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Keratinocyte Overexpression of IL-17C Promotes Psoriasiform Skin Inflammation

Andrew Johnston,*† Yi Fritz,‡† Sean M. Dawes,† Doina Diaconu,† Paul M. Al-Attar,* Andrew M. Guzman,* Cynthia S. Chen,* Wen Fu,† Johann E. Gudjonsson,* Thomas S. McCormick,‡† and Nicole L. Ward†,‡

IL-17C is a functionally distinct member of the IL-17 family that binds IL-17 receptor E/A to promote innate defense in epithelial cells and regulate Th17 cell differentiation. We demonstrate that IL-17C (not IL-17A) is the most abundant IL-17 isoform in lesional psoriasis skin (1058 versus 8 pg/ml; p < 0.006) and localizes to keratinocytes (KCs), endothelial cells (ECs), and leukocytes. ECs stimulated with IL-17C produce increased TNF-α and KCs stimulated with IL-17C/TNF-α produce similar inflammatory gene response patterns as those elicited by IL-17A/TNF-α, including increases in IL-17C, TNF-α, IL-8, IL-1α/β, IL-1F5, IL-1F9, IL-6, IL-19, CCL20, S100A7/A8/A9, DEFB4, lipocalin 2, and peptidase inhibitor 3 (p < 0.05), indicating a positive proinflammatory feedback loop between the epidermis and ECs. Psoriasis patients treated with etanercept rapidly decrease cutaneous IL-17C levels, suggesting IL-17C/TNF-α–mediated inflammatory signaling is critical for psoriasis pathogenesis. Mice genetically engineered to overexpress IL-17C in KCs develop well-demarcated areas of erythematous, flakey involved skin adjacent to areas of normal-appearing uninvolved skin despite increased IL-17C expression in both areas (p < 0.05). Uninvolved skin displays increased angiogenesis and elevated S100A8/A9 expression (p < 0.05) but no epidermal hyperplasia, whereas involved skin exhibits robust epidermal hyperplasia, increased angiogenesis and leukocyte infiltration, and upregulated TNF-α, IL-1α/β, IL-17A/F, IL-23p19, vascular endothelial growth factor, IL-6, and CCL20 (p < 0.05), suggesting that IL-17C, when coupled with other proinflammatory signals, initiates the development of psoriasiform dermatitis. This skin phenotype was significantly improved following 8 wk of TNF-α inhibition. These findings identify a role for IL-17C in skin inflammation and suggest a pathogenic function for the elevated IL-17C observed in lesional psoriasis skin. The Journal of Immunology, 2013, 190: 2252–2262.

Considerable data have been developed in the past two decades regarding IL-17 cytokine family members and the initiation of inflammation by IL-17, specifically IL-17A and IL-17F, cytokines produced by Th17 cells, mast cells, neutrophils, and γδ-T cells (1). IL-17C is a newly cloned member of the IL-17 family, sharing 23% homology with IL-17A, but maps to a different chromosome location (2). Unlike IL-17A, little is currently known about the biological role or importance of IL-17C in promoting inflammation, although several recent reports identified key roles for IL-17C and its receptors IL-17RE/RA in regulating innate immune function in epithelial cells (3–7), promotion of mucosal barrier maintenance (8), promoting Th17 cell responses (9), and potentially, in the skin disease psoriasis (5, 10).

