

IL-31: A new key player in dermatology and beyond

Işın Sinem Bağcı, MD, and Thomas Ruzicka, MD *Munich, Germany*

IL-31 is a novel cytokine expressed in many human tissues and involved mainly in T_H2 -weighted inflammation. IL-31 signals through a receptor complex consisting of IL-31 receptor α and oncostatin M receptor β . The available data show that IL-31 is strongly linked with chronic pruritic skin disorders, such as atopic eczema, and represents a novel target for directed drug therapy. Regulation of immune responses and cellular differentiation and proliferation are recently elucidated effects of IL-31, suggesting a more complex and diverse area of effect for this novel cytokine. This review summarizes the current knowledge on IL-31 and its receptors and the involvement of IL-31 in diseases both in human subjects and mouse models. (J Allergy Clin Immunol 2018;■■■■:■■■-■■■.)

Key words: IL-31, receptors, interleukins, cytokines, pruritus, atopic eczema

IL-31, a novel cytokine, has been defined initially as a “pruritogenic cytokine” because of its increased tissue and serum levels in patients with pruritic and allergic diseases and a potential link between the immune and neuronal systems in inducing pruritus.¹⁻³ However, recent reports indicate a broader list of dermatologic and nondermatologic diseases displaying enhanced IL-31 expression and related proinflammatory and immunomodulatory functions, with effects reaching far beyond the induction of itch.

IL-31 is involved mainly in T_H2 -weighted inflammation through release of various proinflammatory mediators. After binding to IL-31 receptor (IL-31R) complex, it plays a predominant function in mediation of inflammatory itch. Thus inhibition of IL-31 signaling might provide an effective treatment option for chronic pruritic skin diseases, such as atopic eczema (AE; atopic dermatitis). Additionally, maintenance of ongoing inflammation, modulation of immune response, and cell differentiation are recently elucidated effects of IL-31, which might fill in the gaps in the pathophysiology of inflammation. In this review we summarize current knowledge regarding IL-31 and IL-31R, their link with pruritic and nonpruritic diseases, and novel treatment options targeting the IL-31 pathway.

Abbreviations used

AE:	Atopic eczema
CTCL:	Cutaneous T-cell lymphoma
gp130:	Glycoprotein 130
GPL:	Glycoprotein 130–like receptor
IL-31R:	IL-31 receptor
IL-31RA:	IL-31 receptor α
Jak:	Janus kinase
MMP:	Matrix metalloproteinase
OSM:	Oncostatin M
OSMR β :	Oncostatin M receptor β
PI3K:	Phosphoinositide 3-kinase
PLCA:	Primary localized cutaneous amyloidosis
STAT:	Signal transducer and activator of transcription
TRP:	Transient receptor potential
VAS:	Visual analogue scale

IL-31

IL-31 was discovered in 2004 by Dillon et al⁴ as a 4-helix bundle cytokine belonging to the glycoprotein 130 (gp130)/IL-6 cytokine family. Other members of the IL-6 family are leukemia inhibitory factor, oncostatin M (OSM), cardiotrophin-1, ciliary neurotrophic factor, cardiotrophin-like cytokine, IL-6, and IL-11. Members of this family share the common chain of gp130 in their multiunit receptor and are involved in neuronal growth, bone metabolism, cardiac development, and immune regulation, such as T-cell differentiation.^{5,6} In contrast to the other members of this family, IL-31 does not use the common gp130 chain; instead, it uses IL-31 receptor α (IL-31RA).

The gene encoding human IL-31 is located on chromosome 12q24.31, and IL-31 cDNA is composed of an open reading frame encoding a 164-amino-acid precursor and a predicted 141-amino-acid mature polypeptide containing the 4 α -helix structure.^{4,5} IL-31 is suggested to belong to the short-chain cytokine group, although it has 2 long and 2 short helices.⁵

Initially, high levels of IL-31 have been demonstrated in patients with the pruritic skin disorder AE, with higher expression by activated CD4⁺ T_H2 cells⁴ and by skin-homing CD45RO⁺ (memory) cutaneous lymphocyte-associated antigen-positive T cells.⁷ However, lower levels of IL-31 expression have been also reported in T_H1 cells.⁴ Other cell sources of IL-31 are CD8⁺ T cells, monocytes/macrophages, dendritic cells, keratinocytes, eosinophils, basophils, mast cells, and fibroblasts.⁸⁻¹⁰ Apart from the skin, *IL31* mRNA was also found in other tissues, such as the testis, bone marrow, skeletal muscle, kidney, colon, thymus, small intestine, trachea, and dorsal root ganglia.^{1,4}

IL-31 production from cell sources seems to be dependent on IL-4,¹¹ which plays an important role in T_H2 polarization from naive T cells and in maintenance of T_H2 activation.¹² IL-33, a

From the Department of Dermatology and Allergology, Ludwig-Maximilians Universität.

Disclosure of potential conflict of interest: T. Ruzicka has received consulting fees, travel support, and fees for participation in review activities from Chugai Company and has consultant arrangements with Galderma, Dermotreat, and Sebapharma. I. S. Bağcı declares no relevant conflicts of interest.

Received for publication June 17, 2017; revised September 5, 2017; accepted for publication October 25, 2017.

Corresponding author: Işın Sinem Bağcı, MD, Department of Dermatology and Allergology, Ludwig-Maximilians Universität, Frauenlobstr. 9-11, 80337 Munich, Germany. E-mail: Bagci.Isin_Sinem@med.uni-muenchen.de. 0091-6749/\$36.00

© 2017 American Academy of Allergy, Asthma & Immunology
<https://doi.org/10.1016/j.jaci.2017.10.045>

potent inducer of T_H2-associated cytokines, synergizes with IL-4 in the induction of IL-31 secretion.¹³ Both physical and bacterial stress, such as UVB rays, H₂O₂, and staphylococcal enterotoxin B, as well as antimicrobial peptides, increase IL-31 expression.^{1,14}

IL-31R COMPLEX

IL-31RA mediates IL-31 signaling when coupled with oncostatin M receptor β (OSMR β) to form a functional receptor complex.⁴ This receptor complex is expressed by a variety of epithelial and immune cells, including keratinocytes, mast cells, macrophages, eosinophils, basophils, a subset of peripheral neurons, and dorsal root ganglia.^{2,8,9,15} Immunoprecipitation experiments suggest that IL-31 binds predominantly to IL-31RA, but not to OSMR β , in the IL-31R complex. However, on coupling, OSMR β converts IL-31R into the high-affinity receptor and increases IL-31 binding.¹⁶

IL-31RA belongs to the gp130 subfamily of type I cytokine receptors. It displays 28% homology to the common receptor component gp130 but lacks the IgG-like domain at the N-terminus.^{4,17} The human *IL31RA* gene is located on 5q11.2 in tandem with the gp130 gene, displaying an opposite transcriptional orientation.^{17,18} Before its ligand, IL-31, was identified, IL-31RA was named gp130-like monocyte receptor (GLM-R)¹⁷ and glycoprotein 130-like receptor (GPL).¹⁸ Several isoforms of IL-31RA have been described thus far (GPL560, GPL610, GPL626, GPL745, CRL3, and IL-31RAv1-v4)⁵; however, their exact function and tissue distribution remain unclear. The short isoform (GPL560) has been shown to have an antagonizing¹⁶ or lower activity compared with that of the long isoform (GPL745),³ which might suggest a negative or neutralizing effect of some IL-31RA isoforms.

