TNF, but Not IL-6 and IL-17, Is Crucial for the Development of T Cell-Independent Psoriasis-Like Dermatitis in IL1r\(^{-/-}\) Mice

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TNF, but Not IL-6 and IL-17, Is Crucial for the Development of T Cell-Independent Psoriasis-Like Dermatitis in Il1rn−/− Mice

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IL-1 is a proinflammatory cytokine consisting of two molecular species, IL-1α and IL-1β, and IL-1R antagonist (gene: Il1rn) is the endogenous suppressor. Il1rn−/− mice spontaneously develop autoimmune diseases, such as arthritis and aortitis, and a dermatitis that histologically resembles human psoriasis. The pathogenic mechanisms underlying this dermatitis, however, remain to be elucidated. In this study, we demonstrated that the production of inflammatory cytokines and chemokines was enhanced at the site of inflammation. The development of dermatitis was completely suppressed in Tnfsf1a−/− but not in Il6−/− mice, similar to that observed in arthritis and aortitis. However, IL-17 deficiency did not affect the development of dermatitis at all, in clear contrast to that of arthritis and aortitis. Different from arthritis and aortitis, adoptive transfer of Il1rn−/− T cells did not induce dermatitis in the recipient SCID mice and skin lesions developed in Il1rn−/− SCID mice, indicating that T cells are not involved in the development of skin lesions. In support for this, bone marrow cell transplantation experiments showed that TNF produced by skin residential cells, but not bone marrow cell-derived cells, was important for the development of dermatitis. Furthermore, we showed that IL-1 directly enhanced TNF and chemokine expression in keratinocytes. These observations suggest that excess IL-1 signaling directly activates keratinocytes to produce TNF and chemokines, resulting in the development of psoriasis-like skin lesions without the involvement of autoimmunity in Il1rn−/− mice. The Journal of Immunology, 2010, 185: 1887–1893.

Psoriasis is an inflammatory epidermal hyperproliferative skin disease that affects 2–3% of the population worldwide (for comprehensive reviews, see Refs. 1, 2). In this disease, erythematous papules and scaly plaques cover a large percentage of the skin surface. Several lines of evidence, such as the presence of activated CD4+ and CD8+ T cells in psoriatic plaques (3), studies of human skin xenografts in mice (4, 5), and therapeutic efficacy of T cell-targeted drugs (6), suggest the involvement of T cell-mediated immune responses in this disease. Furthermore, the expression of IL-1, TNF, IL-12, IL-17, IL-22, and IL-23 is elevated in psoriatic skins in humans (6–14), and IL-23R gene variations are associated with psoriasis (15–17), suggesting the involvement of these cytokines in the pathogenesis of this skin disease. However, the etiopathogenesis of psoriasis is not elucidated completely.

Previously, we and Nicklin et al. (18–20) demonstrated that Il1rn−/− mice develop chronic arthritis (18) and aortic inflammation (19, 20). These mice also develop cutaneous inflammation characterized by extensive thickening of the epidermis associated with hyperkeratosis of the skin, closely resembling psoriasis in humans (21–23). Because elevated levels of auto-Abs were detected in the sera, and adoptive transfer of Il1rn−/− CD4+ T cells induced arthritis and aortitis in nude mice, it was suggested that T cell-mediated autoimmunity plays an essential role in the development of these inflammatory diseases in Il1rn−/− mice (18, 20, 24). However, the involvement of autoimmunity has not been examined in the skin lesions. Furthermore, we showed that deficiency of TNF, but not IL-6, almost completely suppressed the development of arthritis and aortitis, suggesting the importance of TNF in the pathogenesis of these diseases (20, 24). IL-17 also plays a crucial role in the development of arthritis (25, 26). The involvement of autoimmunity and cytokines in the development of skin inflammation in Il1rn−/− mice, however, remains to be elucidated.

In this report, we investigated the roles of proinflammatory cytokines in the pathogenesis of skin inflammation and demonstrated that TNF, but not IL-6 or IL-17, is crucial in this process. We also examined the involvement of T cell-mediated immunity in the development of cutaneous inflammation in Il1rn−/− mice, revealing that T cells are...
not required for the pathogenesis of skin disease in contrast to the pathogenic mechanisms functioning in arthritis and aortitis.

