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IL-1F5, -F6, -F8, and -F9: A Novel IL-1 Family Signaling System That Is Active in Psoriasis and Promotes Keratinocyte Antimicrobial Peptide Expression

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IL-1F6, IL-1F8, and IL-1F9 and the IL-1R6(RP2) receptor antagonist IL-1F5 constitute a novel IL-1 signaling system that is poorly characterized in skin. To further characterize these cytokines in healthy and inflamed skin, we studied their expression in healthy control, uninvolved psoriasis, and psoriasis plaque skin using quantitative RT-PCR and immunohistochemistry. Expression of IL-1F5, -F6, -F8, and -F9 were increased 2 to 3 orders of magnitude in psoriasis plaque versus uninvolved psoriasis skin, which was supported immunohistologically. Moreover, treatment of psoriasis with etanercept led to significantly decreased IL-1F5, -F6, -F8, and -F9 mRNAs, concomitant with clinical improvement. Similarly increased expression of IL-1F5, -F6, -F8, and -F9 was seen in the involved skin of two mouse models of psoriasis. Suggestive of their importance in inflamed epithelia, IL-1α and TNF-α induced IL-1F5, -F6, -F8, and -F9 transcript expression by normal human keratinocytes. Microarray analysis revealed that these cytokines induce the expression of antimicrobial peptides and matrix metalloproteinases by reconstituted human epidermis. In particular, IL-1F8 increased mRNA expression of human β-defensin (HBD)-2, HBD-3, and CAMP and protein secretion of HBD-2 and HBD-3. Collectively, our data suggest important roles for these novel cytokines in inflammatory skin diseases and identify these peptides as potential targets for antipsoriatic therapies. The Journal of Immunology, 2011, 186: 2613–2622.
time quantitative RT-PCR (qRT-PCR), which we then confirmed by immunohistochemical evaluation. Next, we examined their mRNA expression levels in lesional skin during treatment with the anti–TNF-α biologic etanercept (Enbrel; Immunex). To gain further insight into the role of these cytokines in T cell-mediated skin inflammation, we assessed how their expression was modulated by the inflammatory cytokines IL-1α, TNF-α, IL-17A, and IL-22. IL-1F5 and -1F9 were efficiently induced by IL-1α, IL-17A, and TNF-α. However, although IL-1F9 mRNA and intracellular protein could be induced by these cytokines, secretion of IL-1F9 by keratinocytes required application of extracellular ATP. In terms of effector functions, these newly described cytokines induced the expression of a wide swath of epithelial defense proteins, with IL-1F8 being a particularly efficient inducer of human β-defensin (HBD) secretion. Taken together, our data suggest important roles for these novel cytokines in the pathogenesis of psoriasis and identify these peptides as potential targets for antisporic therapeutic agents.

Materials and Methods

Study population

Twenty individuals with chronic plaque psoriasis and 20 normal controls were enrolled (age range 18–75 yr). Entry criteria were the manifestation of one or more well-demarcated, scaled, erythematous psoriatic plaques that were not limited to the scalp and no systemic antipsoriatic treatments for 2 wk before biopsy. Biopsies sites varied between patients depending on site of active plaques, whereas biopsies of uninvolved and control skin were from the buttocks.

Biopsies were also obtained from uninvolved and lesional skin of individuals responding to treatment for chronic plaque psoriasis with the biologic agent etanercept (Enbrel; Immunex). Thirty subjects were enrolled based on criteria previously published (20). Inclusion criteria included age ≥18 yr, no placebo history of psoriatic plaques in at least 10% body area. Exclusion criteria included use of systemic psoriasis treatments within 4 wk, topical therapy within 2 wk, or severe comorbid diseases. For 12 wk, subjects received etanercept 50 mg twice a week s.c. (open label). At baseline, 6-mm punch biopsies were obtained under local anesthesia (lidocaine) from uninvolved skin and a target plaque. Subsequent biopsies were taken on days 1, 6, 14, 21, and 28 of therapy from the same target plaque.

Informed consent was obtained from all subjects after protocols approved by the Institutional Review Board of the University of Michigan. This study was conducted in compliance with good clinical practice and according to the Declaration of Helsinki Principles.