IL-31RA contains a cytokine-binding domain with 4 conserved cysteines, a WSDWS motif, and a region consisting of 3 fibronectin type III domain repeats. The intracellular part of the longer isoform contains a proline-rich region defining the box1 motif implicated in interaction with Janus kinases (Jaks).¹⁶ Constitutive expression of human and mouse *IL31RA* mRNA can be detected in skin, brain, lung, trachea, skeletal muscle, testis, ovary, prostate, placenta, spleen, thymus, bone marrow, and blood leukocytes.¹⁸

OSMR β not only is a subunit of IL-31R but also couples with gp130 to form type II receptor complex-binding OSM. Its dysregulated expression has been shown in different cancer types, such as cervical squamous cell carcinoma, breast cancer, and malignant melanoma.¹⁹ In addition, mutations in the *OSMR* and *IL31RA* genes have been found to be associated with familial primary localized cutaneous amyloidosis (PLCA).^{20,21}

The intracellular membrane-proximal region of OSMR β contains the proline-rich box1 region (CYPDIPDP), which recruits Jak1 and Jak2. OSMR β is expressed particularly in the vascular system, heart, lung, adipose tissue, skin, bladder, mammary tissue, adrenal gland, and prostate.¹⁹ Three variants of OSMR β have been defined thus far, with varying expression patterns in different cancer types.^{19,22,23} IFN- γ and lipopolysaccharide (LPS) together induce expression of both receptor chains of IL-31R in human monocytes.⁴

Interaction of the IL-31R complex with IL-31 results in activation of the Jak/signal transducer and activator of transcription (STAT) and phosphoinositide 3-kinase (PI3K)/AKT signal-transducing

pathways and also activates different mitogen-activated protein kinase pathways, such as extracellular signal-regulated kinase (ERK), p38, and c-Jun N-terminal kinase (Fig 1).²⁴⁻²⁶ Among subunits of IL-31R, OSMR β seems to be the major subunit in activation of the 3 pathways and signal transmission.

Once activated, Jaks are known to stimulate phosphorylation of the downstream signaling molecules STAT3, STAT5, and, to a lesser degree, STAT1. Tyrosine motifs as recruitment sites for STAT3 and STAT5 have been identified in both IL-31RA and OSMR β receptor subunits.¹⁹ In addition, activation of STAT1, STAT3, and STAT5 was shown in transfectants expressing IL-31RA and OSMR β , but cell lines and primary cells expressing native receptors signaled mainly through STAT3.⁴ However, cells lacking OSMR β have been shown to be unresponsive to IL-31.²⁷

Src homology domain 2-containing protein tyrosine phosphatase 2 and the adapter protein Shc, which have been shown to be involved in mitogen-activated protein kinase activation, can be recruited by OSMR β but not by IL-31RA.^{28,29} Consistently, IL-31–IL-31RA interaction alone was unable to activate ERK1/2 phosphorylation²⁸; however, MAPK cascade through IL-31 stimulation could be activated in a glioblastoma cell line expressing both IL-31RA and OSMR β .¹⁶

Interaction of IL-31 and the IL-31RA/OSMR β receptor complex induces a slight but significant increase in phosphorylation of PI3K but a marked increase in phosphorylation of AKT.¹⁶ Recruitment of Src homology domain 2-containing protein tyrosine phosphatase 2 has also been reported in PI3K phosphorylation; therefore activation of the PI3K/AKT pathway might rely exclusively on OSMR β .³⁰

IL-31 AND PRURITUS: A LINK BETWEEN THE IMMUNE AND NEURAL SYSTEMS?

Although the exact mechanisms underlying pruritus are not fully understood, there are abundant data indicating cross-talk between the immune and neural system in induction of pruritus through activation of cytokine receptors on peripheral nerves. Tissue distribution analysis of IL-31R revealed that IL-31RA is most abundantly expressed in dorsal root ganglia, where cell bodies of cutaneous sensory neurons are located.¹ OSMR β expression was demonstrated in a subset of small-sized nociceptive neurons in the dorsal root ganglia, all of which also colocalized with IL-31RA, which project to the inner portion of lamina II in the dorsal horn of the spinal cord and the dermis of the skin.^{15,31} Not only cutaneous but also intrathecal injections of IL-31 evoked intense itch and induced atopic-like dermatitis in murine skin.³ Evidence was also provided that functional IL-31RA is expressed by a small subpopulation of IL-31RA⁺/transient receptor potential (TRP) V1⁺/TRPA1⁺ neurons, suggesting that IL-31RA-mediated itch is linked to TRP channels.³ In cultured primary sensory neurons, Ca²⁺ release and ERK1/2 phosphorylation were triggered by IL-31, and blockage of ERK1/2 with a specific inhibitor reduced scratching behavior *in vivo*, suggesting that ERK1/2 is involved in IL-31-induced itch transmission.³

A recent study revealed elongation and branching of cutaneous nerve fibers in *Il31*-transgenic and IL-31 pump-equipped mice. The same effect was observed in small-diameter neurons after treatment of isolated dorsal root ganglion neurons with IL-31 *in vitro*.³² These data indicate that IL-31 might communicate directly with sensory nerves through

activation of its high-affinity receptor complex and serve as a critical neuroimmune link between T_H2 cells and sensory neurons for the generation of T cell-mediated inflammatory itch.

Immunohistochemistry studies have shown epidermal expression of IL-31RA and OSMR β ,^{33,34} which makes keratinocytes another important target of IL-31. Keratinocytes are known to produce itch- and pain-related mediators, which can initiate or maintain inflammatory reactions and directly interfere with sensory neurons. Toll-like receptor 2 ligand (Pam3Cys)- or IFN- γ -induced upregulation of both IL-31RA and OSMR β and subsequent keratinocyte activation have been shown in human primary keratinocytes. Additionally, enhanced secretion of CCL2 from keratinocytes was observed after activation with IL-31.³⁵ Therefore an additional indirect role of IL-31 in pruritus through activating IL-31R on keratinocytes, which leads to subsequent release of pruritus-inducing mediators, also comes into question.

In addition to dorsal root ganglia and keratinocytes, eosinophils,³⁶ mast cells,³⁷ and basophils⁹ are other pruritus-associated cellular targets of IL-31. A recent study showed greater release of IL-31 by eosinophils compared with IL-31 release by $CD4^+$ T cells, which could be further increased by T_H2 cytokines.¹⁰ IL-31 could significantly induce chemotaxis, Ca^{2+} mobilization, and release of the proinflammatory cytokines IL-1 β , IL-6, CXCL1, CXCL8, CCL2, CCL18, and CCL26 from eosinophils, which was further enhanced by coculture with keratinocytes but not with fibroblasts.^{10,36} This finding suggests an interaction between keratinocytes and eosinophils through IL-31 and might have particular importance in patients with pruritic skin disorders, such as AE, displaying an eosinophilic infiltration of lesional skin.

