

IL-31: A new link between T cells and pruritus in atopic skin inflammation

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Background: IL-31 is a novel T-cell-derived cytokine that induces severe pruritus and dermatitis in transgenic mice, and signals through a heterodimeric receptor composed of IL-31 receptor A and oncostatin M receptor.

Objective: To investigate the role of human IL-31 in pruritic and nonpruritic inflammatory skin diseases.

Methods: The expression of IL-31 was analyzed by quantitative real-time PCR in skin samples of healthy individuals and patients with chronic inflammatory skin diseases. Moreover, IL-31 expression was analyzed in nonlesional skin of atopic dermatitis patients after allergen or superantigen exposure, as well as in stimulated leukocytes. The tissue distribution of the IL-31 receptor heterodimer was investigated by DNA microarray analysis.

Results: IL-31 was significantly overexpressed in pruritic atopic compared with nonpruritic psoriatic skin inflammation.

Highest IL-31 levels were detected in prurigo nodularis, one of the most pruritic forms of chronic skin inflammation. *In vivo*, staphylococcal superantigen rapidly induced IL-31 expression in atopic individuals. *In vitro*, staphylococcal enterotoxin B but not viruses or T_H1 and T_H2 cytokines induced IL-31 in

leukocytes. In patients with atopic dermatitis, activated leukocytes expressed significantly higher IL-31 levels compared with control subjects. IL-31 receptor A showed most abundant expression in dorsal root ganglia representing the site where the cell bodies of cutaneous sensory neurons reside.

Conclusion: Our findings provide a new link among staphylococcal colonization, subsequent T-cell recruitment/activation, and pruritus induction in patients with atopic dermatitis. Taken together, these findings show that IL-31 may represent a novel target for antipruritic drug development. (*J Allergy Clin Immunol* 2006;117:411-7.)

Key words: IL-31, pruritus, atopic dermatitis, T cells, cytokines, superantigen

Atopic dermatitis is a chronically relapsing inflammatory skin disease with a steadily increasing prevalence of 10% to 20% in children and 1% to 3% in adults.¹ Pruritus represents a predominant symptom of atopic dermatitis. Itching and scratching are important factors in the initiation and maintenance of atopic skin inflammation and lead to a serious impairment of the quality of life of affected patients.^{2,3} Clinically, histamine receptor type 1 antagonists show no or only limited effect, suggesting that histamine is not the major peripheral mediator involved in pruritus in patients with atopic dermatitis.^{2,4} Several other mediators, including neuropeptides, neurotransmitters, proteinases, arachidonic derivatives, and cytokines, have been implicated in atopy-associated pruritus.^{4,5} In particular, skin-infiltrating T cells have been suggested to play a major role in pruritus induction by the production and release of as yet unknown mediators.^{4,6}

Clinically, atopic dermatitis is characterized by eczematous skin lesions showing an inflammatory infiltrate predominantly composed of CD4⁺ and cutaneous lymphocyte associated antigen-positive memory T cells.⁷ In the initial phase of atopic skin inflammation, the infiltrate predominantly consists of IL-4-producing T_H2 cells, whereas chronic lesions frequently show an infiltrate with a T_H1 phenotype.⁷ Although significant insight has been obtained into the immunopathogenesis of atopic diseases, the molecular basis of pruritus in atopic individuals remains elusive.

A recent study by Dillon et al⁸ demonstrated that transgenic overexpression of the novel 4 helix bundle cytokine IL-31 in lymphocytes induces severe pruritus

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Abbreviations used

IL-31RA: IL-31 receptor A
OSMR: Oncostatin M receptor
SEB: Staphylococcal enterotoxin B
TSST-1: Toxic shock syndrome toxin 1

and dermatitis in mice. IL-31 is expressed by T cells, and it signals through a heterodimeric receptor composed of IL-31 receptor A (IL-31RA) and oncostatin M receptor (OSMR), which is expressed on epithelial cells and keratinocytes.^{8,9} Here we report for the first time that human IL-31 is significantly upregulated in pruritic (atopic dermatitis) but not in nonpruritic (psoriasis) forms of chronic skin inflammation. *In vivo*, exposure to staphylococcal superantigen rapidly induced IL-31 expression in atopic individuals. *In vitro*, IL-31 was induced by staphylococcal superantigens but not by T_H1-type or T_H2-type cytokines or viruses in leukocytes. In atopic individuals, activated leukocytes expressed higher levels of IL-31 transcripts compared with healthy, nonatopic subjects. Analysis of the tissue distribution of the IL-31 receptor heterodimer revealed that IL-31RA transcripts are most abundantly expressed in dorsal root ganglia, where the cell bodies of the primary sensory neurons reside. Our findings provide a new link among increased *Staphylococcus aureus* colonization, subsequent T-cell recruitment/activation, and pruritus induction.