Materials and Methods
Mice
Il1rn−/− mice (27), Tnfsf1a−/− mice (28), and Il6−/− mice (29) were backcrossed to BALB/c mice for eight generations. Il17a−/− mice (30) were backcrossed to BALB/c mice for four generations. Tnfsf1a−/− Il1rn−/− mice, Il6−/− Il1rn−/− mice, and Il17a−/− Il1rn−/− mice were obtained by intercrossing these mutant mice to each other. BALB/c mice and BALB/c-scid/scid mice were purchased from Clea (Tokyo, Japan). BALB.B (BALB/c congenic H-2 locus; b/b.) mice were used for all experiments. Mice were housed under specific pathogen-free conditions in an environmentally controlled clean room at the Center for Experimental Medicine, Institute of Medical Science, University of Tokyo (Tokyo, Japan). Experiments were performed according to the institutional ethical guidelines for animal experimentation and the safety guidelines for gene manipulation.

Histological and clinical evaluation of skin inflammation

The incidence of skin lesions of the ears and tail was assessed macroscopically. Skin inflammation was evaluated weekly as the cumulative score of six skin symptoms for each and tail with a maximum score of 12: alopecia, hyperkeratosis, ruberosis, hemorrhage and inunction, microabscess formation, and atrophoderma. The incidence and severity of dermatitis were judged macroscopically as described (18). Briefly, postexamination of each joint weekly for swelling, redness, and joint flexibility, the severity of arthritis was graded from 0–3 for each paw.

For histological evaluation of skin specimens, 10% phosphate-buffered formalin-fixed paraffin sections (5 μm) were stained with H&E. In the case of Il17a−/− mice, the incidence and severity score of skin lesions of the ears at 20–28 wk old was assessed histologically. Skin inflammation was evaluated as the cumulative score of dermal hyperplasia (0–3) and inflammatory area (0–3) with a maximum score of 6.

Adoptive transfer experiments

After removal of RBCs and T cells, bone marrow cells (BMCs; 1 × 10⁷) from 10–16-wk-old female mice were transferred i.v. into female recipient mice aged 5 to 6 wk of age after 750 rad irradiation (24). Irradiated mice that did not receive BMCs died within 2 wk.

T cells were prepared from the spleen and lymph nodes, as described previously (24). CD4⁺ and CD8⁺ T cells were purified using magnetic bead separation on an MACS column (Miltenyi Biotech, Bergisch Gladbach, Germany). The purity of both CD4⁺ T cell and CD8⁺ T cell populations was >95%. T cells (2 × 10⁹) were then injected i.v. into BALB.B-scid/scid mice (24).

Isolation of total RNA and RT-PCR

Total RNAs were isolated from the ear skin tissues using Trizol Reagent (Invitrogen, Carlsbad, CA). First-strand cDNA was synthesized from 1 μg total RNA using the SuperScript III First-Strand Synthesis Kit (Invitrogen). For RT-PCR, we used the following gene-specific primers: 5′-CGT CAG GCA GAA GTT GTG CA-3′ (forward IL-1α); 5′-CAC CGG ACT TTG TTT GC-3′ (reverse IL-1α); 5′-CAG GCA GGC AGT ATC ACT CA-3′ (forward β form of pro-IL-1 (IL-1β)); 5′-AGG CCA CAG GTA TTG TTT CG-3′ (reverse IL-1β); 5′-GAG GCT CTT CCT ACC TTC AGA GA-3′ (forward TNF); 5′-AGC AAA AGA GGA GGC AAC AA-3′ (reverse TNF); 5′-GTT CTC TCG TGG GAA ATC GTG GA-3′ (forward IL-6); 5′-GGA AAT TGG GGT AGG AAG GA-3′ (reverse IL-6); 5′-GTT CTC TGTCCA AGA GA-3′ (forward CCL2); 5′-GAG GCT TCA TTC GGC ACA AC-3′ (reverse CCL2); 5′-TCC AGA GCT TGA GTG TGA CG-3′ (forward CCL2); 5′-AGG CAC ATC AGG TAC CAT CC-3′ (reverse CCL2); 5′-TCC TGC CTC CCA ATC TAT TT-3′ (forward CCL1); 5′-CAC TGG GTA AAG GGG AGT GA-3′ (reverse CCL1); 5′-CTG TCT TTG GCC ACA AC-3′ (forward CXCL1); 5′-TGC TGA GTG TCA CG-3′ (forward CXCL1); 5′-AGG CAC ATC AGG TAC CAT CC-3′ (reverse CXCL2); 5′-AAG TGC TGC CTT CAT TT-3′ (forward CXCL2); 5′-CAG TGG GTA AAG GGG AGT GA-3′ (reverse CXCL1); 5′-CTT GCC TTG GGA TGA CT-3′ (forward CCL2); 5′-AGG CAC ATC AGG TAC CAT CC-3′ (reverse CCL2); 5′-GTT CTC TGTCCA AGA GA-3′ (forward CCL2); 5′-GTT CTC TGTCCA AGA GA-3′ (forward CCL2); 5′-GTT CTC TGTCCA AGA GA-3′ (forward CCL2). Primers were designed empirically under non-saturating conditions.