Johansen et al. (10) initially reported increases in IL-17C mRNA and protein in lesional compared with nonlesional nonlesional human psoriasis skin. IL-17C was rapidly decreased following TNF-α inhibition (11), possibly as a result of NF-κB signaling downstream of TNF-α (4). More recent reports have demonstrated an amelioration of imiquimod-induced psoriasiform skin inflammation in IL-17C– and IL-17RE/RA–deficient mice (5, 12), suggesting that IL-17C contributes to the initiation and/or maintenance of psoriatic skin. Others have also identified a >50-fold increase in keratinocyte (KC)-derived IL-17C following combined IL-17A/TNF-α stimulation (13) along with increases in ∼160 other genes that respond synergistically and ∼196 genes that respond additively that are also found in the human psoriasis transcriptome. These findings suggest that psoriasis therapies targeting IL-17A, in addition to proven TNF-α–targeted biologics, should lead to a significant downregulation in psoriasis-related genes. Indeed, recent clinical reports demonstrate IL-17A–targeted therapeutics are efficacious in psoriasis patients (using ixekizumab; formerly LY2439821; 75 mg), leading to significant clinical improvement, with 83% of patients achieving a 75% reduction in disease severity (Psoriasis Area and Severity Index score 75) and 38% of patients achieving complete clearance (14) by week 12 of the study. Interestingly, targeting IL-17A with the Ab brodalumab (formerly AMG827; 210 mg) resulted in 82% of patients achieving a Psoriasis Area and Severity Index score of 75 and 62% of patients achieving complete clearance (15). The observation that IL-17C and IL-17A share IL-17RA as a coreceptor (5, 6, 9) may provide rationale for why patient responses to bro-

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Abbreviations used in this article: EC, endothelial cell; IBD2, human β-defensin 2; KC, keratinocyte; K5–IL-17C, KC-specific IL-17C; MECA, mouse endothelial cell Ag; VN, healthy control; PN, uninvolved; PF, lesional; qRT-PCR, quantitative RT-PCR; VEGF, vascular endothelial growth factor.

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IL-17C is the most abundant IL-17 cytokine in inflamed skin

Expression of IL-17 family genes were compared in lesional (PP) and uninvolved (PN) skin of psoriasis patients as well as skin from healthy controls (NN) using quantitative RT-PCR (qRT-PCR) (Fig. 1A). Consistent with previous reports (10), we identified significant increases in IL-17A (p < 0.02), IL-17C (p < 0.01), and IL-17F (p < 0.002) gene expression in PP compared with NN (n = 8 each) and significant decreases in IL-17B (p = 0.05) and IL-17D (p = 0.002) in PP compared with NN skin. IL-17RA/B/E expression was not significantly different among NN, PN, or PP skin, whereas IL-17RC (p = 0.02) and IL-17RD (p = 0.01) both decreased in PP compared with control skin.

To explore the significance of these changes in gene expression, we measured IL-17A and IL-17C protein by ELISA (Fig. 1B) and determined both to be significantly increased in PP compared with PN and NN skin (p values as indicated). Interestingly, IL-17C protein expression was ~4-fold greater in PP skin (p = 0.002) and ~125-fold greater than IL-17A protein (p = 0.006). These results demonstrate similar mRNA transcript abundance of IL-17A and IL-17C but also illustrate that IL-17C protein is the most highly expressed IL-17 family member found in human involved psoriasis skin (Fig. 1B, 1058 ± 133 pg/mg IL-17C versus 8 ± 2 pg/mg IL-17A protein). Immunohistochemical staining of healthy control and involved and uninvolved psoriasis skin confirmed the increases in IL-17C and IL-17A protein and demonstrated significantly more IL-17C protein present in psoriasis skin than IL-17A (Fig. 1C). IL-17C colocalized with many cells, including KCs, dermal ECs, and skin-resident and infiltrating leukocytes; IL-17A–positive cells were only observed in the dermal papillae (Fig. 1C). No IL-17A staining was observed in control patient skin.

Despite its gross overexpression in lesional psoriasis skin, we observed that IL-17C is one of the most rapidly downregulated transcripts in the skin of psoriasis patients treated with the anti–TNF-α agent etanercept. Seventy-two hours following etanercept treatment, and prior to any changes in clinical disease, cutaneous IL-17C mRNA expression was significantly suppressed (n = 18; Fig. 1D; p = 0.019).