METHODS

Patients

Six-millimeter punch biopsies were taken, after obtaining informed consent, from nonlesional (n = 10) or lesional (n = 25) skin of patients with atopic dermatitis, lesional skin of patients with psoriasis (n = 24) or prurigo nodularis (n = 5), and healthy skin (n = 12). Patients with atopic dermatitis were identified according to the criteria defined by Hanifin and Rajka.¹⁰ Patients with chronic plaque psoriasis in typical locations were enrolled into the study. Diagnosis of prurigo nodularis was based on typical clinical findings and histopathological examination. All patients with prurigo nodularis had a history of atopy. Furthermore, after obtaining informed consent, peripheral blood was obtained from patients with atopic dermatitis and healthy, nonatopic controls for PBMC separation. Moreover, patients with atopic dermatitis (n = 6) with a history of house dust mite allergy underwent atopic dermatitis patch testing as described previously.¹¹ Briefly, atopy patch tests were performed with house dust mite antigens containing a mix of *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* species (Chemotechnique Diagnostics, Malmö, Sweden). All 6 patients had positive reactions to repeated atopy patch tests. Another collective of atopic dermatitis patients (n = 6) underwent staphylococcal enterotoxin B (SEB) patch tests. For this, SEB (Sigma, St Louis, Mo) at 0.226 µg/µL in 0.9% NaCl solution was applied in Finn chambers (Epitest Ltd, Hyrylä, Finland) on healthy-appearing dorsal skin of the patients. Topical exposure to SEB induced skin lesions clinically and histopathologically resembling atopic dermatitis. Skin specimens were obtained before and 2, 6, and 48 hours after protein allergen or superantigen expo-

sure. These studies were approved by the appropriate local ethics committees.

Cell isolation and cell culture

PBMCs of healthy individuals were isolated and cultured in RPMI 1640 containing 10% FCS in the presence of 10⁶ plaque forming unit (PFU)/mL HSV-1 (KOS strain) attenuated with γ-irradiation, 10⁶ PFU/mL intact influenza virus (PR8 strain), SEB (1 µg/mL; Sigma), IFN-γ (50 ng/mL; R&D Systems Inc, Minneapolis, Minn), or IL-4 (50 ng/mL; R&D Systems Inc) for 6 or 24 hours or left untreated. Moreover, PBMCs were treated with SEB (1 µg/mL; Sigma) or toxic shock syndrome toxin 1 (TSST-1; 50 ng/mL; Sigma) for 6 or 24 hours or left untreated. PBMCs isolated from peripheral blood obtained from patients with atopic dermatitis and healthy nonatopic controls were treated with IL-2 (10 ng/mL; R&D Systems Inc), anti-CD3 antibody (0.5 µg/mL; R&D Systems Inc), or SEB (1 µg/mL; Sigma) for 6 hours or left untreated.

Quantitative real-time PCR (TaqMan) analysis

Quantitative real-time PCR analyses were performed as previously described.¹² Briefly, skin biopsies were homogenized in liquid nitrogen by using a Mikro-Dismembrator U (Braun Biotech, San Diego, Calif), and RNA was extracted with TRIzol reagent (Invitrogen, Carlsbad, Calif). RNA 4 µg was treated with DNase I (Boehringer, Mannheim, Germany) and reverse-transcribed. Primers specific for human IL-31 were as follows: IL-31 forward, 5'-GCCAGCCGCCAAAC-3'; IL-31 reverse, 5'-GCTGTCTGATTGTCTTGAGATATGC-3'. Primers and probes specific for human CC chemokine ligand (CCL)17, CCL26, CXCL chemokine ligand (CXCL)10, and 18S RNA were obtained from Applied Biosystems (Foster City, Calif). cDNA 25 ng was amplified per reaction in the presence of either SYBR green master mix or TaqMan universal master mix (Applied Biosystems). Gene-specific PCR products were measured by means of an ABI PRISM 7000 Sequence Detection Systems (Applied Biosystems; stage 1, 50°C for 2 minutes; stage 2, 95°C for 10 minutes; stage 3, 95°C for 15 seconds, 60°C for 1 minute, repeated 40 times). Target gene expression was normalized on the basis of the values of the expression of 18S RNA.