Statistics

Repeated measures two-way ANOVA-Fisher’s protected least significant difference (post hoc test) or the χ² for independence tests were used for statistical evaluation of incidence. Two-way ANOVA was used for the evaluation of severity scores.

Results

Cutaneous inflammation develops in Il1rn−/− mice

Il1rn−/− mice on a BALB/c background spontaneously developed skin inflammation of the ears and tail. We initially observed rubefaction, dry skin, and mild cornification, which was followed by progressive inflammation, the development of crusted microabscess-like lesions usually encompassing the ears and tail, and occasional epilation of ears and tail (Fig. 1, arrows). Cutaneous inflammation was first observed at 4 to 5 wk of age, similar in onset to the arthritis and aortitis in these mice (18, 20). The incidence increased with age, reaching ~60% by 24 wk of age (Fig. 2).

Histopathologically, the ears and tail of Il1rn−/− mice exhibited extensive thickening of the epidermis (acanthosis) associated with hyperkeratosis of the skin (Fig. 1D, 1F; bold bars). The majority of keratinocytes retained their nuclei in the cornified cellular layer. We also observed a massive infiltration of neutrophils and monocytes into the epidermis and dermis. With disease progression, Munro’s microabscess-like lesions were formed intraepidermally with neutrophilic infiltration (Fig. 1D). These histological features of the Il1rn−/− epidermis resembled those seen in human psoriasis vulgaris, as reported previously (21, 22).

TNF, but not IL-6 or IL-17, plays a crucial role in the development of skin inflammation in Il1rn−/− mice

We next examined the expression of cytokines and chemokines in these skin lesions. The expression of inflammatory cytokines, including TNF, IL-1α, IL-1β, and IL-6, was augmented in the lesions (Fig. 3A). The expression of chemokine genes, such as CXCL1 (Groα), CXCL2 (Groβ), CXCL10 (IFN-γ-inducible protein-10), and CCL20 (MIP-3α), that are seen in psoriatic lesions of human patients (31–33), was also augmented in inflammation-positive skin in comparison with the inflammation-negative skin of Il1rn−/− mice or the skin of wild-type (WT) mice (Fig. 3A).

TNF plays a crucial role in the development of arthritis and aortitis in Il1rn−/− mice (20, 24). TNF and IL-6 have also been implicated in the development of cutaneous inflammation (34, 35). Thus, we...
examined the cutaneous pathology in mice deficient in the IL-1R antagonist and TNF or IL-6 genes. Homozygous TNF deficiency (Tnfsf1a<sup>-/-</sup>) completely suppressed the development of cutaneous inflammation in II1rn<sup>-/-</sup> mice (Fig. 2). In contrast to the skin of II1rn<sup>-/-</sup> mice, skin histology of Tnfsf1a<sup>-/-</sup> II1rn<sup>-/-</sup> mice was normal (Fig. 4A,4B). In contrast, deficiency in IL-6 (Il6<sup>-/-</sup>) resulted in an increased incidence of dermatitis and a more severe pathology of the lesions in II1rn<sup>-/-</sup> mice both macroscopically (Fig. 2) and microscopically (Fig. 4C,4D).