Endothelial cells and keratinocytes produce proinflammatory molecules in response to IL-17C and IL-17C and TNF-α, respectively

Others have previously demonstrated direct effects of IL-17C on fibroblasts, monocyctic cells, and peritoneal exudates (2, 24), and IL-17C has the capacity to elicit antimicrobial peptides from epithelial cells (5, 6); more recent studies have revealed IL-17C regulates Th17 cell differentiation and Th17 cell–derived IL-17A and IL-17F (9). To further identify cell responsiveness to IL-17C, we stimulated human dermal microvascular ECs with IL-17C and observed statistically significant increases in TNF-α and IL-6 mRNA (p < 0.05; Fig. 2A), with no significant effect on IL-1α/β, IL-8, or IL-17RE/A/C. The increase in TNF-α was further confirmed at the protein level (Fig. 2B), identifying a novel cellular target for IL-17C promotion of inflammation.
Given that KCs are the major source of IL-17C in the skin and that others have recently identified increases in S100A8/A9, RegIIIβ/γ, human β-defensin 2 (hBD2), and hG-CSF in epithelial cells following IL-17C exposure (5, 6), we sought to further investigate the role of IL-17C in primary human KCs. Primary human KCs responded poorly to IL-17C alone (Fig. 2C); however,
the addition of suboptimal TNF-α (2 ng/ml) led to a significant induction of candidate genes previously identified to respond either synergistically or additively to IL-17A/TNF-α (13) (Fig. 2C) and known to contribute to psoriasis pathogenesis. Additive increases in KC-derived IL-17C, TNF-α, IL-8, IL-1α/β, IL-1F5, IL-6, S100A8/A9, and lipocalin 2 were observed along with synergistic increases in KC-derived IL-1F9, IL-19, CCL20, S100A7, hBD2 (DEFB4), and peptidase inhibitor 3 following stimulation with IL-17C/TNF-α.

K5–IL-17C mice develop a psoriasiform skin phenotype

In psoriasis patients, there is ∼125-fold more IL-17C than IL-17A protein in lesional skin (Fig. 1B), and IL-17C is localized principally to activated KCs (Fig. 1C). To model this increase and to test the hypothesis that IL-17C plays a contributing and critical role in psoriasis pathogenesis, we genetically engineered mice to overexpress murine IL-17C in KCs using a conditional tetracycline-repressible binary approach (Fig. 3A) similar to models we have previously published (23). This controlled system allows us to modulate increases in IL-17C and recapitulate levels observed in lesional human psoriasis (Fig. 1C). K5–IL-17C double-transgenic mice appeared normal at birth; however, as early as 8 wk of age, well-demarcated areas of dorsal skin began to develop a thickened appearance with sloughing of epidermis and erythema, whereas adjacent areas of skin appeared relatively normal (Fig. 3B). In severely affected K5–IL-17C animals, alopecia was observed. Almost all mice developed ear involvement by the time they were 12 wk of age. qRT-PCR of uninvolved and involved skin from K5–IL-17C mice revealed ∼11- and ∼18-fold increases in IL-17C gene expression in K5–IL-17C uninvolved and involved skin, respectively, compared with littermate controls (n = 9 to 10 each group; p = 0.04 and 0.009; Fig. 3C). Western blotting confirmed the increases in cutaneous IL-17C protein in uninvolved and involved K5–IL-17C skin compared with control mice (Fig. 3D).

Histological examination of uninvolved K5–IL-17C dorsal skin compared with littermate control skin revealed modest increases in epidermal thickness (acanthosis) in uninvolved skin (11.5 ± 0.9 μm control skin versus 16.1 ± 0.6 μm; p = 0.006). In contrast, involved skin of K5–IL-17C animals exhibited robust epidermal hyperplasia (70.0 ± 5.2 μm; p < 0.001 versus controls and un-
involved K5–IL-17C skin), loss of the granular cell layer, thickening of the interfollicular epidermal layers, and confluent parakeratotic scale (Fig. 3E). This increase in epidermal thickness occurred concurrent with increases in cell proliferation, indicated by Ki67 staining, and decreases in KC terminal differentiation, indicated by loricrin in uninvolved skin and involved K5–IL-17C skin compared with control mouse skin (Fig. 3F). H&E-stained skin sections also revealed an apparent increase in dermal blood vessels and a dense immune cell infiltrate (Fig. 3E).