Statistical analysis

For statistical analysis of IL-31 expression, the nonparametric Mann-Whitney *U* test was used. A value of *P* < .05 was considered to be statistically significant.

RNA extraction and DNA microarray hybridization

A gene expression database of the normal human body has been generated as described.¹³ Briefly, postmortem human samples were obtained from Zoion Diagnostics (Hawthorne, NY). Three hundred samples representing 63 tissues with at least duplicate samples were included in this study. RNA was extracted by TRIzol reagent (Invitrogen) with additional purification on RNeasy columns (Qiagen, Valencia, Calif). RNA quality was confirmed by electrophoresis. Five micrograms of total RNA from each sample was processed for microarray analysis as described.¹³ The biotinylated cRNA was hybridized to the Affymetrix Human Genome U133 Plus 2.0 gene array for human beings, stained with streptavidin phycoerythrin conjugate and scanned by the GeneChip Scanner 3000 as described in the Affymetrix (Santa Clara, Calif) technical manual. Expression data were normalized for chip-to-chip variability by applying RMA or Robust Multichip Average algorithm¹⁴ using a commercially available software, ArrayAssist (Jobion Labs, La Jolla, Calif).

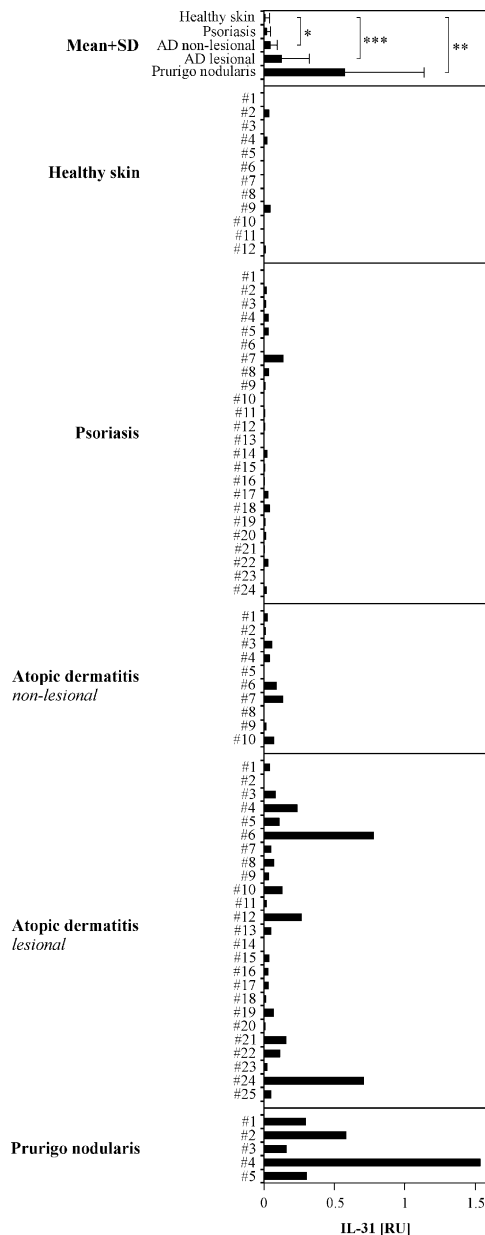


FIG 1. Quantitative real-time PCR analysis of IL-31 mRNA in healthy skin (n = 12), psoriasis (n = 24), nonlesional (n = 10) or lesional (n = 25) skin of atopic dermatitis (AD), and lesional skin (n = 5) of prurigo nodularis. Results are shown as relative units compared with 18S RNA. Measurements of individual samples and means + SDs are shown. * $P < .05$; ** $P < .01$; *** $P < .001$, Mann-Whitney U test.

