

Interleukin-31: A Novel Diagnostic Marker of Allergic Diseases

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Abstract Interleukin-31 (IL-31) is a newly discovered cytokine associated with chronic skin inflammation and pruritus. Patients with atopic dermatitis, chronic spontaneous urticaria, allergic contact dermatitis, prurigo nodularis, primary cutaneous lymphoma and mastocytosis exhibit increased serum levels of IL-31 protein and elevated IL-31 mRNA in the skin. Interestingly, in some of these diseases, IL-31 serum levels correlate with disease activity. In the present review, we particularly focus on studies investigating IL-31 as a novel diagnostic biomarker indicating the severity of allergic diseases. We highlight a recent study on IL-31 in mastocytosis, which reports on elevated serum levels of IL-31 in adults correlating with the severity of disease categories, tryptase levels and percentage of bone marrow infiltration. We conclude that growing knowledge about IL-31, its receptors and signaling pathways serves to better understand the pathogenesis of allergic diseases and may lead to the development of novel treatment approaches.

Keywords Allergy · Asthma · Atopic dermatitis · Cytokine · Diagnosis · Disease severity · Interleukin-31 · IL-31 · IL-31 mRNA · Immune response · Inflammation · Mast cells · Mastocytosis · Pruritus · Skin · Diagnostic marker

Introduction

A series of recent studies reported on prominent functions of the novel cytokine interleukin-31 (IL-31). Current data demonstrate that IL-31 plays a major role in the induction of chronic inflammation [1, 2•] and regulates various processes of innate and adaptive immunity in tissues that are exposed to the environment [2•]. In fact, cytokines play a critical role in the control of immune responses. The most recent additions to the ever-growing family of cytokines include IL-27, IL-28A, IL-28B, IL-29 and IL-31 [3]. Increased IL-31 serum levels have been observed in different skin diseases as well as in inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis [1, 2•, 4]. Inflammatory bowel diseases are characterized by ongoing mucosal inflammation in which dysfunction of the host immunologic response is involved [5]. Moreover, IL-31 further stimulates secretion of proinflammatory cytokines, chemokines and matrix metalloproteinases [2•, 6].

IL-31 belongs to the family of IL-6 cytokines, which also includes IL-6, IL-11, IL-27, oncostatin M (OSM), leukemia inhibitory factor (LIF), ciliary neurotrophic factor, neuropoietin, cardiotrophin-1 and cardiotrophin-like cytokine [1, 7, 8], and signals through a receptor complex composed of IL-31RA and oncostatin M receptor β (OSMR β) [1, 2•].

IL-31 Polymorphisms

Sequencing the entire IL-31 gene provided new insights into the presence of specific IL-31 polymorphisms. An association analysis of IL-31 gene variants in atopic and nonatopic eczema demonstrated a significant association of a common IL-31 haplotype with the nonatopic type of eczema [9]. Additionally, analysis of peripheral blood mononuclear cells (PBMCs) in healthy individuals revealed a strong induction of IL-31

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mRNA expression upon stimulation, which was more pronounced in individuals homozygous for a certain risk haplotype, suggesting that altered regulation of IL-31 gene expression is a disease-promoting factor [9]. In contrast, investigating genomic DNA of patients with epidermolysis bullosa pruriginosa failed to demonstrate an association between IL-31 gene polymorphisms and disease phenotype [10].

Recently, distinct IL-31 polymorphisms have been associated with the development of atopic eczema and nonatopic hand dermatitis [11]. Furthermore, single-base extension analysis was used to detect the genotypes of IL-31 single nucleotide polymorphisms (SNPs) to compare the genotype and allele frequencies of the IL-31 SNPs between patients with asthma and healthy controls as well as among patients with atopic asthma, nonatopic asthma and healthy controls [12]. There were no significant differences in the genotype and allele frequencies of the IL-31 SNPs between patients with asthma and healthy controls, and similarly, the SNPs were not associated with the susceptibility to atopic asthma [12]. In atopic dermatitis, the frequency of a distinct IL-31 gene variant was increased compared to controls, and was linked to a slightly increased risk of development of atopic dermatitis [13]. Furthermore, the genotypes of the studied variants were associated with the severity of moderate atopic dermatitis, and a statistically significant correlation between moderate pruritus and genotype was observed [13].