To further explore these changes, dermal angiogenesis was examined using MECA staining. Increases in MECA-positive staining was observed between control and uninvolved K5–IL-17C skin, which was further amplified in involved skin (Fig. 4A). VEGF protein increased between control and uninvolved K5–IL-17C skin (79.9 ± 6.5 pg/ml control versus 127.9 ± 11.4 pg/ml uninvolved K5–IL-17C; p = 0.07) and involved K5–IL-17C skin (258.9 ± 54.1 pg/ml; p = 0.02 versus control) and was localized to KCS, infiltrating leukocytes, and cutaneous nerves (Fig. 4B). Primary human KCS and dermal microvascular ECs both directly responded to stimulation with IL-17C by producing 52 (p = 0.05) and 20% more (p = 0.04) VEGF mRNA (Fig. 4C), respectively. No differences in angiopoietin or Tie2 expression were observed.

Cell type–specific examination and quantification of the inflammatory infiltrate in K5–IL-17C mouse skin revealed significant increases in CD4+ T cells, CD8+ T cells, CD11c+ myeloid dendritic cells, and F4/80+ macrophages in K5–IL-17C involved skin compared with both control mouse skin and K5–IL-17C uninvolved skin (Fig. 5). Modest, but insignificant (p = 0.09), increases in CD8+ T cells were seen in uninvolved K5–IL-17C skin compared with controls. Similar observations were seen in the affected ear skin of K5–IL-17C animals (Supplemental Fig. 1).

To explore the molecular signature of K5–IL-17C skin, we examined changes in candidate cytokines, chemokines, and innate defense molecules directly related to the histological and immunophenotypic changes observed in the skin (Fig. 5) and that have been proposed to contribute to the pathogenesis of psoriasis (25, 26). Very few significant gene changes were observed between control littermate skin and uninvolved K5–IL-17C skin, but increases in transcript level were observed for S100A8 (p = 0.04; n = 4–6) and S100A9 (p = 0.02) and IL-17F (p = 0.04; Fig. 6A).

![FIGURE 4. K5–IL-17C mouse skin has increases in dermal angiogenesis and VEGF. (A) MECA-immunostained dorsal skin of control mouse skin and K5–IL-17C mouse uninvolved and involved skin. (B) VEGF ELISA and immunohistochemistry demonstrate increases in VEGF protein in uninvolved and involved K5–IL-17C skin compared with littermate control skin. (C) qRT-PCR of primary human KCS and ECs stimulated with IL-17C (200 ng/ml) demonstrates significant increases in VEGF mRNA. Scale bars as noted. *p < 0.05 compared with control mouse, **p < 0.05 compared with uninvolved K5–IL-17C skin (B). *p < 0.05 compared with control stimulated (C).](image-url)
most likely derived from IL-17C direct effects on KCs (5) and T cells (9) (Figs. 3, 5). Comparison between involved K5–IL-17C skin with littermate control skin revealed significant increases in many of the hallmark psoriasis-transcriptome genes, including the proinflammatory cytokines and chemokines, TNF-α, IL-1α, IL-1β, IL-6, and CCL20, Th1- and Th17-derived cytokines IFN-γ and IL-17A, and the myeloid-derived cytokines IL-12 and IL-23 with sustained expression of the innate defense markers DefB3 (the murine homolog of hBD2), S100A8, and S100A9 (Fig. 6A; *p < 0.05). Genes that changed significantly between uninvolved and involved skin included IL-6 (*p = 0.05), IL-1b (*p = 0.004), IL-23p19, DefB3, S100A8, and S100A9 (all *p = 0.03).

Gene-expression changes between control mouse skin and involved K5–IL-17C skin were further validated at the protein level (Fig. 6B–D). Increases in IL-12/23p40, S100A8, and S100A9 proteins were observed (Fig. 6B) as well as increases in TNF-α, IL-6, and IL-17A proteins (Fig. 6C) between uninvolved K5–IL-17C and control mouse skin. Moreover, additional inflammatory molecules CS/C5A, CD54, IL-16, CXCL1, CCL2, CCL3, CXCL2, TIMP-1, and TREM-1 also increased between involved K5–IL-17C skin and control mouse skin (Fig. 6D).