RESULTS

IL-31 is upregulated in atopic dermatitis but not in psoriasis

To analyze the expression of IL-31 in pruritic and nonpruritic chronic inflammatory skin diseases, quantitative real-time PCR analysis was performed of IL-31 mRNA expression in healthy skin (n = 12) and

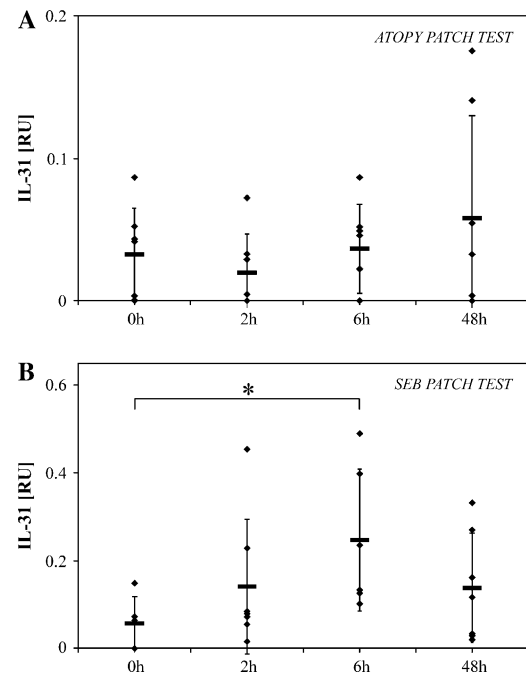


FIG 2. Regulation of IL-31 expression in atopic individuals *in vivo*. Quantitative real-time PCR analysis of IL-31 mRNA in skin samples of patients with atopic dermatitis (A) subjected to patch test with house dust mite allergen (n = 6) or (B) SEB (n = 6) for 0, 2, 6, and 48 hours. Results are shown as relative units compared with 18S RNA. * $P < .05$, Mann-Whitney U test.

nonlesional (n = 10) and lesional (n = 25) skin of atopic dermatitis as well as lesional skin of patients with psoriasis (n = 24) or prurigo nodularis (n = 5). Our results showed that human IL-31 is significantly ($P < .001$) upregulated in the pruritic atopic dermatitis but not in the nonpruritic psoriasis lesions (Fig 1). Although IL-31 mRNA levels were variable among individual patients, 14 out of 25 patients with atopic dermatitis (56%) showed markedly increased IL-31 mRNA levels in lesional skin, exceeding the mean + 2 SD of IL-31 transcripts observed in healthy skin. Interestingly, in lesional atopic dermatitis skin, IL-31 mRNA levels showed a significant correlation with mRNA levels of CCL26 ($r = 0.657$; $P < .05$; Pearson correlation), a chemokine that has previously been associated with atopic dermatitis and whose serum levels have been shown to be strongly correlated with disease activity in patients with atopic dermatitis.¹⁵ In contrast with atopic dermatitis, psoriasis lesions showed no difference in IL-31 mRNA expression compared with healthy skin. Interestingly, nonlesional skin of patients with atopic dermatitis also exhibited 4-fold higher IL-31 mRNA levels in comparison with healthy skin ($P < .05$; Fig 1). Notably, in prurigo nodularis, one of the most pruritic forms of chronic skin inflammation, IL-31 expression was unparalleled in comparison with other chronic inflammatory skin diseases. Compared with healthy skin, prurigo nodularis lesions showed a 50-fold upregulation of IL-31 mRNA ($P < .001$; Fig 1), and transcripts were 4.5-fold