Mast cells play an important role in the induction of pruritus and allergic reactions through mediators, such as histamine or tryptase, which can directly modulate sensory nerves.³⁸ Mast cells have also been shown to be a source of IL-31.³⁹ The skin-derived antimicrobial peptides human β -defensins and LL-37 enhanced IL-31 gene expression and IL-31 production and release in a human mast cell line and in peripheral blood-derived cultured mast cells. However, concentrations of IL-31 produced by human β -defensins and LL-37 were low compared with the doses of IL-31 needed to exert its stimulatory functions.³⁹

Recently, basophils have been shown to be a strong source of IL-31. Stimulation of isolated basophils and $CD4^+$ T cells from the same healthy donors resulted in a significantly greater release of IL-31 from basophils than from $CD4^+$ T cells.⁹ Additionally, IL-31 induced chemotaxis of basophils and secretion of IL-4 and IL-13 from these cells.⁹ These results suggest an orchestrating role of IL-31 on other inflammatory cells related to pruritus and proinflammatory effects through release of other inflammatory mediators. Thus IL-31 has been shown to have direct or indirect connections with several pathways related to pruritus; however, further studies are required to enlighten the exact role of IL-31 in patients with pruritic disorders.

Animal models of IL-31 and pruritus

The ability of IL-31 to induce pruritus has been demonstrated in various species. Severe pruritus, alopecia, and skin lesions similar to human AE developed in either *Il31*-transgenic mice or wild-type mice after recombinant mouse IL-31 administration.⁴ Skin lesions, which developed because of excessive scratching

behavior, displayed similar histopathologic features as those in patients with AE.⁴ In an AE-like murine model, intradermal IL-31 injection caused a gradual increase in long-lasting scratching about 3 hours after administration, followed by a gradual decrease lasting for more than 24 hours.⁴⁰ *Il31* mRNA expression was associated with scratching behavior in the same murine model,⁴¹ which was reduced by anti-IL-31 antibody.⁴² IL-31RA-deficient mice showed a lower T_H2 immune response after nasal allergen administration but a stronger response after intraperitoneal administration.⁴³ Variation of immune responses in different tissues of IL-31RA-deficient mice might be related to distribution of different IL-31RA isoforms or varied compensatory activity of OSMR β in different tissues.

Systemically or locally (intravenous, subcutaneous, or intradermal) injected canine IL-31 rapidly induced pruritic behavior in the majority of dogs tested, and endogenous canine IL-31 was detected in the serum of dogs with AE but not in that of healthy control dogs.⁴⁴ Recently, the anti-canine IL-31 mAb lokivetmab was licensed by the US Department of Agriculture for the treatment of canine AE. Similarly, administration of recombinant cynomolgus IL-31 elicited an immediate scratching response in cynomolgus monkeys, which was inhibited by humanized anti-human IL-31 mAb administration in a dose-dependent manner.⁴⁵

Pathogenetic role of IL-31 in human chronic inflammatory skin diseases

The most prominent effect of IL-31 in inflammatory skin disorders is induction of pruritus. A human study investigating skin prick testing with IL-31 in healthy volunteers and patients with AE revealed no immediate but a late itch response. No significant difference in the initiation time, duration, and intensity of pruritus was observed between healthy control subjects and patients with AE.⁴⁶ This late response is similar to that seen in murine models; however, it differs from immediate pruritus in dogs and monkeys. An explanation suggested by the authors of this study⁴⁶ is the possible dominant indirect pruritic effect of IL-31 through keratinocytes and secondary inflammatory mediators in human subjects and mice as opposed to a direct effect in dogs and monkeys.

Other than induction of pruritus, the effects of IL-31 on keratinocyte differentiation and release of other proinflammatory cytokines might be involved in the pathogenesis of chronic inflammatory skin. Treatment of organotypic 3-dimensional skin models with IL-31 caused a disturbed keratinocyte differentiation caused by altered expression of genes encoding structural proteins, such as desmoglein, desmocollin, and filaggrin, and a subsequent increase in allergen and irritant penetration.⁴⁷ Moreover, IL-31 stimulated the expression of many genes encoding components of the IL-1 signaling network and increased the release of IL-1 α ,⁴⁷ enhanced expression of which causes hyperkeratosis and an inflammatory skin phenotype.^{48,49} Also, low doses of IL-31 stimulated expression of antimicrobial peptides, probably with the cooperation of IL-1 signaling, which could be inhibited by the IL-1R antagonist anakinra.⁴⁷ In addition to IL-1, IL-31 has been shown to stimulate the secretion of several other proinflammatory cytokines, such as IL-4, IL-6, IL-8, IL-13, IL-16, and IL-32; chemokines; and matrix metalloproteinases (MMPs) from other tissues,^{9,50} suggesting a proinflammatory role of IL-31 also in chronic skin inflammation.

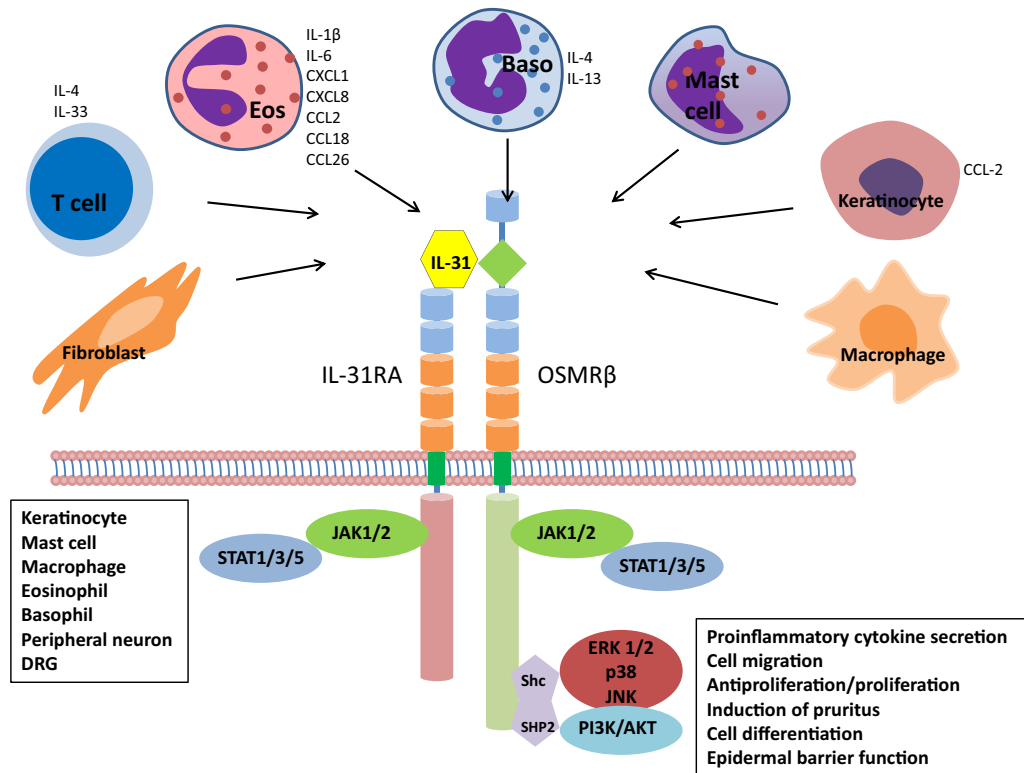


FIG 1. Cell sources, associated cytokines, and signaling pathway of IL-31. *Left box*, IL-31R-expressing cells. *Right box*, Biological effects of IL-31. JNK, c-Jun N-terminal kinase; SHP2, Src homology domain 2-containing protein tyrosine phosphatase 2.