**TNF-α inhibition improves the K5–IL-17C mouse skin phenotype**

Psoriasis patients treated with the TNF-α inhibitor etanercept show significant improvement in disease severity (27–29) and have rapid decreases in IL-17C (Fig. 1D). To examine the effects of TNF-α inhibition in K5–IL-17C mice, animals were systemically treated with either anti–TNF-α or negative control murine IgG2a,k mAbs for 8 wk as described previously (30). Significant improvement in the gross appearance of individual animals treated with TNF-α inhibitors was observed (Fig. 7A), although some level of skin disease was still present. Significant decreases in epidermal thickness and infiltrating CD4+ and CD8+ T cell numbers were identified (Fig. 7B), although these failed to return to control mouse levels. Decreases in neither CD11c+ nor F4/80+ cells were seen (data not shown). Examination of elevated proinflammatory cytokines in treated mice demonstrated sustained levels of IL-17C, as expected based on its genetic overexpression (Fig. 7C), and robust decreases to control levels for IFN-γ, IL-6, and IL-1β and more modest decreases in S100A8 and DefB3. CCL20, IL-17A, and IL-1α levels remained elevated (Fig. 7C).

**Discussion**

In this study, we have identified IL-17C as a contributing proinflammatory cytokine critical for psoriasis pathogenesis. This conclusion is supported by the following data: 1) IL-17C is the most abundantly expressed IL-17 cytokine at the protein level in lesional psoriasis skin and colocalizes with KCs, ECs, and skin-resident and infiltrating leukocytes; 2) IL-17C elicits increases in TNF-α from human dermal microvascular ECs and, when combined with TNF-α, produces additive and synergistic increases in key psoriasis-related proinflammatory cytokines, chemokines,
and innate defense molecules from human KCs; 3) mice engineered to overexpress IL-17C in KCs develop a psoriasis-like dermatitis containing clinical, histological, cellular, and molecular changes that mimic human psoriasis and that are improved with TNF-α inhibition; and 4) K5–IL-17C mice provide in vivo evidence demonstrating synergistic effects of IL-17C and TNF-α/IL-17A in promoting psoriasiform skin disease.

The biological relevance of increased IL-17C in psoriasis is poorly understood, and the role of IL-17C in psoriasis pathogenesis remains unclear. One potential mechanism by which IL-17C-mediated skin inflammation may occur is by activating host defense pathways in human epidermal KCs, as others have recently identified increases in expression of hBD2, S100A7/8/9, CXCL1/2/3, CCL20, TNFAIP6, and TNIP3 at levels similar to or greater than those observed in K5–IL-17C skin. The biological relevance of increased IL-17C in psoriasis is poorly understood, and the role of IL-17C in psoriasis pathogenesis remains unclear. One potential mechanism by which IL-17C-mediated skin inflammation may occur is by activating host defense pathways in human epidermal KCs, as others have recently identified increases in expression of hBD2, S100A7/8/9, CXCL1/2/3, CCL20, TNFAIP6, and TNIP3 at levels similar to or greater than those observed in K5–IL-17C skin.

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than those elicited by IL-17A (5). These gene changes are remi-
niscent of those previously identified from human KCs following
stimulation with IL-17A/TNF-α, as part of the signature psoriasis
transcriptome (13, 31). In our experiments, we failed to identify
significant changes in these transcripts in primary human KCs
following IL-17C stimulation alone (Fig. 2C), perhaps reflective
of differences in source of primary KCs (neonate foreskin versus
adult buttoc). However, increases in the antimicrobial transcripts,
S100A8 and S100A9 were observed in uninvolved skin of K5–IL-
17C mice (Fig. 6), prior to increases in other proinflammatory
cytokines, and models transcriptional gene changes we have ob-
served previously in uninvolved psoriasis patient skin (32).
Moreover, IL-17C stimulation lead to increases in EC-derived
proinflammatory cytokines, including TNF-α (Fig. 2A, 2B); and
primary human KCs stimulated with both IL-17C and subthresh-
old levels of TNF-α produced significant increases in these as well
as other key innate defense, chemokine, and proinflammatory
cytokine transcripts (Fig. 2C). These findings suggest a potential
feedback loop occurs between KCs (producing IL-17C) and ECs
(responding by producing TNF-α), which may serve to promote
self-sustaining inflammation. In vivo support for this feedback
loop is evidenced by the increases in dermal angiogenesis in un-
involved skin of K5–IL-17C mice (Fig. 4) that precedes increases
in cutaneous TNF-α expression, the development of involved skin
lesions, and the upregulation of the these same KC-derived and
psoriasis-related transcripts (Fig. 6). Our in vitro data suggest that
IL-17C may indirectly promote dermal angiogenesis by eliciting
VEGF from both ECs and KCs (Fig. 4), which in turn promotes
angiogenesis and additional TNF-α production.