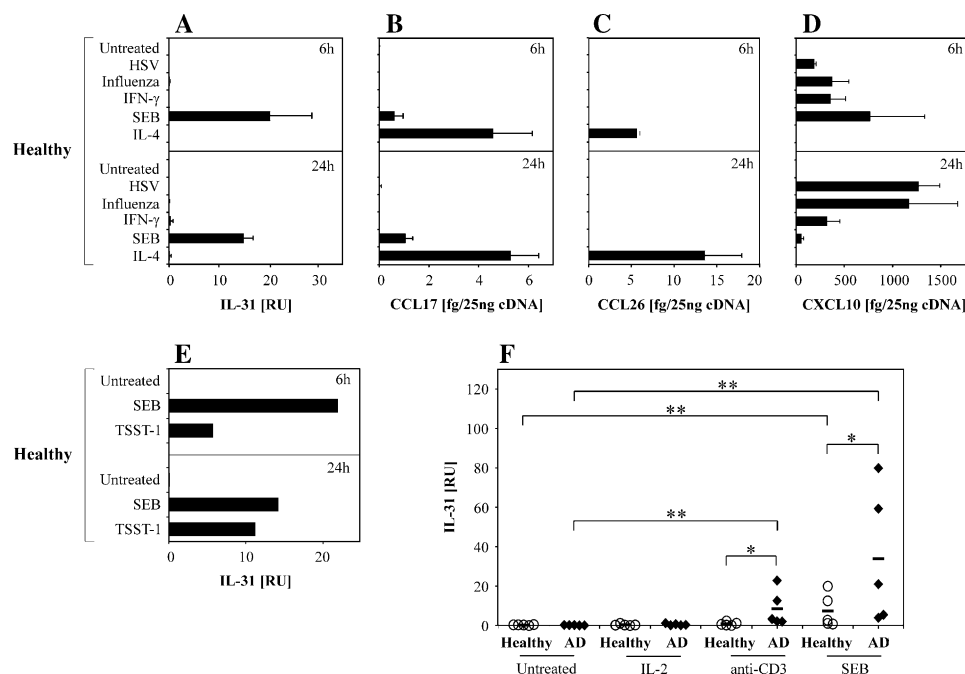


FIG 3. Regulation of IL-31 expression in leukocytes. **A-D**, IL-31, CCL17, CCL26, and CXCL10 expression in peripheral blood mononuclear cells (PBMCs) treated with HSV, influenza virus, IFN- γ , SEB, or IL-4. Means $\pm$ SDs of 3 donors. **E**, IL-31 expression in PBMCs after treatment with SEB or TSST-1 and **(F)** in PBMCs from healthy subjects ($n = 5$) and patients with atopic dermatitis (AD; $n = 5$) treated with IL-2, anti-CD3, or SEB. Quantitative real-time PCR analysis. Results are shown as relative units compared with 18S RNA, or as femtograms of target gene in 25 ng total cDNA. * $P < .05$; ** $P < .01$, Mann-Whitney U test.

upregulated compared with lesional atopic dermatitis ($P < .01$). The absence of antibody reagents directed against human IL-31 prevented us from confirming these observations at the protein level.

Staphylococcal superantigen rapidly induces IL-31 in patients with atopic dermatitis

Topical exposure of nonlesional skin of patients with atopic dermatitis to relevant allergens induces skin lesions mimicking atopic dermatitis, supporting a crucial role for allergens in triggering atopic skin inflammation.¹⁰ To investigate whether IL-31 is regulated by allergen exposure, patients with atopic dermatitis ($n = 6$) with a history of house dust mite allergy were subjected to atopy patch testing with house dust mite allergens (*D pteronyssinus* and *D farinae*), and IL-31 mRNA expression was analyzed by quantitative real-time PCR. Allergen exposure induced IL-31 mRNA in a subset of patients ($n = 3$); however, this trend was not observed in all patients (Fig 2, A). On average, we could observe an induction, although not statistically significant, 48 hours after allergen exposure.

Colonization with *S aureus* occurs in 90% of atopic individuals, and it represents a trigger factor for atopic skin inflammation.^{7,16} To investigate the regulation of IL-31 by superantigen exposure, IL-31 mRNA expression was analyzed in skin specimen of patients with atopic dermatitis ($n = 6$) before as well as 2, 6, and 48 hours after patch testing with the superantigen SEB. Quantitative real-time PCR analyses showed that IL-31 mRNA was significantly

induced in skin samples already 6 hours after exposure to SEB ($P < .05$; Fig 2, B).

Superantigen exposure induces IL-31 *in vitro*

To investigate further the regulation of IL-31 in leukocytes, we stimulated PBMCs obtained from healthy individuals with extrinsic and intrinsic trigger factors of atopic dermatitis. Quantitative real-time PCR analyses of IL-31 in PBMCs treated with staphylococcal superantigen, type 1 or type 2 T-cell effector cytokines, herpes simplex, or influenza virus showed that IL-31 was rapidly and selectively upregulated by SEB (Fig 3, A), confirming our *in vivo* results.