IL-31 and pruritic skin disorders

AE is a chronic inflammatory skin disease associated with intense pruritus. There is emerging evidence that IL-31 can play a role in the mechanism underlying pruritus in patients with AE. *IL31* mRNA expression was increased in skin biopsy specimens of patients with AE compared with normal skin and correlated with *IL4* and *IL13* mRNA expression.⁵¹ Atopy patch testing with staphylococcal enterotoxin B, which is frequently found in the skin of patients with AE, induced a rapid IL-31 expression in atopic subjects.¹ Patients with AE have higher levels of CD45RO⁺ cutaneous lymphocyte-associated antigen-positive T cells that produce IL-31.⁷ IL-31 serum levels are greater in adult and pediatric patients with AE compared with those in nonatopic healthy control subjects^{52,53} and correlate with disease activity.⁵³⁻⁵⁵ Furthermore, T_H2-polarized T cells costimulated with antigen and staphylococcus enterotoxin B produce high levels of IL-31.⁵⁶ Previous results showed that repeated delivery of IL-31 is required to induce pruritus in mouse models.^{44,57} The frequent presence of bacterial products, such as staphylococcus enterotoxin B, on the skin of patients with AE might continuously increase IL-31 levels or lead to surpassing a threshold, which is required to initiate the itching behavior.

In the acute phase AE lesions are dominated by T_H2 cytokines, whereas chronic-phase AE lesions contain both T_H1- and T_H2-derived cytokines.^{58,59} Although IL-31 can be expressed by T_H1 cells, T_H2 cells seem to be a stronger source for IL-31 production. Thus the relationship between IL-31 and T_H1-weighted inflammation is less clear. Immunohistochemistry

evaluation of several T_H1- and T_H2-weighted pruritic skin diseases found the highest expression of IL-31 in skin samples of patients with AE.³³ However, *IL31* mRNA expression and immunoreactivity were not increased in T_H1-weighted nonpruritic psoriasis vulgaris or in pruritic psoriasis inversa.^{33,51} These data suggest that IL-31 can be functionally related to pruritus in patients with AE but is not a distinct feature of all pruritic skin disorders.

In addition to AE, IL-31 levels in human skin samples revealed increased expression of *IL31* mRNA in prurigo nodularis and allergic contact dermatitis.^{1,51} Prurigo nodularis, one of the most pruritic skin disorders, showed the highest IL-31 expression at the mRNA level¹ but a lower expression compared with that seen in patients with AE at the protein level.³³ Recent reports revealed the genetic aspect of the link between IL-31 and eczematous diseases and demonstrated that the *IL31* gene polymorphism is associated with increased risk of atopic and nonatopic eczema.⁵⁸⁻⁶²

After these findings, several groups investigated the possible relation of IL-31 with other pruritic skin disorders (Fig 2 and Table I). In patients with cutaneous T-cell lymphoma (CTCL), the malignant T-cell population has been shown to produce IL-31.⁶³ IL-31 and IL-31R expression was increased in skin samples of patients with CTCL.³⁴ In addition, increased serum levels of IL-31 that correlated with disease severity⁶⁴ and pruritus have been detected in patients with CTCL.^{34,63} The most common types of CTCL, mycosis fungoides and Sézary syndrome, are characterized by a T_H2-type cytokine profile,⁶⁵ which supports the T_H2-weighted proinflammatory role of IL-31, leading to induction of pruritus, with immunomodulatory effects contributing to disease progression.



FIG 2. IL-31-related pruritic skin disorders. **A, AE.** **B,** Prurigo nodularis. **C,** CTCL (mycosis fungoides). **D,** PLCA (interscapular type). **E,** Mastocytosis (urticaria pigmentosa). **F,** Chronic spontaneous urticaria. **G,** Bullous pemphigoid. **H,** Dermatitis herpetiformis.

Increased tissue expression of IL-31RA and OSMR β has been shown in skin specimens of patients with PLCA. However, cutaneous and serum IL-31 levels were not significantly higher in patients.⁶⁶ Although it is a highly pruritic skin disorder, IL-31 seems not to be directly associated with pruritus in patients with PLCA. Previous reports demonstrated an association between familial PLCA and mutations in *OSMR* and *IL31RA* genes.^{20,21} Therefore targeting IL-31R might be a therapeutic option in resistant cases.

Increased serum levels of IL-31 have been detected in patients with mastocytosis,^{67,68} with a positive correlation between serum levels and disease severity, tryptase levels,⁶⁷ and pruritus.⁶⁸ Moreover, distinct polymorphic variants of the *IL31* gene have been shown to be more common in patients with mastocytosis compared with control subjects.⁶⁸ Interestingly, increased serum levels of IL-31 were higher in *KIT* D816V-positive adult

patients, suggesting not only the role of IL-31 in the induction of pruritus in mastocytosis but also a possible pathophysiologic association with *KIT* mutation-dependent manifestations of the disease.⁶⁸

In patients with chronic spontaneous urticaria, serum levels of IL-31 have been found to be greater than in healthy control subjects but lower than in patients with AE.⁶⁹ Interestingly, basophils have been shown to be the predominant cells expressing IL-31 in skin lesions of patients with chronic spontaneous urticaria.⁹ After treatment with omalizumab, a decrease in serum levels of IL-31 occurred; however, no correlation between IL-31 levels and urticaria severity was observed.⁷⁰

Most recently, serum levels and tissue expression of IL-31 have been found to be increased in patients with bullous pemphigoid and dermatitis herpetiformis.⁷¹ Immunohistochemistry examination of lesional and perilesional skin specimens

TABLE I. IL-31-related T_H1- and T_H2-weighted diseases

T _H 1 weighted	T _H 2 weighted
Prurigo nodularis	AE
Chronic urticaria	Allergic asthma
	Allergic rhinitis
	CTCL
	Bullous pemphigoid
	Dermatitis herpetiformis
	Allergic contact dermatitis

revealed a greater number of IL-31⁺ cells in lesional specimens. Thus the authors suggested a contribution of IL-31 to blister formation in pruritic autoimmune blistering diseases.⁷¹

IL-31 in patients with nondermatologic diseases

Allergic asthma and rhinitis. Allergic asthma and rhinitis are characterized by aberrant T_H2 activation and constitute the atopic triad along with AE. Increased IL-31 protein and mRNA levels have been shown both in patients with allergic asthma and those with rhinitis (Table I).⁷²⁻⁷⁴ IL-31 single nucleotide polymorphisms were significantly correlated with serum IgE levels in asthmatic patients.⁷⁵ Among patients with asthma/rhinitis with positive specific IgE levels, patients with dust mite and mugwort allergy had higher IL-31 levels.⁷² Increased local secretion of T_H2 cytokines and mucin production have been reported in patients with allergic rhinitis after induction with IL-31.⁷⁴ Therefore the IL-31 pathway might be a potential target in the treatment of allergic asthma and rhinitis.