The TNF gene is located within the MHC locus, and mice deficient for this gene were generated on the C57BL/6+CBA background (TT2 ES line, H-2 locus; b/b) (28). Although we backcrossed Tnfsf1a<sup>-/-</sup> mice onto the BALB/c strain (H-2 locus; d/d) for eight generations, these animals still retained the same H-2<sup>b</sup> locus as that seen in TT2 ES cells. To exclude possible involvement of the MHC locus in the development of the skin lesions in II1rn<sup>-/-</sup> mice, we examined the incidence on these different genetic backgrounds. We found that II1rn<sup>-/-</sup> mice on the C57BL/6 background did not develop skin inflammation. In contrast, II1rn<sup>-/-</sup> mice backcrossed onto the BALB.B strain, which are congenic for the C57BL/6 H-2 locus (b/b), developed similar skin lesions as those seen in II1rn<sup>-/-</sup> mice on the BALB/c background (incidence: 52.3%; average score: 5.8 at 20 wk of age). These results argue against the possibility that MHC differences are responsible for suppression of the psoriasiform lesions in Tnfsf1a<sup>-/-</sup> II1rn<sup>-/-</sup> mice. Thus, TNF itself likely plays a critical role in the development of cutaneous inflammation in II1rn<sup>-/-</sup> mice.

Table I.  **IL-17–independent development of dermatitis in II1rn<sup>-/-</sup> mice**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Incidence (%)</th>
<th>Severity Score</th>
</tr>
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<tbody>
<tr>
<td>II17a&lt;sup&gt;-/-&lt;/sup&gt;</td>
<td>5/6 (83.3)</td>
<td>3.7</td>
</tr>
<tr>
<td>II1rn&lt;sup&gt;-/-&lt;/sup&gt;</td>
<td>11/16 (68.8)</td>
<td>2.8</td>
</tr>
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</table>

II1rn<sup>-/-</sup> mice were crossed with II17a<sup>-/-</sup> mice, and the development of psoriasis-like dermatitis was examined at 20–28 wk of age.
We have also examined involvement of IL-17 in the development of this skin lesion, because IL-17 plays a crucial role in the development of arthritis (26) and aortitis (36) in these mice. The results showed that both incidence and severity of the ear inflammation were not affected by the deficiency of IL-17, in clear contrast to the case of arthritis (Fig. 4E, Table I). These results indicate that whereas TNF is required for the development of the skin inflammation in Il1rm−/− mice, IL-6 and IL-17 are dispensable.

T cells are not involved in the development of dermatitis in Il1rm−/− mice

We next examined whether T cells are involved in the development of cutaneous inflammation in Il1rm−/− mice. We generated T cell- and B cell-deficient Il1rm−/− mice by crossing breeding with scid/scid mice. Il1rm−/−-scid/scid mice developed similar dermatitis as that seen in Il1rm−/−-scid+/+ or Il1rm−/−+/+ mice, indicating that T and B cells are not involved in the development of skin lesions (Table II).

We confirmed this by adoptive transfer of T cells. Peripheral CD4+ cells and CD8+ T cells were separately purified from the spleens and lymph nodes of Il1rm−/− mice and transferred into scid/scid mice. Then, animals were monitored for both arthritic and psoriatic scores weekly. Four weeks posttransfer, a number of the mice that received Il1rm−/−-CD4+ T cell developed arthritis; by 12 wk, all of the mice were affected, although those mice that received Tnfsf1a−/− T cells were not (Table III). In contrast, transfer of Il1rm−/−-CD4+ T cells did not induce skin lesions. Mice receiving Il1rm−/−-CD8+ T cells also did not develop skin lesions. These results indicate that T cell-mediated immunity is not involved for the development of skin lesions in Il1rm−/− mice, in clear contrast to arthritis development.

Excess IL-1 signaling in resident skin cells is responsible for the development of dermatitis

Next, we analyzed the origin of the pathogenic cells in skin lesions. As BMC-derived cells are responsible for the arthritis and aortitis that develop in these mice (20, 24), we examined the involvement of BMC-derived cells in the development of dermatitis. Il1rm−/− BMCs induced cutaneous inflammation at a low incidence (one out of six) at 20 wk, but not at 12 wk, posttransplantation into WT mice (Table II). In contrast, arthritis was observed as early as 12 wk after adoptive transfer (two out of six), with increasing incidence (four out of six) 20 wk posttransplantation. Although the development of arthritis in Il1rm−/− mice was completely suppressed by normal BMC transplantation, Il1rm−/− mice receiving BMCs from WT mice developed dermatitis (four out of nine and two out of nine at 12 wk and 20 wk, respectively) posttransplantation (Table IV). Thus, resident cells of the skin were primarily responsible for the development of cutaneous inflammation, in contrast to the development of arthritis, which is largely mediated by BMC-derived cells.