Compared with IL-31, other atopic dermatitis associated genes such as CCL17 and CCL26^{15,17,18} showed predominant regulation by the T_H2 cytokine IL-4 but little or no regulation after superantigen treatment (Fig 3, B, C). In particular, CCL26 was exclusively induced by IL-4 (Fig 3, C), in good agreement with previous studies.¹⁹ Although treatment with viruses or IFN- γ did not modulate IL-31 expression in leukocytes, these stimuli were potent inducers of the CXCR3 ligand CXCL10, a T_H1 -associated chemokine shown to play a role in autoimmune skin inflammation such as psoriasis and cutaneous lupus erythematosus.²⁰⁻²² Among the examined genes, the selective induction of IL-31 expression by SEB represented a unique regulation pattern.

To investigate the effect of other superantigens on the expression of IL-31, the expression of this cytokine was

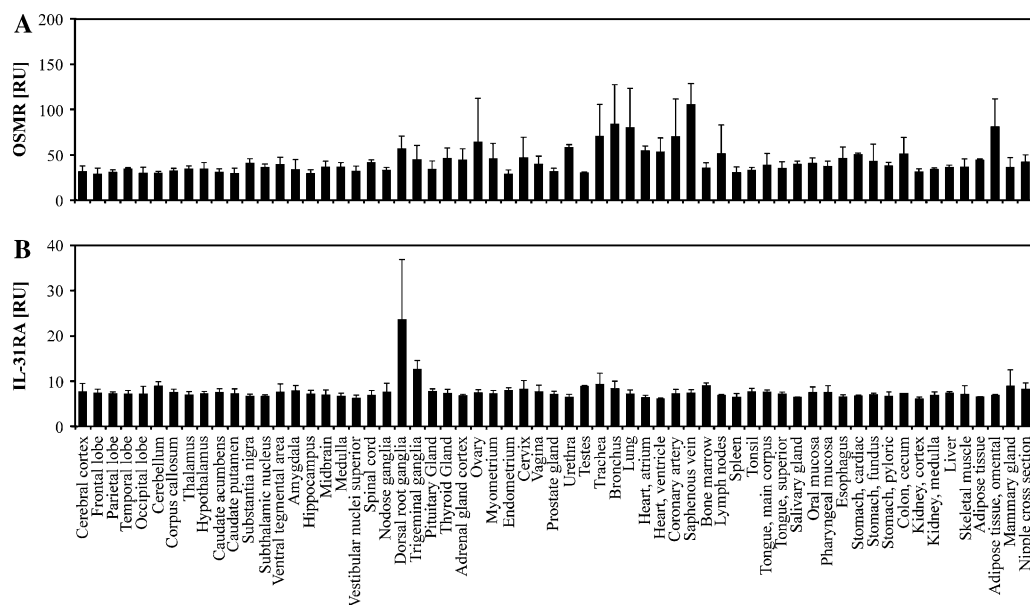


FIG 4. Expression pattern of OSMR (A) and IL-31RA (B) in human tissues and organs. RNA from 300 samples representing 63 tissues from 2 male and 2 female donors were processed for microarray analysis by using Affymetrix Human Genome U133 Plus 2.0 gene array. Data are expressed as relative units (average intensity values). Means + SDs are shown.

compared in PBMCs stimulated with SEB and another staphylococcal superantigen, TSST-1. Similarly to SEB, TSST-1 treatment induced IL-31 expression in PBMCs (Fig 3, E).

To determine whether there are differences between atopic dermatitis patients and healthy individuals in the expression and regulation of IL-31, PBMCs from healthy nonatopic subjects ($n = 5$) and patients with atopic dermatitis ($n = 5$) were treated with IL-2, anti-CD3, or SEB (Fig 3, F). No difference was observed in IL-31 mRNA levels between unstimulated PBMCs obtained from patients with atopic dermatitis and those from healthy controls. SEB induced IL-31 in PBMCs in both groups ($P < .01$; Fig 3, F); however, it caused a significantly higher induction in PBMCs from patients with atopic dermatitis than in PBMCs from healthy controls ($P < .05$; Fig 3, F). Similarly, higher IL-31 levels were detected in PBMCs from patients with atopic dermatitis than in those from healthy controls after treatment with anti-CD3 ($P < .05$; Fig 3, F). In contrast, IL-2 treatment did not upregulate IL-31 expression in PBMCs, either in patients with atopic dermatitis or in healthy controls.