Real-time qRT-PCR

After removal from the skin, biopsies were snap-frozen in liquid nitrogen and stored at −80°C until use. Biopsies were pulverized with a hammer while still frozen, dissolved in RLT buffer (Qiagen, Chatsworth, CA), homogenized using glass beads (Biospec Products, Bartlesville, OK), and total RNA was isolated (RNaseasy Mini kit; Qiagen). A total of 200 ng mRNA was reverse transcribed (High Capacity cDNA Transcription Kit; Applied Biosystems, Foster City, CA) and transcripts quantified using a 7900HT Fast Real-Time PCR system (Applied Biosystems) using TaqMan primer sets provided by Applied Biosystems (IL1A Hs00174092_m1, IL1B Hs00909788_m1, IL1B Hs00174097_m1, IL18 Rn00126001_m1, IL1RN Hs00174099_m1, MIP1α Mm01337545_m1, MIP1β Mm00457645_m1, MIP2 Mm01337545_m1, and RPLP0 Hs00433264_m1) and 18S rRNA housekeeping gene (Hs99999901_s1). Data were tested for normality and statistical significance calculated using Student t test or Mann–Whitney U test as appropriate using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA).

Immunohistochemistry

Human skin biopsies were snap frozen in OCT (Tissue-Tek, Sakura), sectioned at 5 μm, and stained with mouse anti-human IL-1F5 (5 μg/ml; R&D Systems, Minneapolis, MN), IL-1F8 (5 μg/ml; R&D Systems), goat anti-human IL-1F6 (15 μg/ml; R&D Systems), or rat anti-human IL-1F9 (10 μg/ml; Santa Cruz Biotechnology). Subsequently, the appropriate species of secondary detection kit was used (Vectorstain ABC; Vector Laboratories) followed by visualization with 3,3′-DAB substrate (Vector Laboratories, San Diego, CA) and counterstaining with CAT hematoxylin (Biocare Medical). The appropriate isotype control Abs were used at the same concentrations as the primary detection Abs and gave no discernable staining.

Adult mice were euthanized, their hair shaved, and skin from the back was processed for paraffin sectioning. For paraffin sectioning, skin was placed in 10% buffered formalin (Surgipath Medical Industries, Richmond, IL) overnight at 4°C prior to dehydration and embedding (Sakura Finetech, Torrance, CA). Immunohistochemistry was performed on 5-μm-thick paraffin sections using high-temperature Ag retrieval solution (DakoCytomation, Carpinteria, CA) for anti-mouse IL-1F6/FIL1 (1:100 dilution; R&D Systems) or matched goat IgG isotype control (R&D Systems). The Ab and isotype control were detected using anti-goat IgG ABC Kits (Vector Laboratories) and visualized with 3,3′-DAB substrate (Vector Laboratories). Slides were counterstained with hematoxylin. For each animal, one image was taken for an n = 6.

Keratinocyte culture

Normal human keratinocyte (NHK) cultures were established from sun-protected adult human skin as described (21) in serum-free medium optimized for high-density keratinocyte growth (Medium 154; Invitrogen/ Cascade Biologies, Portland, OR). NHKs were used for experiments in the second or third passage. All cells were plated at 3000 cells/cm² and maintained to 4-d postconfluence. Cultures were then starved of growth factors in unsupplemented medium M154 for 24 h before use. Experiments were carried out under low-calciion (0.1 mM) conditions. Cultures were stimulated with recombinant human cytokines from R&D Systems: TNF-α (10–10 ng/ml), IL-1α (10 ng/ml), IL-17A (2 and 10 ng/ml), and IL-22 (10 ng/ml).

Reconstituted human epidermal (RHE) cultures were obtained from MatTek (EPI-200; MatTek, Ashland, MA). After overnight equilibration in 5% normal maintenance medium (MatTek), medium was refreshed and supplemented with recombinant human cytokines as indicated. Medium was sampled at 24 and 48 h. In addition, 4-mm-diameter discs were punched from RHE cultures and formalin fixed, paraffin embedded, sectioned at 5 μm, and stained for HBD-2 expression (1:200 dilution, goat anti-BD-2; PeproTech, Rocky Hill, NJ) or IL-1F9 expression (10 μg/ml; Santa Cruz Biotechnology) and visualized with 3,3′-DAB (BD Pharmingen).