Inflammatory bowel diseases. The IL-31R complex is expressed in the intestinal mucosa.⁷⁶ IL-31 induced secretion of chemokines (CXCL8 [IL-8], CXCL1, CCL7, CXCL3, CCL13, and CCL15), proinflammatory cytokines (IL-6, IL-16 and IL-32), and MMPs (MMP-1, MMP-3, MMP-25 and MMP-7) from colonic subepithelial myofibroblasts.⁵⁰ Increased migration and diverse modulation of cell proliferation depending on cell density (predominant antiproliferative effect) was observed in IL-31-induced intestinal epithelial cells.⁷⁶ In addition, *IL31* mRNA expression was increased in the inflamed lesions of patients with Crohn disease and ulcerative colitis.⁷⁶ Taken together, IL-31 might play a role in inflammatory bowel diseases by promoting proinflammatory gene expression and modulating intestinal barrier function. Interestingly, an anti-inflammatory effect of IL-31 on T_H2 inflammation has also been reported after intestinal *Trichuris muris* infection,⁷⁷ which is contradictory to the proposed proinflammatory role of IL-31. Because the distribution of IL-31R isotypes in the mouse model is not mentioned in the latter study,⁷⁷ this result might be related to the enhanced expression of antagonizing IL-31RA subtypes in mouse intestines. However, further studies are required to elucidate the exact role of IL-31 in patients with intestinal diseases.

Malignancies. Although gain and loss of OSMR β expression have been related to different cancer entities,¹⁹ there is limited evidence for the association of IL-31 with malignancies. Increased serum levels of IL-31 have been reported in several hematologic and solid tumors,^{64,67,78,79} but the *in vitro* studies have demonstrated antiproliferative activity of IL-31 in lung and intestinal cell lines.^{25,76} Murine colon carcinoma cells

depleted of IL-31 exhibited increased invasive and migratory properties *in vitro* and faster tumor growth *in vivo*, which were both reversed by exogenous IL-31.⁸⁰ Compatibly, IL-31 was effective in suppressing proliferation by altering expression of cell-cycle proteins, including upregulation of p27(Kip1) and downregulation of cyclin B1, CDC2, CDK6, MCM4, and retinoblastoma through activation of STAT3.²⁵ IL-31 infusion reduced the number of metastatic lesions in the lungs of mice with metastatic breast carcinoma, and combination of chemotherapy with a long-lived IL-31-IgG fusion protein reduced tumor growth, angiogenesis, and pulmonary metastasis to a greater extent than when chemotherapy was used alone.⁸⁰ Additionally, serum IL-31 levels were negatively correlated with the progression of human non-small cell lung cancer.⁸¹ These findings indicate a possible future role of IL-31 in the treatment of malignancies.

Osteoporosis. Serum levels of IL-31 have been shown to be higher in postmenopausal osteoporotic female patients compared with healthy postmenopausal control subjects. However, the difference was statistically significant only in older subjects (age >65 years), and no significant correlation between the severity of osteoporosis and IL-31 levels has been found.⁸² Similar to the effects of IL-31 on keratinocyte differentiation through destruction of structural proteins, these results indicate that IL-31 can participate in the inflammatory process in various tissues either as a proinflammatory or an immunomodulatory cytokine and lead both to tissue destruction and “inflammaging.”

THERAPEUTIC APPROACHES

The first human study investigating the blockade of IL-31 signaling was performed with nemolizumab (CIM331), a humanized anti-human IL-31RA mAb, in healthy subjects and patients with AE.⁸³ Single subcutaneous administration of nemolizumab significantly reduced visual analogue scale (VAS) scores for pruritus and the use of topical steroids. In parallel with the decrease in pruritus, an increase in sleep efficiency was observed. Exacerbation of AE and folliculitis were the most common adverse events in patients with AE receiving nemolizumab or placebo. Increased creatine phosphokinase and hepatic enzyme activity (aspartate transaminase and alanine transaminase) was more common in healthy control subjects receiving nemolizumab than in control subjects receiving placebo, which might be related to exercise or concomitant medication.⁸³ A phase 2 trial compared the effects of subcutaneous nemolizumab (0.1, 0.5, or 2.0 mg/kg) and placebo administration every 4 weeks in patients with AE. At week 12, VAS scores for pruritus, Eczema Area Severity Index scores, SCORAD scores, and body surface area of AE involvement were decreased, whereas several parameters assessing sleep quality and the Dermatology Quality of Life Index improved in the nemolizumab group compared with the placebo group, with a dose of 0.5 mg/kg every 4 weeks showing the best benefit/risk profile.⁸⁴ Regarding adverse events, exacerbation of AE and peripheral edema occurred more frequently in patients receiving nemolizumab than placebo.⁸⁴ Fifty-two-week extension of a phase 2 study assessing long-term efficacy and safety of nemolizumab showed up to 80% improvement in VAS and Eczema Area Severity Index scores, which shows breakage of the itch-scratch cycle and inhibition of IL-31-related

proinflammatory environment led to a pronounced improvement in the severity of AE.⁸⁵

Blockade of IL-31 through the caninized, anti-canine IL-31 mAb lokivetmab (ZTS-00103289) has been shown to reduce pruritus and skin lesions in dogs with AE.⁸⁶ No serious adverse events and drug interactions between lokivetmab and other concomitantly administered medications were observed in a recent study assessing the safety profile of lokimetvab.⁸⁷ Thus in addition to the highly effective blockade of the IL-31 pathway with IL-31RA mAb in patients with AE, a humanized anti-human IL-31 mAb (BMS-981164) might be another alternative for these patients; however, no current information about the phase I study of single-dose BMS-981164 administration in patients with AE and healthy subjects is available thus far.

CONCLUSIONS AND OUTLOOK

Since the first description of IL-31 in 2004, numerous studies led to a general understanding about the biology of this novel cytokine. The generation of mAbs targeting the IL-31 pathway poses an exciting development in the era of pruritic skin diseases. However, current knowledge shows that the effects of IL-31 are not limited to the induction of pruritus but that it has a broad spectrum of action as a proinflammatory and immunomodulatory cytokine; thus it fills one of the gaps between healthy and inflamed tissue. Future studies are required to understand the exact mechanism of IL-31, to elucidate further indications of inhibiting its pathway, and to define the role of IL-31-targeted interventions in the management of chronic inflammatory diseases.