The similarity between genes upregulated by IL-17A and IL-17C
suggests they may be functionally redundant on epithelial cells;
although transcript levels of IL-17A and IL-17C suggest IL-17A

**FIGURE 7.** Systemic inhibition of TNF-α in K5–IL-17C mice leads to improvement in disease severity. (A) Photographs of the same severely affected K5–IL-17C mouse before and after 8 wk of TNF-α Ab treatment. (B) Representative images of H&E-stained and CD4- and CD8-immunostained dorsal skin of K5–IL-17C involved skin treated with either anti–TNF-α Abs or IgG and quantitation of epidermal thickness and CD4+ and CD8+ cell numbers. The dashed line represents control mouse levels. *p < 0.05 compared with K5–IL-17C involved plus IgG. (C) Real-time quantitative PCR analyses of key innate defense molecules and psoriasis-related proinflammatory cytokines/chemokines demonstrate decreases in IFN-γ, IL-6, and IL-1β in involved skin between K5–IL-17C + IgG and K5–IL-17C + TNF-α-treated mice. *p < 0.05 compared with control mice.

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**2260 IL-17C PROMOTES SKIN INFLAMMATION**
may be expressed more robustly in lesional psoriasis tissue, our protein data demonstrate there is ~125-fold more IL-17C protein present than IL-17A and differences in signaling strength based solely on the local concentration of ligand, and the number of cells producing and responding to the ligand cannot be overlooked (Fig. 1B, 1C). The discrepancy between cytokine mRNA and protein level correlation is consistent with a recent report (33) and may reflect differences in nontranslational regulation, cytokine storage, and cellular source.

Previous reports have identified the importance of synergistic and additive responses to IL-17A and TNF-α as a hallmark of IL-17A biology and of psoriasis (13). Recently, similar synergies have been identified between IL-17C/TNF-α on bBD2 expression by primary human KCs (5), and IL-17C/IL-22 synergism drives S100A8/A9 production in colonic epithelial cells (6). This phenomenon is recapitulated in this study (Fig. 2C) with 16 gene transcripts being either additively or synergistically induced by IL-17C/TNF-α.

Studies examining IL-17C–IL-17RE interactions have recently revealed that IL-17C regulates Th17 cell differentiation and production of IL-17A and IL-17F (9), cytokines known to promote skin inflammation in the imiquimod model of psoriasiform dermatitis (5) and that are upregulated in psoriasis lesional skin (Fig. 1A). These findings suggest synergy may occur not only between IL-17C and TNF-α but also IL-17C and IL-17A, such that the proinflammatory feedback loop may include the epidermis, the vasculature, and also Th17 cells. In K5–IL-17C skin, increases in IL-17A/F, TNF-α, and IL-6 were found in uninvolved skin compared with control mouse skin (Fig. 6), perhaps reflective of IL-17C direct effects on ECs (Fig. 2A, 2B) and T cells (9). Whether IL-17A/F and IL-6 also synergize with IL-17C, similar to TNF-α, has yet to be explored. Taken together, these data support the idea of a crucial role for IL-17C–TNF-α synergism (IL-17A and IL-17C) in the molecular fingerprint of psoriasis and demonstrate the capacity of IL-17C to augment an immune response concurrent with IL-17A/TNF-α. This concept is supported by clinical observations that psoriasis patients treated with the anti-TNF-α agent etanercept exhibit rapid decreases in cutaneous IL-17C expression (within 72 h; Fig. 1D), prior to skin improvement and reported decreases in circulating levels of IL-17A and IL-22 (34). Others have reported similar outcomes in psoriasis patients treated with the TNF-α inhibitor adalimumab in whom IL-17C gene expression decreased within 4 d of the initial treatment, whereas IL-17A/IL-17F and IL-22 failed to decrease significantly until 14 d posttreatment, and IL-23p19 and IFN-γ did not drop significantly until 84 d (11). Moreover, recent clinical trials targeting the common IL-17A/C receptor IL-17RA (using brodalumab; formally AMG841) also demonstrated rapid decreases in IL-17C mRNA (within 2 wk) (35) that occurred prior to clinical disease improvement and preceded the gradual decreases of IL-17A and IL-22, which reached baseline nonlesional levels by 6 wk (36).