RNA processing and microarray hybridization

RHE cultures were removed from their support filters and dissolved in RLT buffer (Qiagen), homogenized using glass beads (Biospec), and total RNA was isolated (RNeasy Mini kit; Qiagen). RNA quantity and quality were measured using an Agilent 2100 Bioanalyzer (Agilent Technologies, Palo Alto, CA). Only samples yielding intact 18S and 28S rRNA profiles were used. cDNA was prepared by random priming (murine IL-1 family genes (IL-1A Hs00999900_01_m, IL-1B Hs00174759_1, matrix metalloproteinases (MMP) 1 Hs00239581_m1, IL1RAP [R3] Hs00374056_m1, MMP9 Hs00234579_m1, IL-1R4 Hs01073300_m1, MMP10 Hs00239587_m1, IL-1R5 Hs00175381_m1, MMP19 Hs00275699_m1, IL1rL2 [R6] Hs00909276_m1, IL-17R Hs00187256_m1, and RPLP0 Hs99999902_m1). All values were normalized to the expression of the housekeeping gene RPLP0. Mouse skin mRNA was extracted, reverse transcribed, and cDNAs quantified as above using primers for murine IL-1 family genes (IL-1A Hs00999900_01_m, IL-1B Hs00174759_1, matrix metalloproteinases (MMP) 1 Hs00239581_m1, IL-1R4 Hs01073300_m1, MMP9 Hs00234579_m1, IL-1F8 Hs00133754_m1, and IL-1F9 Hs00046332_m1) and 18S rRNA housekeeping gene (Hs99999901_s1). Data were tested for normality and statistical significance calculated using Student t test or Mann–Whitney U test as appropriate using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA).

ELISAs

Estimation of HBD-2 was carried out as previously described (23). IL-8 ELISA was performed as recommended (R&D Systems). Secreted HBD-3 was measured using maxisorb microtiter plates (Nunc) coated overnight at 4°C with 50 μg/ml rabbit anti-human BD-3 Ab (PeproTech) diluted to 5 μg/ml in PBS. Plates were blocked with 200 μl 1% BSA (in PBS) for 1 h at room temperature (RT). After washing four times with 300 μl PBS-0.05% Tween-20, 50 μl/well samples and standards were added in duplicate and incubated for 2 h at RT. After washing, 50 μg/ml biotinylated
The Journal of Immunology 2615

We also assessed the expression of all IL-1 receptor transcripts in also detected in the mononuclear cell infiltrate in lesional skin. lesions compared with healthy control skin as assessed inm involved psoriasis skin, we went on to examine whether these cytokines were overexpressed in two established mouse models of psoriasis. We analyzed mRNA from lesional and unaffected control skin from the KC-Tie2 [Tg(RKT5-TA1)Dmt × Tg(TekOS-Tek) Dmt] transgenic model (25, 26) and the imiquimod-induced mouse model (27) of psoriasis (Fig. 3). In both of these mouse models, the inflamed skin showed striking and significant overexpression of IL-1α, IL-1F5, -1F6, -1F8, and -1F9 transcripts compared with skin from monogenic control littermates (Fig. 3A) or nonimmunod-treated skin (Fig. 3B), respectively. Moreover, immunohistochemistry revealed robust expression of IL-1F6 in the lesional skin of KC-Tie2 mice (Fig. 3C) compared with monogenic littermates (Fig. 3D).

Psoriasis-associated cytokines induce IL-1F5, -1F8, and -1F9 expression by keratinocytes

To begin to understand the induction of IL-1 cytokines in inflamed skin, we treated normal NHK with the psoriasis-associated cytokines TNF-α, IL-1α, IL-17A, and IL-22. Stimulation of NHK with TNF-α dose-dependently induced IL-1F5, -1F8, and -1F9 mRNAs (Fig. 4A). IL-1α treatment led to dose-dependently increased expression of IL-1F5, -1F8, and -1F9 (Fig. 4B). IL-17A induced IL-1F6 and -1F9 expression (Fig. 4C, 4D), and although IL-22 alone was ineffective, it potentiated the effects of IL-17A for the induction of IL-1F6 (p < 0.05) and IL-1F9 (p < 0.001) (Fig. 4C, 4D).