Skin resident cell-derived TNF is crucial for the development of dermatitis

To identify the cells producing pathogenic TNF in Il1rm−/− mice, we examined the effects of Il1rm−/− BMCs transplanted into Tnfsf1a−/−Il1rm−/− mice and of Tnfsf1a−/−Il1rm−/− BMCs transplanted into Il1rm−/− mice (Table IV). All of the transfer experiments involving TNF deficiency were carried out with mice on the BALB.C background. Il1rm−/− recipient mice developed dermatitis 12 wk posttransplantation, irrespective of the origin of the BMCs (WT or Tnfsf1a−/− Il1rm−/− mice). In contrast, no skin lesions developed in Tnfsf1a−/−Il1rm−/− mice posttransfer of either WT or Il1rm−/− mouse BMCs, although some Il1rm−/− mice developed dermatitis after 20 wk. These results suggest that TNF produced by cells of the recipient animal was responsible for the skin inflammation.

Consistent with this notion, the TNF mRNA was induced by treatment with either IL-1α (0.1 and 1 μg/ml) or IL-1β (0.1 and 1 μg/ml) in purified, cultured keratinocytes (Fig. 3B), indicating that TNF is induced in keratinocytes upon activation with IL-1. These results are in contrast to the observation that BMC-derived TNF is important in the development of arthritis; arthritis developed in Tnfsf1a−/−Il1rm−/− mice transplanted with Il1rm−/− BMCs, and TNF deficiency in the donor Il1rm−/− BMCs suppressed the development of arthritis in WT recipient mice.

Discussion

In this report, we analyzed the pathogenic mechanisms of dermatitis histologically resembling psoriasis in BALB/c-I1rm−/− mice. Although it was reported that abundant CD4+ T cell infiltration is observed in the skin lesions in these mice (21, 22), we showed that the pathogenesis of dermatitis is T cell independent, because dermatitis developed similarly in Il1rm−/− mice on the scid/scid background, and adoptive transplantation of Il1rm−/− CD4+ T cells did not induce keratinocyte hyperproliferation or cutaneous inflammation (Tables II, III). These results clearly contrast with other diseases, such as arthritis and aortitis, that develop simultaneously in this mutant mouse by a T cell-dependent autoimmune mechanism (18, 20, 24), indicating that the psoriasis-like dermatitis is not caused by the autoimmune mechanism.

We showed that dermatitis was induced in Il1rm−/− mice transplanted with WT BMCs, whereas Il1rm−/− BMC-transplanted WT mice did not develop dermatitis, suggesting that resident cells rather than bone marrow (BM)-derived cells are responsible for the development of dermatitis (Table IV). In contrast, arthritis developed in WT mice transplanted with Il1rm−/− BMCs and not in Il1rm−/− mice transplanted with WT BMCs, indicating that BM-derived cells are important for the development of arthritis.

Furthermore, we showed that TNF deficiency in Il1rm−/− mice completely suppressed the development of skin inflammation, indicating that TNF plays a crucial role in the development of skin lesions. Because Il1rm−/−Tnfsf1a−/− mice transferred with WT BMCs could not develop dermatitis, it was suggested that resident cell-derived TNF is important for the development of dermatitis (Table IV). In contrast, the development of arthritis in Il1rm−/− BMC-transplanted WT mice or Il1rm−/−CD4+ cell-transplanted scid/scid mice was suppressed by the deficiency of TNF in the donor cells, indicating that TNF produced by CD4+ T cells is responsible for the development of arthritis. When Il1rm−/− BMCs were transferred into Il1rm−/−Tnfsf1a−/− mice, dermatitis did not develop at 12 wk posttransplantation, but some mice developed dermatitis at later stages (two out of seven at 20 wk), suggesting that some BM-derived cells also contribute to the production of TNF at later stages. In this context, it is interesting to note that Il1rm−/− BMC-transplanted WT mice developed dermatitis at a later stage, although the incidence was low (one out of six at 20 wk). These observations may suggest that BM-derived cell-mediated immune responses are also involved in the skin lesions at a later stage.
Consistent with these observations, the expression of TNF together with various chemokines, including CXCL1 and CXCL2, was upregulated in the inflammatory sites of Il1m^−/− mice. It was suggested that this elevated TNF production is directly induced by excess IL-1 signaling in Il1m^−/− mice without involvement of autoimmunity, because IL-1 directly induced TNF in keratinocytes. TNF induction in response to IL-1 signaling is also known in other diseases (35). TNF may induce inflammation by activating leukocytes and endothelial cells to express proinflammatory cytokines and chemokines (37), which promote the infiltration of neutrophils and monocytes into inflammatory sites. In support for this notion, it was reported that transgenic TNF expression can cause inflammation in the joints and CNS without involvement of autoimmunity (38, 39). In recent clinical trials, blockade of TNF using a mAb against TNF (infliximab) or a soluble TNFR fusion protein (etanercept) ameliorated disease in psoriasis patients, suggesting a role for TNF in the pathogenesis of this disease (40, 41).