K5–IL-17C mice treated with TNF-α inhibitors also showed significant improvement in their disease severity (Fig. 7), although disease was not reversed. This most likely reflects the sustained levels of IL-1α and IL-17A that may synergize with sustained level of IL-17C. TNF-α is known to regulate IL-17C expression via NF-κB (p65/p50) (4); therefore it is possible that efficacy of TNF-α inhibition in psoriasis patients actually reflects decreases in IL-17C; thus, TNF-α inhibition may not be completely effective in K5–IL-17C mice because of the high levels of IL-17C, which are being genetically expressed and cannot be regulated by blockade of TNF-α.

In conclusion, our results suggest that IL-17C is a highly sensitive member of the IL-17 family and that IL-17C may serve as a novel mechanism for amplifying Th17/Th22/TNF-α–mediated inflammatory signaling critical for psoriasis pathogenesis. Support for the sensitivity of IL-17C in other models of inflammatory disease are provided by kinetic studies showing that IL-17C induction precedes that of IL-17A and other Th17/Th22 cytokines (IL-22) in a murine colitis model (5). These data support the concept of a crucial role for both IL-17A and IL-17C synergizing with TNF-α to generate the molecular fingerprint of psoriasis. In this study, we propose that IL-17C serves as a critical cytokine mediating psoriasis and that psoriasiform skin inflammation is likely to be driven by numerous IL-17C–producing activated KCs in psoriasis tissue rather than the comparatively modest numbers of IL-17A–producing cells that likely initiate the primary response and then feed into the self-sustaining proinflammatory cascade of events. The increases in cytokines are likely reflective of the increased presence of skin-infiltrating immune cells and proliferating KCs and signal a synergistic immune response between IL-17C with TNF-α and IL-17A (Fig. 2) (5). This synergistic increase may also reflect changes associated with IL-1β, which we found elevated compared with control skin, supporting and elaborating recent work illustrating similar IL-17C–IL-1β and IL-17C–TNF-α synergy (5).

Although the cause of psoriasis is unknown, the currently proposed hypothesis is that in patients with a susceptible genetic background, some stimulus, perhaps an infection, leads to a coordinated series of events involving cutaneous cells and cytokines that, once started, initiates a self-sustained vicious proinflammatory signal resulting in KC hyperproliferative cell-cycle response. Recent reports have identified IL-17C as a key innate immune defense cytokine that is rapidly and robustly upregulated following infection or TLR stimulation (5, 6, 9). Our data support the supposition of a crucial role for IL-17C–TNF-α synergism (IL-17A and IL-17C) in the molecular fingerprint of psoriasis and, when taken together, provide evidence indicating that IL-17C synergizes with TNF-α as well as IL-17A to initiate and sustain KC activation and promote epidermal hyperplasia. Our results demonstrate a potential inflammatory feedback loop among the endothelium, the epidermis, and Th17 cells that can be amplified by IL-17C. Once triggered, this loop is sufficient to promote chronic skin inflammation and acanthosis, two cutaneous characteristics of psoriasis. Because IL-17C appears to act upstream of many proinflammatory cytokines critical in psoriasis pathogenesis, including IL-1β, IL-17A/F, IL-22, IL-6, IL-8, VEGF, and TNF-α [our data and others (2, 5, 6, 9, 24)], targeting IL-17C as an early upstream regulator of these cytokines may provide a more encompassing therapeutic strategy for the effective treatment of psoriasis. Taken together, our findings support prior work (5) demonstrating a need for IL-17C signaling for imiquimod-elicited psoriasiform skin inflammation and demonstrate a pathogenic role for the elevated IL-17C observed in lesional psoriasis skin.

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References