The induction of IL-1F9 protein was confirmed in IL-1α– and TNF-α–treated RHE cultures (Fig. 4E). Individually, both IL-1α (Fig. 4F) and TNF-α (Fig. 4F) could induce keratinocyte expression of IL-1F9; however, a combination of the two cytokines was most effective (Fig. 4E, 4F). Although this stimulation was particularly efficient at inducing IL-1F9 protein expression in tissue as detected immunohistochemically, little secreted IL-1F9 was detected in conditioned culture medium. Given that like IL-1α, IL-1F5–IL-1F9 do not have leader sequences that target their secretion (7), and IL-1α is likely secreted by an ATP-dependent alternative pathway (28), we stimulated NHK with exogenous ATP for 2 h following 24 h of cytokine stimulation (Fig. 4C, 4F). Application of ATP markedly induced secretion of IL-1F9 from the keratinocyte cultures, as measured by ELISA of conditioned medium at 2 h (Fig. 4F).

IL-1F9 functions as an inducer of antimicrobial peptide and MMP expression by keratinocytes

Although induction of NF-κB activation by IL-1F6 (10), -1F8 (10), and -1F9 (10, 12) has been demonstrated, no function has been assigned to these cytokines. Thus, we treated RHE cultures with IL-1F5, -1F6, -1F8, and -1F9 and performed microarray analyses using the Affymetrix Human Gene ST 1.0 platform (Affymetrix). IL-1F5, -1F6, -1F8, and -1F9 upregulated (>2-fold) 52, 69, 77, and 37 transcripts and downregulated (>2-fold) 246, 54, 20, and 11 transcripts, respectively. A heat map illustrating a selection of psoriasis and inflammation-associated transcripts is shown in Fig. 5. Subsequent qRT-PCR analysis confirmed that several antimicrobial peptides (AMP) are significantly induced by IL-1F8, including HBD-2 (DEFB4), lipocalin2 (Fig. 6C), HBD-3 (Fig. 6D), CAMP (Fig. 6F), elafin (Fig. 6G), serpinB1 (Fig. 6H), and IL-8 (Fig. 6I). IL-1F8–induced secretion of the defensins HBD-2 and HBD-3 into the conditioned cell-culture medium was detected by ELISA (Fig. 6B, 6E). The upregulation of HBD-2 protein expression by IL-1α– and IL-1F8–treated RHE cultures...
could also be detected immunohistochemically as shown in Fig. 6J–L. Collectively, these data illustrate the induction of AMP by IL-1F8.

Our microarray analysis also highlighted a number of MMP as targets of IL-1F8 and IL-1F9 treatment of RHE cultures (Fig. 5), which is of interest, as a number of MMPs are overexpressed in lesional psoriasis skin (29, 30). Using qRT-PCR, we demonstrate that IL-1F8 could significantly induce 3.6-fold and 2.6-fold increases in MMP9 and MMP19 mRNA, respectively (Fig. 7C, 7G), and IL-1F9 induced 2.8-fold and 2.9-fold increases in MMP10 and MMP19 transcript expression, respectively (Fig. 7E, 7G). Interestingly, MMP1 (18-fold, p < 0.05) and MMP9 (2.8-fold, p < 0.01) were significantly elevated in lesional psoriasis skin (Fig. 7).