IL-31-Producing Cells

Ongoing research is also addressing the cellular sources for IL-31. CD4⁺ T-cells, particularly activated T_H2 cells, peripheral blood and skin-homing CD45R0 CLA⁺T-cells, have been found to represent a major cellular source for IL-31 [14]. It has also been demonstrated that IL-31 delays apoptosis of eosinophils and significantly stimulates eosinophils, but not keratinocytes, to secrete proinflammatory cytokines such as IL-1 β , IL-6, atopic dermatitis-related chemokines CXCL1, CXCL8, CCL2 and CCL18 [15]. Transwell insert experiments demonstrated that a direct interaction between eosinophils and keratinocytes is required for IL-31-induced cytokine and chemokine release [15].

Activated monocytes, macrophages, eosinophils, basophils, dorsal root ganglia and keratinocytes have been described to express the IL-31 receptor complex [2•]. In addition, primary human eosinophils have been reported to constitutively express the functional receptor complex for IL-31 [16]. Moreover, IL-31RA was found to be expressed on dermal fibroblasts [16]. Another study revealed that human PBMCs, T-cells, monocytes, macrophages, and immature and especially mature dendritic cells produce IL-31 mRNA and IL-31 protein following exposure to UV irradiation or treatment with hydrogen peroxide [17]. Hydrogen peroxide,

but not UV irradiation, led to a moderate upregulation of IL-31 mRNA expression in epidermal keratinocytes and dermal fibroblasts [17].

IL-31 activated STAT-3 phosphorylation in human primary keratinocytes, which was augmented after preactivation with TLR-2 ligands or T_H1- and T_H2- associated cytokines that enhanced the secretion of CCL2 [18]. This effect was not observed in keratinocytes from patients with atopic dermatitis, which show an impaired expression of TLR-2 [18]. Together, these findings implicated a functional role of IL-31 in human primary keratinocytes and provided a new link between TLR-2 ligands and IL-31 [18].

In an experimental approach using polyclonal and purified protein derivative of tuberculin-specific T-cell clones, IL-31 was expressed by all investigated T_H2 clones, but not by T_H1, T_H17 or T_H22 clones [19]. Interestingly, this expression was dependent on autocrine IL-4 production by these clones, and T_H1 clones were able to express IL-31 when IL-4 was added to the cultures [19].

Next, staphylococcal exotoxins significantly upregulated IL-31RA expression on monocytes and macrophages, but not on dendritic cells, at both the mRNA and the protein level [20]. Furthermore, IL-31 enhanced the secretion of IL-1 β , IL-6 and IL-18, suggesting that IL-31 induces proinflammatory functions in activated human monocytes and macrophages after stimulation with staphylococcal exotoxins [20]. In a follow-up study, prestimulation of human macrophages with staphylococcal exotoxins resulting in upregulation of the IL-31 receptor in the presence of IL-31 showed that IL-31 strongly activated STAT-1 and -5, but not STAT-3 [21]. Thus, IL-31 can be produced by a large variety of immune cells with or without stimulation.

IL-31 in Mast Cells and Mastocytosis

Another major cellular source for IL-31 is mast cells. An initial study demonstrated that mast cells are involved in the malignant process of Philadelphia chromosome-negative myeloproliferative disorders (MPDs) associated with pruritus, which led to the hypothesis that mast cells play an important role in the development of pruritogenesis in MPDs [22]. MPD mast cells released significantly elevated levels of pruritogenic factors, including histamine and IL-31, compared to normal mast cells [22]. Furthermore, the presence of pruritus in MPDs was statistically correlated with increased numbers of mast cells, decreased apoptosis and elevated plasma levels of IL-31 [22].

Further experiments studying mast cells as a potential source for IL-31 showed that antimicrobial peptides are able to enhance IL-31 gene expression and IL-31 protein production and release in the human mast cell line LAD2 as well as in peripheral blood-derived cultured mast cells [23]. Moreover,

the expression of IL-31 was elevated in psoriatic skin mast cells, and antimicrobial peptides enhanced its expression *in vivo* in rat skin mast cells [23].

