells. Vβ6+ T cell and neutrophil accumulation were also observed in mice that received IFN-γ−/− deficient Dsg3H1-Th17 cells (Th17-IFN-γ−/− H1). Ab treatments were given on days 0 and 7. Representative data of more than three independent experiments are shown. *p < 0.05.

**FIGURE 4.** Effect of anti-cytokine Abs and deletion of the IFN-γ gene. (**A**) Change in body weight of mice that received Dsg3H1-Th17 cells and were treated with isotype control IgG (ISO), anti–IL-17 Ab (αIL-17), or anti–IL-12/23 p40 Ab (αp40). Abs (0.1 mg/body) were injected i.p. on days 0 and 7 (n = 6). (**B**) Change in body weight of recipient mice after adoptive transfer of IFN-γ+/+ Dsg3H1-Th17 cells or IFN-γ−/− Dsg3H1-Th17 cells (n = 9). Appearance of skin and tail (**C**) and histology (**D**) of Rag2−/− mice that received Dsg3H1-Th17 cells and were treated with Abs or mice that received IFN-γ−/− deficient Dsg3H1 T cells (Th17-IFN-γ−/− H1). Results examined by histology after HE staining (original magnification ×200). Representative data of at least three independent mice. (**E** and **F**) FACS analysis, on day 14, of epidermal cell suspensions from the skin, spleen, mesenteric LN (mLN), or skin-draining LN (sLN) of Ab-treated mice that received Dsg3H1-Th17 cells or IFN-γ−/− deficient Dsg3H1-Th17 cells (Th17-IFN-γ−/− H1). Ab treatments were given on days 0 and 7. Representative data of more than three independent experiments are shown. *p < 0.05.
these results demonstrate that pathogenic conversion of Th17 cells to Th1/17 cells by host IL-12 and/or IL-23 was necessary for the disease but that IFN-γ itself from Th1/17 cells was not essential.

Discussion

Our present study demonstrated that cutaneous psoriasis-like immunopathology can be caused by the epidermis-specific recognition of Th17 cells, and our system provides a useful tool for analyzing and treating psoriasis. Essential roles for IL-17 and Th17 cells are well established in human psoriasis. However, we still do not know much about the molecular and cellular nature of pathogenic Th17 cells for the development of psoriasis. In addition, there is no murine TCR-defined Th17 cell–dependent psoriasis model for the development of new therapeutics, with the exception of human psoriasis xenograft mouse models (13, 14). It is well established that IL-17 plays pivotal roles in human psoriasis; however, γδT cells were shown to be important sources of IL-17 in most murine acute skin inflammation models (22, 23). Because our current transfer model is clearly dependent on TCR-specific Th17 cells, this could be useful for investigating the mechanism of Th17 cell–mediated psoriasis. For example, the role of IFN-γ from IFN-γ+IL-17+ Th (Th1/17) cells in the development of psoriasis has not been clarified. Using this model, we showed that IFN-γ is not essential for the development of the skin lesion. To our knowledge, this is the first demonstration of a dispensable role for IFN-γ in Th1/17 cells in a psoriasis model. Of course, this does not mean that Th1/17 is not pathogenic. Our model will facilitate investigations aimed at a deeper understanding of the pathogenic role and developmental mechanism of Th1/17 cells.

In addition, our model could be used to evaluate the therapeutic agents for T cell–mediated psoriasis. We showed that anti–IL-23 and anti–IL-17 Abs are effective in preventing skin lesions induced by Dsg3-specific Th17 cells in vivo. This supports our proposal that our model resembles human psoriasis, as well as suggests a potential usefulness of this model in the development of new drugs. For example, CTLA4-Ig, chemokine receptor antagonists, and small molecule JAK inhibitors have been planned to apply to various human inflammatory and autoimmune diseases. The efficacy of such agents targeting T cells in psoriasis could be tested in our model, whereas acute γδT cell–dependent models may not be suitable.

Despite the notion that these skin-infiltrating T cells are autoreactive in nature, there have been few studies of the target Ags, which remain largely unknown, because, unlike Abs that recognize native proteins, TCRs recognize protein peptides in the context of class I or II MHCs. MHC polymorphism and the difficulty in preparing a screening library for peptide–MHC complexes have hampered progress in defining Ag specificity in T cells that infiltrate in inflammatory skin diseases. Consequently, it has not been completely established that autoreactive T cells contribute to the pathogenesis of inflammatory skin diseases, such as psoriasis. We bypassed this problem by using Dsg3-specific TCR-tg mice; however, identification of skin-targeting TCRs in psoriasis is still necessary to establish animal psoriasis models.

Our Dsg3-specific T cell–transfer system can provide different types of skin disease models by selecting proper effector T cells in vitro. Our previous work indicates that epidermis-specific Th1 cells induce interface dermatitis, and epidermis-specific Th2 cells plus B cells induce autoimmune production (25). In this study, we showed that epidermis-specific Th17 cells induce psoriasis. Thus, our system, a model of experimental autoimmune dermatitis (EAD), provides a unique tool for analyzing autoimmune skin diseases developed in response to various subsets of autoreactive CD4+ T cells. Our results also strongly suggest that the pathologic features are primarily determined by cytokines from effector T cells rather than from TCR specificity, although TCRs seem to be necessary to recruit and expand T cells in the skin where the Ag is present.

IFN-γ and IL-17 are both critical for the development of Th17-type inflammatory diseases, such as experimental autoimmune encephalomyelitis and inflammatory bowel disease. We also observed such Th1/Th17 cells in the skin lesions after transfer of Th17 cells generated in vitro (Fig. 2A). In our EAD models, IFN-γ, but not IL-17, was necessary for the induction of interface dermatitis (26), whereas IL-17, but not IFN-γ, was essential for psoriasis-like disease caused by Dsg3-specific CD4+ T cells. This is surprising because Th1/17 cells are thought to be pathogenic Th17 cells (33, 34). Our data clearly demonstrate that IFN-γ from Th1/17 cells is dispensable for the pathogenicity of skin-infiltrated T cells. However, because anti–IL-12/IL-23–p40 Ab blocked accumulation of CD4+ T cells in the skin, IL-12– and/or IL-23–mediated maturation (i.e., generation of Th17-type autoreactive T cells in vivo) must be necessary for the development of psoriasis-like disease. Th1/17 differentiation requires RORγt and T-bet. In addition, STAT3 and STAT4 may also be essential (33, 34). These critical molecules in Th1/Th17 differentiation may be potential targets to modulate disease activity, and our EAD model should provide a useful tool for the in-depth evaluation and screening of therapeutic agents.

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Disclosures

The authors have no financial conflicts of interest.

References