REFERENCES

1. Sonkoly E, Muller A, Lauerma AI, Pivarcsi A, Soto H, Kemeny L, et al. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol* 2006;117:411-7.
2. McCandless EE, Rugg CA, Fici GJ, Messamore JE, Aleo MM, Gonzales AJ. Allergen-induced production of IL-31 by canine Th2 cells and identification of immune, skin, and neuronal target cells. *Vet Immunol Immunopathol* 2014;157:42-8.
3. Cevikbas F, Wang X, Akiyama T, Kempkes C, Savinko T, Antal A, et al. A sensory neuron-expressed IL-31 receptor mediates T helper cell-dependent itch: involvement of TRPV1 and TRPA1. *J Allergy Clin Immunol* 2014;133:448-60.
4. Dillon SR, Sprecher C, Hammond A, Bilsborough J, Rosenfeld-Franklin M, Presnell SR, et al. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol* 2004;5:752-60.
5. Zhang Q, Putheti P, Zhou Q, Liu Q, Gao W. Structures and biological functions of IL-31 and IL-31 receptors. *Cytokine Growth Factor Rev* 2008;19:347-56.
6. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol* 2014;6:a016295.
7. Bilsborough J, Leung DY, Maurer M, Howell M, Boguniewicz M, Yao L, et al. IL-31 is associated with cutaneous lymphocyte antigen positive skin homing T cells in patients with atopic dermatitis. *J Allergy Clin Immunol* 2006;117:1124.
8. Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Cramer R, et al. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β , and TNF- α : receptors, functions, and roles in diseases. *J Allergy Clin Immunol* 2016;138:984-1010.
9. Raap U, Gehring M, Kleiner S, Rüdrieh U, Eiz-Vesper B, Haas H, et al. Human basophils are a source of—and are differentially activated by—IL-31. *Clin Exp Allergy* 2017;47:499-508.
10. Kunsleben N, Rüdrieh U, Gehring M, Novak N, Kapp A, Raap U. IL-31 induces chemotaxis, calcium mobilization, release of reactive oxygen species, and CCL26 in eosinophils, which are capable to release IL-31. *J Invest Dermatol* 2015;135:1908-11.
11. Stott B, Lavender P, Lehmann S, Pennino D, Durham S, Schmidt-Weber CB. Human IL-31 is induced by IL-4 and promotes TH2-driven inflammation. *J Allergy Clin Immunol* 2013;132:446-54.e5.
12. Sokol CL, Barton GM, Farr AG, Medzhitov R. A mechanism for the initiation of allergen-induced T helper type 2 responses. *Nat Immunol* 2008;9:310-8.
13. Maier E, Werner D, Duschl A, Bohle B, Horejs-Hoeck J. Human Th2 but not Th9 cells release IL-31 in a STAT6/NF- κ B-dependent way. *J Immunol* 2014;193:645-54.
14. Cornelissen C, Brans R, Czaja K, Skazik C, Marquardt Y, Zwadlo-Klarwasser G, et al. Ultraviolet B radiation and reactive oxygen species modulate interleukin-31 expression in T lymphocytes, monocytes and dendritic cells. *Br J Dermatol* 2011;165:966-75.
15. Bando T, Morikawa Y, Komori T, Senba E. Complete overlap of interleukin-31 receptor A and oncostatin M receptor beta in the adult dorsal root ganglia with distinct developmental expression patterns. *Neuroscience* 2006;142:1263-71.
16. Diveu C, Lak-Hal AH, Froger J, Ravon E, Grimaud L, Barbier F, et al. Predominant expression of the long isoform of GP130-like (GPL) receptor is required for interleukin-31 signaling. *Eur Cytokine Netw* 2004;15:291-302.
17. Ghilardi N, Li J, Hongo JA, Yi S, Gurney A, de Sauvage FJ. A novel type I cytokine receptor is expressed on monocytes, signals proliferation, and activates STAT-3 and STAT-5. *J Biol Chem* 2002;277:16831-6.
18. Diveu C, Lelièvre E, Perret D, Lak-Hal AH, Froger J, Guillet C, et al. GPL, a novel cytokine receptor related to GP130 and leukemia inhibitory factor receptor. *J Biol Chem* 2003;278:49850-9.
19. Hermanns HM. Oncostatin M and interleukin-31: cytokines, receptors, signal transduction and physiology. *Cytokine Growth Factor Rev* 2015;26:545-58.
20. Arita K, South AP, Hans-Filho G, Sakuma TH, Lai-Cheong J, Clements S, et al. Oncostatin M receptor-beta mutations underlie familial localized cutaneous amyloidosis. *Am J Hum Genet* 2008;82:73-80.
21. Lin MW, Lee DD, Liu TT, Lin YF, Chen SY, Huang CC, et al. Novel IL31RA gene mutation and ancestral OSMR mutant allele in familial primary cutaneous amyloidosis. *Eur J Hum Genet* 2010;18:26-32.
22. Kausar T, Sharma R, Hasan MR, Saraya A, Chattopadhyay TK, Gupta SD, et al. Overexpression of a splice variant of oncostatin M receptor beta in human esophageal squamous carcinoma. *Cell Oncol (Dordr)* 2011;34:177-87.
23. Chen D, Chu CY, Chen CY, Yang HC, Chiang YY, Lin TY, et al. Expression of short-form oncostatin M receptor as a decoy receptor in lung adenocarcinomas. *J Pathol* 2008;215:290-9.
24. Cornelissen C, Lüscher-Firzlaff J, Baron JM, Lüscher B. Signaling by IL-31 and functional consequences. *Eur J Cell Biol* 2012;91:552-66.
25. Chattopadhyay S, Tracy E, Liang P, Robledo O, Rose-John S, Baumann H. Interleukin-31 and oncostatin-M mediate distinct signaling reactions and response patterns in lung epithelial cells. *J Biol Chem* 2007;282:3014-26.
26. Ip WK, Wong CK, Li ML, Li PW, Cheung PF, Lam CW. Interleukin-31 induces cytokine and chemokine production from human bronchial epithelial cells through activation of mitogen-activated protein kinase signalling pathways: implications for the allergic response. *Immunology* 2007;122:532-41.
27. Maier E, Mittermeir M, Ess S, Neuper T, Schmiedlechner A, Duschl A, et al. Prerequisites for functional interleukin 31 signaling and its feedback regulation by suppressor of cytokine signaling 3 (SOCS3). *J Biol Chem* 2015;290:24747-59.
28. Dreuw A, Radtke S, Pflanz S, Lippok BE, Heinrich PC, Hermanns HM. Characterization of the signaling capacities of the novel gp130-like cytokine receptor. *J Biol Chem* 2004;279:36112-20.
29. Hermanns HM, Radtke S, Schaper F, Heinrich PC, Behrmann I. Non-redundant signal transduction of interleukin-6-type cytokines. The adapter protein Shc is specifically recruited to the oncostatin M receptor. *J Biol Chem* 2000;275:40742-8.
30. Miyakawa Y, Rojnuckarin P, Habib T, Kaushansky K. Thrombopoietin induces phosphoinositide 3-kinase activation through SHP2, Gab, and insulin receptor substrate proteins in BAF3 cells and primary murine megakaryocytes. *J Biol Chem* 2001;276:2494-502.
31. Tamura S, Morikawa Y, Miyajima A, Senba E. Expression of oncostatin M receptor beta in a specific subset of nociceptive sensory neurons. *Eur J Neurosci* 2003;17:2287-98.
32. Feld M, Garcia R, Buddenkotte J, Katayama S, Lewis K, Muirhead G, et al. The pruritus- and TH2-associated cytokine IL-31 promotes growth of sensory nerves. *J Allergy Clin Immunol* 2016;138:500-8.e24.
33. Nobbe S, Dziunycz P, Mühleisen B, Bilsborough J, Dillon SR, French LE, et al. IL-31 expression by inflammatory cells is preferentially elevated in atopic dermatitis. *Acta Derm Venereol* 2012;92:24-8.
34. Natkemper LA, Martinez-Escala ME, Gelman AB, Singer EM, Rook AH, Guitart J, et al. Cutaneous T-cell lymphoma and pruritus: the expression of IL-31 and its receptors in the skin. *Acta Derm Venereol* 2016;96:894-8.
35. Kasraie S, Niebuhr M, Baumert K, Werfel T. Functional effects of interleukin 31 in human primary keratinocytes. *Allergy* 2011;66:845-52.