**Discussion**

Epidermal inflammation is driven by the coordinated action of a number of cytokines and growth factors, including the IL-1 family. With the discovery of IL-1F5 (4–7, 31), IL-1F6 (7), IL-1F8 (5, 7), and IL-1F9 (6), these cytokines, together with their receptors IL-1R6(RP2) and IL-1R3(RAcP), form a novel and distinct IL-1 signaling system. Because overexpression of IL-1F6 in the basal keratinocytes of an IL-1F5–deficient mouse led to psoriasiform hyperplasia (9), we proceeded to characterize this cytokine family in human psoriasis skin. Expression of IL-1F5, -1F6, -1F8, and -1F9 transcripts were increased 2 to 3 orders of magnitude in PP versus PN skin (Fig. 1), which was supported immunohistologically and is in accord with the earlier findings that IL-1B (32), IL-18 (33), IL-1F5 (17), IL-1F6 (9), and IL-1F9...
(9, 17) are all markedly elevated in lesional psoriasis skin. IL-1α mRNA and protein have been previously shown to be decreased in psoriasis plaques (32), which is consistent with the data we present in this study (Fig. 1A). Interestingly, neither receptor for these cytokines was differentially expressed (IL-1R3 and IL-1R6; Supplemental Fig. 1). We also found significantly decreased expression of IL-1α, IL-1β, IL-1F5, IL-1F6, IL-1F8, and IL-1F9 mRNAs in skin during treatment of psoriasis with etanercept (Fig. 2), which is consistent the earlier findings that two other IL-1 family members, IL-1β (34) and IL-18 (35), are downregulated during effective treatment of psoriasis and with studies in a mouse-human psoriasis xenograft system that show markedly decreased IL-1F6 expression in the skin lesions during effective treatment with etanercept (36).

Given the marked expression of these cytokines in psoriasis lesions and that the overexpression of IL-1F6 leads to psoriasis...
Form inflammation in the mouse (9), we examined two mouse models of psoriasis (Fig. 3) and determined that IL-1F5, -1F6, -1F8, and -1F9 were all dramatically elevated in the lesional skin of both KC-Tie2 and imiquimod-treated mice. We also demonstrate that IL-1F6 protein was robustly expressed in the lesional skin of KC-Tie2 mice (Fig. 3C). It is particularly striking that in

**FIGURE 4.** The inflammatory cytokines IL-1α, TNF-α, and IL-17A induce expression of IL-1 family members by cultured keratinocytes. Postconfluent NHK were treated as indicated for 24 h, and qRT-PCR analyses revealed induction of IL-1F5, -1F6, and -1F9 by TNF-α (A) and IL-1α treatment (B). IL-1F6 (C) and -1F9 (D) transcripts were induced by IL-17A, which could be augmented by IL-22. IL-1α and TNF-α promote keratinocyte IL-1F9 expression (E) but extracellular ATP (1 mM, 2 h) is required for optimal secretion of IL-1F9 into the culture medium as analyzed by IL-1F9 ELISA (F). IL-1F9 was expressed in the upper spinous layers of cultures of reconstituted human epidermis as manifested by immunohistochemical staining with Abs against IL-1F9 (E) (original magnification ×200). Bars, mean ± SD (n = 3). Statistical significance indicated: *p < 0.05, **p < 0.01, ***p < 0.001 versus no treatment, and ♦p < 0.05 for IL17A+ IL-22 versus IL-17A alone.

**FIGURE 5.** Microarray analysis revealed the induction of AMP and molecules involved in the remodeling and barrier function of the epidermis. RHE cultures were stimulated for 24 h with 25 ng/ml rIL-1α or 5 μg/ml IL-1F5, -1F6, -1F8, or -1F9 and analyzed using Affymetrix Human Gene ST 1.0 microarrays (Affymetrix). x-axis contains data from replicate RHE cultures. Color key: dark red, 3-fold increased expression; dark blue, 2.5-fold decreased expression compared with the average expression values of the untreated (control) cultures.
the KC-Tie2 mice, IL-1F6 mRNA is expressed 25 times more abundantly than that of its receptor antagonist IL-1F5 (Fig. 3A).

Although IL-1F6, -1F8, and -1F9 have been shown to activate NF-κB (10, 12), JNK, and/or ERK1/2-mediated pathways in cell lines (10), no function has yet been assigned to these molecules in skin. Thus, we treated reconstituted epidermal cultures with rIL-1F6, -1F8, and -1F9 and performed microarray analysis. Strikingly, these cytokines induced a broad pattern of increased AMP, MMP, and growth factor expression (Fig. 5). In particular, IL-1F8 was effective at inducing keratinocytes to express HBD-2 and HBD-3, the secretion of which was readily detectable in conditioned culture medium (Fig. 6). This is an interesting observation in light of the fact that the mononuclear cell infiltrate in psoriasis plaques is positive for IL-1F6, -1F8, and -1F9 immunoreactivity (Fig. 1H–K) and that the expression of these cytokines can be induced in blood monocytes in culture (A. Johnston, unpublished observation) and thus may contribute to AMP and MMP expression in inflamed skin. In addition, the mutual induction of IL-1α, IL-1β, and IL-1F9 may act as a positive-feedback loop driving AMP expression by the epidermis. It is interesting to note that the increases in MMP expression in PP versus PN or healthy control skin tend to be larger than those induced by cytokine treatment of RHE cultures (Fig. 7). These differences may relate to the fact that RHE cultures continue to express the regenerative maturation program of epidermal differentiation that is also characteristic of psoriasis (37), though they are capable of reverting to a more normal differentiation profile after grafting to immunocompromised mice (38).