Dorsal root ganglia are an abundant source of IL-31RA

To identify putative target cells for IL-31, we determined the expression pattern of human IL-31RA and OSMR in 63 different human tissue specimens derived from 4 female and 4 male donors, respectively (Fig 4). Analysis of data sets obtained from genome-wide gene expression studies using DNA microarrays demonstrated that among all examined tissues, dorsal root ganglia showed the highest IL-31RA mRNA levels, whereas in

all other tissues, this receptor chain was expressed at a low level (Fig 4, B). Moreover, OSMR was homeostatically expressed at relatively high levels in all examined tissues (Fig 4, A).

DISCUSSION

Accumulating evidence indicates that chronic inflammatory skin diseases such as atopic dermatitis and psoriasis are T-cell-mediated diseases.^{1,23} Although skin-infiltrating effector memory T cells represent histopathological hallmarks of both atopic dermatitis and psoriasis, their clinical phenotype is distinctly different. Besides other symptoms, atopic skin inflammation is accompanied by severe pruritus,⁵ whereas psoriatic lesions rarely itch.²⁴

Because the transgenic overexpression of murine IL-31 causes severe pruritus and dermatitis in mice,⁸ we hypothesized that human IL-31 may have a role in the pathogenesis of human chronic inflammatory skin diseases. Comparison of IL-31 mRNA expression in pruritic and nonpruritic inflammatory skin diseases and healthy skin showed that human IL-31 was overexpressed in the pruritic atopic dermatitis but not in the nonpruritic psoriatic lesions, compared with healthy skin. These results suggest a role for this T-cell-derived cytokine and its signaling pathway in skin inflammation and pruritus in atopic dermatitis. Interestingly, IL-31 mRNA was elevated not only in the lesional but also in the nonlesional skin of patients with atopic dermatitis. This finding may provide a clue for the clinical observation that atopic individuals frequently report episodes of pruritus at sites of healthy-appearing nonlesional skin.^{1,5}

Prurigo nodularis represents one of the most pruritic forms among inflammatory skin diseases, which is frequently associated with an atopic phenotype.^{25,26} The patients are frequently tormented by pruritus of intense severity, provoking scratching, excoriation, and scarring as well as the disturbance of sleep.²⁶ Hence, the patients' quality of life is severely affected. Notably, lesional skin of patients with prurigo nodularis showed the highest levels of IL-31 mRNA, further supporting a role for IL-31 in the pathogenesis of pruritus.

In atopic dermatitis, several external trigger factors contribute to skin inflammation and pruritus.^{1,5} Topical exposure of nonlesional skin of patients with atopic dermatitis to relevant allergens induces skin lesions resembling atopic dermatitis, supporting an important role for specific allergens in triggering atopic skin inflammation.¹⁰ IL-31 mRNA was upregulated in skin specimens of a subset of atopic patients with a history of house dust mite allergy after topical exposure to *D farinae* and *D pteronyssinus* antigens *in vivo*. These findings suggest that exposure to specific allergens might partially contribute to the elevated levels of IL-31 in atopic dermatitis lesions. However, the fact that this upregulation was not observed in all patients suggested the presence of other factors inducing IL-31 in atopic skin.

More than 90% of atopic dermatitis skin lesions are colonized with *S aureus*,^{7,16,27} and the number of bacteria on the skin correlates with the severity of skin lesions.²⁸ As many as 65% of *S aureus* strains isolated from atopic skin lesions produce exotoxins with superantigenic properties, which may penetrate the skin barrier and contribute to the exacerbation and maintenance of atopic skin inflammation.²⁷ IL-31 transcripts were rapidly induced after topical exposure of the nonlesional skin of patients with atopic dermatitis to the staphylococcal superantigen SEB *in vivo*. Moreover, IL-31 was rapidly and selectively upregulated in PBMCs treated with staphylococcal superantigens (SEB and TSST-1) *in vitro*, whereas other trigger factors of atopic dermatitis such as T_H1-type or T_H2-type cytokines or viruses did not induce its expression. Preliminary observations in PBMCs of a house dust mite-sensitive patient with atopic dermatitis cultured in the presence or absence of the recombinant allergen *Der p* 2 suggest that specific allergen is not a major inducer of IL-31 in leukocytes (data not shown). Taken together, our findings suggest that *S aureus*-derived superantigens may play an important role in the regulation of IL-31 production. Similarly to the regulation of IL-31, SEB and other *S aureus*-derived products have been shown to induce the expression of CCL18 and CCL1, chemokines implicated in the recruitment of T cells and dendritic cell precursors into atopic dermatitis lesions.²⁹⁻³¹ Hence, the recruitment of relevant leukocyte subsets into atopic skin and the subsequent production of IL-31 in T cells may contribute to the maintenance and exacerbation of inflammation and pruritus in atopic skin colonized with *S aureus*.