36. Cheung PF, Wong CK, Ho AW, Hu S, Chen DP, Lam CW. Activation of human eosinophils and epidermal keratinocytes by Th2 cytokine IL-31: implication for the immunopathogenesis of atopic dermatitis. *Int Immunol* 2010;22:453-67.
37. Yamaoka K, Okayama Y, Kaminuma O, Katayama K, Mori A, Tatsumi H, et al. Proteomic approach to FcεpsilonRI aggregation-initiated signal transduction cascade in human mast cells. *Int Arch Allergy Immunol* 2009;149(suppl 1):73-6.
38. Steinhoff M, Neisius U, Ikoma A, Fartasch M, Heyer G, Skov PS, et al. Proteinase-activated receptor-2 mediates itch: a novel pathway for pruritus in human skin. *J Neurosci* 2003;23:6176-80.
39. Niyonsaba F, Ushio H, Hara M, Yokoi H, Tominaga M, Takamori K, et al. Antimicrobial peptides human beta-defensins and cathelicidin LL-37 induce the secretion of a pruritogenic cytokine IL-31 by human mast cells. *J Immunol* 2010;184:3526-34.
40. Arai I, Tsuji M, Takeda H, Akiyama N, Saito S. A single dose of interleukin-31 (IL-31) causes continuous itch-associated scratching behaviour in mice. *Exp Dermatol* 2013;22:669-71.
41. Takaoka A, Arai I, Sugimoto M, Yamaguchi A, Tanaka M, Nakaike S. Expression of IL-31 gene transcripts in NC/Nga mice with atopic dermatitis. *Eur J Pharmacol* 2005;516:180-1.
42. Grimstad O, Sawanobori Y, Vestergaard C, Bilsborough J, Olsen UB, Gronhøj-Larsen C, et al. Anti-interleukin-31-antibodies ameliorate scratching behaviour in NC/Nga mice: a model of atopic dermatitis. *Exp Dermatol* 2009;18:35-43.
43. Saito S, Aoki A, Arai I, Takaishi S, Ito H, Akiyama N, et al. Regulation of Th2 responses by different cell types expressing the interleukin-31 receptor. *Allergy Asthma Clin Immunol* 2017;13:23.
44. Gonzales AJ, Humphrey WR, Messamore JE, Fleck TJ, Fici GJ, Shelly JA, et al. Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. *Vet Dermatol* 2013;24:48-53, e11-2.
45. Lewis KE, Holdren MS, Maurer MF, Underwood S, Meengs B, Julien SH, et al. Interleukin (IL) 31 induces in cynomolgus monkeys a rapid and intense itch response that can be inhibited by an IL-31 neutralizing antibody. *J Eur Acad Dermatol Venereol* 2017;31:142-50.
46. Hawro T, Saluja R, Weller K, Altrichter S, Metz M, Maurer M. Interleukin-31 does not induce immediate itch in atopic dermatitis patients and healthy controls after skin challenge. *Allergy* 2014;69:113-7.
47. Hänel KH, Pfaff CM, Cornelissen C, Amann PM, Marquardt Y, Czaja K, et al. Control of the physical and antimicrobial skin barrier by an IL-31-IL-1 signaling network. *J Immunol* 2016;196:3233-44.
48. O'Shaughnessy RF, Choudhary I, Harper JJ. Interleukin-1 alpha blockade prevents hyperkeratosis in an in vitro model of lamellar ichthyosis. *Hum Mol Genet* 2010;19:2594-605.
49. Groves RW, Mizutani H, Kieffer JD, Kupper TS. Inflammatory skin disease in transgenic mice that express high levels of interleukin 1 alpha in basal epidermis. *Proc Natl Acad Sci U S A* 1995;92:11874-8.
50. Yagi Y, Andoh A, Nishida A, Shiota Y, Nishimura T, Hashimoto T, et al. Interleukin-31 stimulates production of inflammatory mediators from human colonic subepithelial myofibroblasts. *Int J Mol Med* 2007;19:941-6.
51. Neis MM, Peters B, Dreuw A, Wenzel J, Bieber T, Mauch C, et al. Enhanced expression levels of IL-31 correlate with IL-4 and IL-13 in atopic and allergic contact dermatitis. *J Allergy Clin Immunol* 2006;118:930-7.
52. Nygaard U, Hvid M, Johansen C, Buchner M, Fölster-Holst R, Deleuran M, et al. TSLP, IL-31, IL-33 and sST2 are new biomarkers in endophenotypic profiling of adult and childhood atopic dermatitis. *J Eur Acad Dermatol Venereol* 2016;30:1930-8.
53. Raap U, Wichmann K, Bruder M, Ständer S, Wedi B, Kapp A, et al. Correlation of IL-31 serum levels with severity of atopic dermatitis. *J Allergy Clin Immunol* 2008;122:421-3.
54. Raap U, Weißmantel S, Gehring M, Eisenberg AM, Kapp A, Fölster-Holst R. IL-31 significantly correlates with disease activity and Th2 cytokine levels in children with atopic dermatitis. *Pediatr Allergy Immunol* 2012;23:285-8.
55. Ezzat MH, Hasan ZE, Shaheen KY. Serum measurement of interleukin-31 (IL-31) in paediatric atopic dermatitis: elevated levels correlate with severity scoring. *J Eur Acad Dermatol Venereol* 2011;25:334-9.
56. Biedermann T, Skabytska Y, Kaesler S, Volz T. Regulation of T cell immunity in atopic dermatitis by microbes: the yin and yang of cutaneous inflammation. *Front Immunol* 2015;6:353.
57. Bilsborough J, Mudri S, Chadwick E, Harder B, Dillon SR. IL-31 receptor (IL-31RA) knockout mice exhibit elevated responsiveness to oncostatin M. *J Immunol* 2010;185:6023-30.
58. Szegedi K, Kremer AE, Kezic S, Teunissen MB, Bos JD, Luiten RM, et al. Increased frequencies of IL-31-producing T cells are found in chronic atopic dermatitis skin. *Exp Dermatol* 2012;21:431-6.
59. Leung DY, Bieber T. Atopic dermatitis. *Lancet* 2003;361:151-60.
60. Hong CH, Yu HS, Ko YC, Chang WC, Chuang HY, Chen GS, et al. Functional regulation of interleukin-31 production by its genetic polymorphism in patients with extrinsic atopic dermatitis. *Acta Derm Venereol* 2012;92:430-2.
61. Lan CC, Tu HP, Wu CS, Ko YC, Yu HS, Lu YW, et al. Distinct SPINK5 and IL-31 polymorphisms are associated with atopic eczema and non-atopic hand dermatitis in Taiwanese nursing population. *Exp Dermatol* 2011;20:975-9.
62. Schulz F, Marenholz I, Fölster-Holst R, Chen C, Sternjak A, Baumgrass R, et al. A common haplotype of the IL-31 gene influencing gene expression is associated with nonatopic eczema. *J Allergy Clin Immunol* 2007;120:1097-102.
63. Singer EM, Shin DB, Nattkemper LA, Benoit BM, Klein RS, Didigu CA, et al. IL-31 is produced by the malignant T-cell population in cutaneous T-Cell lymphoma and correlates with CTCL pruritus. *J Invest Dermatol* 2013;133:2783-5.
64. Ohmatsu H, Sugaya M, Suga H, Morimura S, Miyagaki T, Kai H, et al. Serum IL-31 levels are increased in patients with cutaneous T-cell lymphoma. *Acta Derm Venereol* 2012;92:282-3.
65. Kim EJ, Hess S, Richardson SK, Newton S, Showe LC, Benoit BM, et al. Immunopathogenesis and therapy of cutaneous T cell lymphoma. *J Clin Invest* 2005;115:798-812.
66. Tey HL, Cao T, Nattkemper LA, Tan VW, Pramono ZA, Yosipovitch G. Pathophysiology of pruritus in primary localized cutaneous amyloidosis. *Br J Dermatol* 2016;174:1345-50.
67. Hartmann K, Wagner N, Rabenhorst A, Pflanz L, Leja S, Förster A, et al. Serum IL-31 levels are increased in a subset of patients with mastocytosis and correlate with disease severity in adult patients. *J Allergy Clin Immunol* 2013;132:232-5.
68. Lange M, Gleń J, Zabłotna M, Nedoszytko B, Sokółowska-Wojdyło M, Rębała K, et al. Interleukin-31 polymorphisms and serum IL-31 level in patients with mastocytosis: correlation with clinical presentation and pruritus. *Acta Derm Venereol* 2017;97:47-53.
69. Raap U, Wiecek D, Gehring M, Pauls I, Ständer S, Kapp A, et al. Increased levels of serum IL-31 in chronic spontaneous urticaria. *Exp Dermatol* 2010;19:464-6.
70. Altrichter S, Hawro T, Hänel K, Czaja K, Lüscher B, Maurer M, et al. Successful omalizumab treatment in chronic spontaneous urticaria is associated with lowering of serum IL-31 levels. *J Eur Acad Dermatol Venereol* 2016;30:454-5.
71. Bonciani D, Quintarelli L, Del Bianco E, Bianchi B, Caproni M. Serum levels and tissue expression of interleukin-31 in dermatitis herpetiformis and bullous pemphigoid. *J Dermatol Sci* 2017;87:210-2.
72. Chai R, Liu B, Qi F. The significance of the levels of IL-4, IL-31 and TLSP in patients with asthma and/or rhinitis. *Immunotherapy* 2017;9:331-7.
73. Lei Z, Liu G, Huang Q, Lv M, Zu R, Zhang GM, et al. SCF and IL-31 rather than IL-17 and BAFF are potential indicators in patients with allergic asthma. *Allergy* 2008;63:327-32.
74. Liu W, Luo R, Chen Y, Sun C, Wang J, Zhou L, et al. Interleukin-31 promotes helper T cell type-2 inflammation in children with allergic rhinitis. *Pediatr Res* 2015;77:20-8.
75. Yu JJ, Han WC, Yun KJ, Moon HB, Oh GJ, Chae SC. Identifying polymorphisms in IL-31 and their association with susceptibility to asthma. *Korean J Pathol* 2012;46:162-8.
76. Dambacher J, Beigel F, Seiderer J, Haller D, Göke B, Auernhammer CJ, et al. Interleukin 31 mediates MAP kinase and STAT1/3 activation in intestinal epithelial cells and its expression is upregulated in inflammatory bowel disease. *Gut* 2007;56:1257-65.
77. Perrigoue JG, Zaph C, Guild K, Du Y, Artis D. IL-31-IL-31R interactions limit the magnitude of Th2 cytokine-dependent immunity and inflammation following intestinal helminth infection. *J Immunol* 2009;182:6088-94.
78. Ferretti E, Tripodo C, Pagnan G, Guarnotta C, Marimipietri D, Corrias MV, et al. The interleukin (IL)-31/IL-31R axis contributes to tumor growth in human follicular lymphoma. *Leukemia* 2015;29:958-67.
79. Zeng X, Zhang Z, Gao QQ, Wang YY, Yu XZ, Zhou B, et al. Clinical significance of serum interleukin-31 and interleukin-33 levels in patients of endometrial cancer: a case control study. *Dis Markers* 2016;2016:9262919.
80. Davidi S, Fremder E, Kan T, Raviv Z, Timaner M, Karin N, et al. The antiangiogenic role of the pro-inflammatory cytokine interleukin-31. *Oncotarget* 2017;8:16430-44.
81. Naumnik W, Naumnik B, Niewiarowska K, Ossolinska M, Chyczewska E. Novel cytokines: IL-27, IL-29, IL-31 and IL-33. Can they be useful in clinical practice at the time diagnosis of lung cancer? *Exp Oncol* 2012;34:348-53.
82. Ginaldi L, De Martinis M, Ciccarelli F, Saitta S, Imbesi S, Mannucci C, et al. Increased levels of interleukin 31 (IL-31) in osteoporosis. *BMC Immunol* 2015;16:60.