Decorin and betacellulin (BTC) were both consistently downregulated by the IL-1 family cytokines in our microarray experiments (Fig. 5), and both of these transcripts are heavily downregulated in lesional psoriasis skin (23, 39). BTC is the only epidermal growth factor receptor ligand that is decreased in psoriasis skin (23, 40). Its role in skin biology is largely unknown, although transgenic overexpression of the extracellular domain of BTC in the mouse leads to alterations in hair follicle development and cycling and increased angiogenesis at experimental wounding sites (41). Decorin has been reported to interact with TGF-β (42), and via this interaction, it is thought to participate in cell cycle control (43).

Whereas others have shown that IL-1F9 is induced in NHK by treatment with IL-1α and TNF-α (5), in this study, we demonstrate that treatment with exogenous ATP is required for secretion of IL-1F9 into the medium (Fig. 4E, 4F). The same phenomenon was recently described for IL-1F6 release from transfected murine bone marrow-derived macrophages (44). IL-1F6, -1F8, and -1F9, like IL-1α and -1β, lack signal sequences for conventional secretion (7) via the endoplasmic reticulum/Golgi pathway and are secreted via a nonclassical pathway involving multivesicular bodies and exosomes (28) in a process triggered by extracellular...
ATP. Interestingly, like IL-1α (45), one role of IL-1F5, IL-1F6, IL-1F8, and/or IL-1F9 may involve acting as a transcription factor and as such would not require secretion. To that end, both IL-1F7 (46) and IL-1F11 (IL-33) (47) translocate to the nucleus, where they function as a transcription factors.

We typically required microgram per milliliter quantities of IL-1F5, IL-1F6, IL-1F8, and/or IL-1F9 for in vitro activity, which is consistent with earlier findings (10, 12). Thus, we must consider the possibility that these cytokines require some form of posttranslational modification that is not included in the commercial recombinant

FIGURE 7. IL-1F8 induces MMP expression by RHE cultures. RHE cultures were stimulated for 24 h with 25 ng/ml rIL-1α or 5 μg/ml IL-1F5, -1F6, -1F8, or -1F9. qRT-PCR revealed increases in MMP1 (2.8-fold; A), MMP9 (3.6-fold; C), MMP10 (3.6-fold; E), and MMP19 (2.6-fold; G) transcripts in response to IL-1F8, whereas IL-1F9 induced 2.8-fold and 2.9-fold increases in MMP10 (E) and MMP9 (G), respectively. MMP1 (B) and MMP9 (D) were both significantly overexpressed in psoriasis lesions (PP) compared with symptomless skin (healthy control or PN) altered expression of MMP10 (F) and MMP19 (H) was not statistically significant. Bars, mean ± SD (n = 9). Statistical significance indicated: *p < 0.05, **p < 0.01.
preparations we have used, such as glycosylation (48), and/or trimming of N-terminal amino acid residues (36). It will be important to focus on understanding how these molecules might function intracellularly as transcription factors and to further characterize how they are processed within the cell for secretion, as both modes of action may be important in tissue homeostasis and defense.

IL-1 was the first cytokine discovered in skin (49), and with the discovery that IL-1 is crucial for T cell differentiation (50, 51), IL-1 immunobiology is undergoing a renaissance. In light of the current study, we now have a better understanding of the broader role of IL-1 family in the pathobiology of psoriasis. Further, given that we have shown that these new IL-1 family members are able to drive AP activity on human basophils, allergen-reactive Th2 cells, iNKT and NK cells.