In several psoriatic lesions, because TNF may also be induced in T cells or dendritic cells by autoimmune mechanisms other than direct induction in keratinocytes by excess IL-1 signaling (42).

Recently, it was suggested that IL-23 is involved in the development of psoriasis, because IL-23 expression is elevated in psoriatic skin lesions (43). IL-23 induces psoriasiform dermatitis (44), polymorphisms in IL-23p19, IL-23p40, and IL-23R are associated with the development of psoriasis (15–17), and the Ab against IL-23p40 can ameliorate the disease (45, 46). Because IL-23 is primarily important for the differentiation and survival of Th17 cells (47), and IL-17 expression is augmented in psoriatic skins, it is suggested that IL-17 is also involved in the development of psoriasis. In support for this, it was recently reported that anti-IL-17 is effective to treat psoriasis, indicating that Th17 plays an important role in the pathogenesis of psoriasis (6, 48). We showed, however, that IL-17 was not involved in the development of skin lesions in Il1m^−/− mice. IL-6, which is crucial for the development of Th17, was also not involved, or it may have a protective role instead. This is consistent with the observation that T cells are not involved in the pathogenesis of this skin lesion, given that IL-17 is mainly produced by Th17 cells (49). Thus, the pathogenic mechanism of dermatitis in Il1m^−/− mice is clearly different from that of psoriasis, although the histology appears similar. Nonetheless, we think it is possible that some subset of psoriasis may be induced without involvement of autoimmunity, as shown in Il1m^−/− mice. Consistent with this idea, some proportion of psoriasis patients is refractory against anti-p40 treatment that blocks differentiation of Th17 and Th1 cells (6).

Table III. T cells are not involved in the development of dermatitis

<table>
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<tr>
<th>Donor</th>
<th>Recipient</th>
<th>Incidence (Average Score)</th>
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<tr>
<td></td>
<td></td>
<td>Dermatitis</td>
</tr>
<tr>
<td>II1m^−/− (CD4+)</td>
<td>BALB.B−scid/scid</td>
<td>0/5 (0.0)</td>
</tr>
<tr>
<td>II1m^−/− (CD8+)</td>
<td>BALB.B−scid/scid</td>
<td>0/9 (0.0)</td>
</tr>
<tr>
<td>II1m^−/− Tnfsa^−/− (CD4+)</td>
<td>BALB.B−scid/scid</td>
<td>0/11 (0.0)</td>
</tr>
<tr>
<td>II1m^−/− Tnfsa^−/− (CD8+)</td>
<td>BALB.B−scid/scid</td>
<td>0/6 (0.0)</td>
</tr>
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</table>

CD4^+ or CD8^+ T cells (5.0 × 10^7/mouse) were transferred into BALB.B−scid/scid mice, and the incidence and average score of arthritis and dermatitis were examined after 12 wk of transplantation. Values are expressed as the number of diseased mice per total number of mice examined. Average scores in affected mice are given in parentheses.

Table IV. IL-1 and TNF in resident skin cells are involved in the development of dermatitis in II1m^−/− mice

<table>
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<tr>
<th>Incidence (Average Severity Score)</th>
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<tbody>
<tr>
<td>Donor</td>
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<tr>
<td></td>
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<tr>
<td>WT</td>
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<td>II1m^−/−</td>
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BMCs (1 × 10^7) were injected into lethally irradiated recipient mice, and the development of dermatitis and arthritis was examined at 12 wk and 20 wk posttransplantation. Values are expressed as the number of diseased mice per total number of mice examined. Average severity score is given in parentheses.