83. Nemoto O, Furue M, Nakagawa H, Shiramoto M, Hanada R, Matsuki S, et al. The first trial of CIM331, a humanized antihuman interleukin-31 receptor A antibody, in healthy volunteers and patients with atopic dermatitis to evaluate safety, tolerability and pharmacokinetics of a single dose in a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2016;174:296-304.
84. Ruzicka T, Hanifin JM, Furue M, Pulka G, Mlynarczyk I, Wollenberg A, et al. Anti-interleukin-31 receptor A antibody for atopic dermatitis. *N Engl J Med* 2017;376:826-35.
85. Kabashima K, Furue M, Hanifin JM, Pulka G, Wollenberg A, Galus R, et al. Nemolizumab in patients with moderate-to-severe atopic dermatitis: randomized, phase II long-term extension. Presented at: 75th Annual Meeting of the American Academy of Dermatology; Orlando, Fla; 2017.
86. Michels GM, Ramsey DS, Walsh KF, Martinon OM, Mahabir SP, Hoevers JD, et al. A blinded, randomized, placebo-controlled, dose determination trial of lokivetmab (ZTS-00103289), a caninized, anti-canine IL-31 monoclonal antibody in client owned dogs with atopic dermatitis. *Vet Dermatol* 2016;27:478-e129.
87. Michels GM, Walsh KF, Kryda KA, Mahabir SP, Walters RR, Hoevers JD, et al. A blinded, randomized, placebo-controlled trial of the safety of lokivetmab (ZTS-00103289), a caninized anti-canine IL-31 monoclonal antibody in client-owned dogs with atopic dermatitis. *Vet Dermatol* 2016;27:505-e136.