In unstimulated PBMCs from patients with atopic dermatitis, IL-31 levels did not differ from those in PBMCs from healthy, nonatopic controls. However, after

SEB or anti-CD3 stimulation, PBMCs from patients with atopic dermatitis expressed higher levels of IL-31 mRNA compared with nonatopic subjects. This observation suggests that atopic individuals have an increased tendency to produce higher levels of IL-31 in response to external trigger factors, which may contribute to the development of pruritus in these patients. The finding that IL-2 stimulation alone did not regulate IL-31 expression in atopic or nonatopic individuals indicates that the observed regulation of IL-31 is not the result of enhanced T-cell proliferation alone. Further studies are needed to clarify the molecular mechanisms of the regulation of IL-31 in atopic individuals and whether the dysregulation of IL-31 is associated with single nucleotide polymorphisms or other genetic alterations.

Genome-wide gene expression studies in 63 different human tissues, including a large set of tissue samples from the central and the peripheral nervous system, showed for the first time that among all examined tissues, dorsal root ganglia expressed the highest levels of IL-31RA mRNA. IL-31RA transcripts had been previously detected in several tissues including skin, thymus, prostate, and bone marrow^{8,32}; however, expression in the peripheral nervous system has not been assessed. This finding is particularly interesting because the sensation of itch, similar to pain, is directly mediated by unmyelinated C fibers of primary sensory neurons whose cell bodies reside within dorsal root ganglia.^{2,4} Hence, dorsal root ganglia represent the site of mRNA production for afferent sensory neurons. Similar to IL-31RA, several cytokine and chemokine receptors have been detected in dorsal root ganglia, and signaling through these receptors is thought to contribute to hyperalgesia during inflammation.³³⁻³⁵ Moreover, functional OSMR, the other essential receptor subunit for IL-31 signaling, has been detected on a specific subset of nociceptive neurons in dorsal root ganglia,^{36,37} which project to the dermis of the skin.³⁷ These observations suggest that T-cell-derived IL-31 might induce pruritus by directly modulating the function of sensory neurons.

The absence of available antibody reagents directed against human IL-31 prevented us from studying the expression of IL-31 at the protein level. Further studies will be necessary to identify the cell types coexpressing IL-31RA and OSMR in the dorsal root ganglia and within the skin. Moreover, future studies will address the regulation of the IL-31 receptor heterodimer in the skin and in dorsal root ganglia.

Taken together, our findings provide evidence that the novel 4 helix bundle cytokine IL-31 is abundantly expressed in pruritic atopic but is absent in nonpruritic psoriatic skin inflammation. With the findings of Dillon et al⁸ showing the induction of severe pruritus and chronic dermatitis after lymphocyte-specific overexpression of IL-31 in mice, our observations in humans point to an important role for this novel cytokine in the pathogenesis of atopic dermatitis and pruritus. Furthermore, in human keratinocytes, IL-31 induces several chemokine genes⁸ that have been associated with atopic skin inflammation such as CCL17,¹⁷ CCL22,³⁸ and CCL1.²⁹ Hence, elevated

levels of IL-31 in atopic dermatitis lesions may enhance skin inflammation through the induction of chemokines, which subsequently leads to the recruitment of T cells. In turn, activated skin-infiltrating T cells may become new sources of IL-31, thereby amplifying atopic skin inflammation and pruritus.

Because pruritus has a high impact on the quality of life, the management of pruritus in atopic skin inflammation is an urgent medical need. Our findings suggest that IL-31 and its signaling pathway represent interesting novel targets for the development of antipruritic drugs.

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