Autoimmune diseases such as collagen-induced arthritis (50), arthritis that developed in human T cell leukemia virus-I transgenic mice (36) and SKG mice (51), and experimental autoimmune encephalomyelitis (52) are suppressed in Il6^−/− mice. Because these diseases are also dependent on IL-17, it is suggested that IL-6 may be important for the development of Th17 cells (49). We found, however, that the skin lesion was not suppressed but rather exacerbated in Il6^−/− Il1m^−/− mice. The development of arthritis and aortitis in Il6^−/− Il1m^−/− mice was also not affected by the deficiency of IL-6 (20, 36). Because the development of arthritis in Il1m^−/− mice is strictly dependent on IL-17, these results suggest that excess IL-1 signaling caused by the deficiency of IL-1R antagonist may compensate for the deficiency of IL-6 in the development of Th17 cells. Furthermore, because IL-6 has protective activity against injury and promotes tissue regeneration (53), IL-6 deficiency may be rather harmful for the development of skin lesions in this setting. Consistent with the notion that IL-6 is important for the development of Th17 cells, the development of arthritis in several other arthritis models, such as anti-type II collagen Ab-induced arthritis (36, 54) and KxB/N mouse serum-induced arthritis (55, 56), in which arthritis develops in an IL-17-independent manner, is not suppressed by the deficiency of IL-6 (49).

The roles of keratinocyte abnormalities versus abnormal immune function in the pathogenesis of psoriasis have been elusive. The
SCID-human psoriasis skin xenograft model requires activated CD4+ T cells to develop skin lesions (5). Similarly, in the keratinocyte-specific STAT3-expressing transgenic mouse model (K5.Stat3C mice), cooperation between STAT3 activation in keratinocytes and activated T cells is required for the development of psoriatic lesions (57). In contrast, the epidermal-specific IκB kinase 2 knockout mice develop psoriasiform cutaneous inflammation that shares many features of psoriasis, including dependence on intact TNF signaling, but is T cell independent (58). Nevertheless, mice that depleted both JunB and c-Jun genes in a keratinocyte-specific manner also develop psoriasis-like skin disease without involvement of autoimmunity (59). The expression of a variety of inflammatory cytokines and chemokines is upregulated in the keratinocytes of these mice. TNF and T cells are not essential for the development of skin disease in these mice, whereas the development of arthritis in the same mouse is strictly dependent on both T cells and TNF (59). Thus, in this model, epidermal alteration is sufficient to initiate skin lesions. Although these phenotypes seen in JunB- and c-Jun–deficient mice are similar to our model, the pathogenic mechanisms are apparently different between these two models, because the AP-1 proteins, similar to our model, the pathogenic mechanisms are apparently completely, however, that immune responses function in involvement of the immune system. We do not exclude the possibility that immune responses function in the elicitation phase, because abundant dendritic cells and activated T cells are detected in psoriasiform lesions of affected Il1rn−/− mice (21, 22). Consistent with this possibility, we observed development of dermatitis in Il1rn−/− BMC-transferred WT mice at the late stage, although the incidence was low (Table IV). The involvement of immune reactions in the elicitation of psoriasiform skin lesions is also implicated in cases of Stat3 transgenic mice and JunB/c-Jun–deficient mice (57, 59). However, the contribution of the immune responses, if any, should be marginal, because we could not observe any amelioration of the lesions in SCID mice.

In summary, we demonstrated that excess IL-1 signaling causes skin lesions that histologically resemble psoriasis in humans. The development of lesions was dependent on locally produced TNF, but not on IL-6 or IL-17. T cell immunity was not involved in the development of inflammation, which contrasted the pathogenesis of arthritis and aortitis, in which T cell-mediated autoimmunity plays a crucial role. These observations clearly demonstrate that skin lesions histologically similar to psoriasis can be induced without involvement of autoimmunity. Thus, it may be possible that a part of psoriasis–like skin lesions in humans is caused by the excess signaling of IL-1 without involvement of autoimmunity. Il1rn−/− mice will be another good model to investigate pathogenesis of skin diseases.

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Disclosures
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