Since mastocytosis is characterized by clonal expansion of mast cells, particularly in skin and bone marrow, and symptoms include pruritus, urticaria pigmentosa, anaphylaxis, flushing, headache, diarrhea and osteoporosis [24–26], we aimed to clarify whether IL-31 levels are increased in mastocytosis and whether IL-31 levels differ between disease categories. In our study [27•], expression of IL-31 was analyzed in the serum of 50 patients with different categories of mastocytosis. We found that serum levels of IL-31 are significantly increased in patients with mastocytosis compared to healthy controls (Fig. 1a). Interestingly, within the group of 38 adult patients (Fig. 1b), those with advanced categories exhibited significantly elevated IL-31 levels compared to those with non-advanced categories. Furthermore, IL-31 correlated with tryptase levels (Fig. 1c) and the percentage of mast cell infiltrates in bone marrow. There was also a trend of increased IL-31 expression in patients with osteosclerosis compared to patients with normal bone density, osteopenia or osteoporosis. These data reflect again the association between advanced categories of mastocytosis and high IL-31 levels. In contrast, other clinical parameters, including skin lesions and presence of mast cell activation symptoms such as pruritus, anaphylaxis, flushing and diarrhea, failed to affect levels of IL-31. Immunohistochemistry in skin and bone marrow biopsies of patients with mastocytosis showed that the expression of IL-31 clearly colocalized with tryptase-positive mast cells, demonstrating that mast cells serve as a major source for IL-31 in mastocytosis.

IL-31 in Atopic Dermatitis

IL-31 has also been described to play a key role in the pathogenesis of atopic dermatitis. Severe pruritus is the primary symptom of atopic dermatitis, and IL-31 has been implicated in contributing to itching via activation of the IL-31 receptor on sensory nerve cells [20]. Recently, IL-31 and gastrin-releasing peptide have been reported to be involved in the development of itch, making the estimation of itch intensity a future reality [28]. Previous studies observed elevated plasma or serum IL-31 levels in patients with atopic dermatitis [8]. IL-31 expression was not only increased in patients with atopic dermatitis, but also in those with allergic contact dermatitis [29]. In both diseases, expression of IL-31 was associated with the expression of the T_H2 cytokines IL-4 and IL-13 [29, 30]. Additionally, known atopic dermatitis-related cytokines are IL-5, IL-13 and TNF- α , with emerging importance for IL-17, which seems to drive airway inflammation following cutaneous exposure to antigens [31]. Statistically increased mRNA levels of IL-31 were found in cutaneous biopsies of patients with atopic dermatitis as well as

allergic contact dermatitis, irrespective of the severity of the disease and serum IgE levels [29]. On the other hand, IL-31 serum levels in atopic dermatitis also correlated with disease activity and severity [30].

Similarly, in another study investigating 55 patients with atopic dermatitis, IL-31 serum levels were significantly elevated compared to controls [32]. Furthermore, serum IL-31 levels correlated with total serum IgE and the subjective itch intensity [32]. Moreover, specific correlations between the serum IL-31 level and serum IgE, eosinophil cationic protein, disease severity and certain degrees of itch intensity were identified [32]. Besides, PBMCs of patients with atopic dermatitis secreted significantly increased IL-31 compared to PBMCs of healthy controls upon stimulation with staphylococcal exotoxin [33].

In a pediatric group of patients with atopic dermatitis, serum IL-31 levels were significantly elevated during flare or quiescence compared to controls [34]. Serum IL-31 levels were particularly increased in patients with high disease severity compared with the patient groups of moderate or low severity and also correlated positively with a severity score [34].

Other investigations showed an increased immunoreactivity of IL-31 in infiltrating cells in atopic dermatitis compared with other skin diseases [35]. For instance, IL-31 expression was increased in the inflammatory infiltrates in skin biopsies taken from subjects with atopic dermatitis, whereas IL-31 and IL-31RA protein immunoreactivity was not increased in biopsies from subjects with other T_H2 -induced and pruritic skin diseases, including mycosis fungoides, Sézary syndrome and alopecia areata [35].

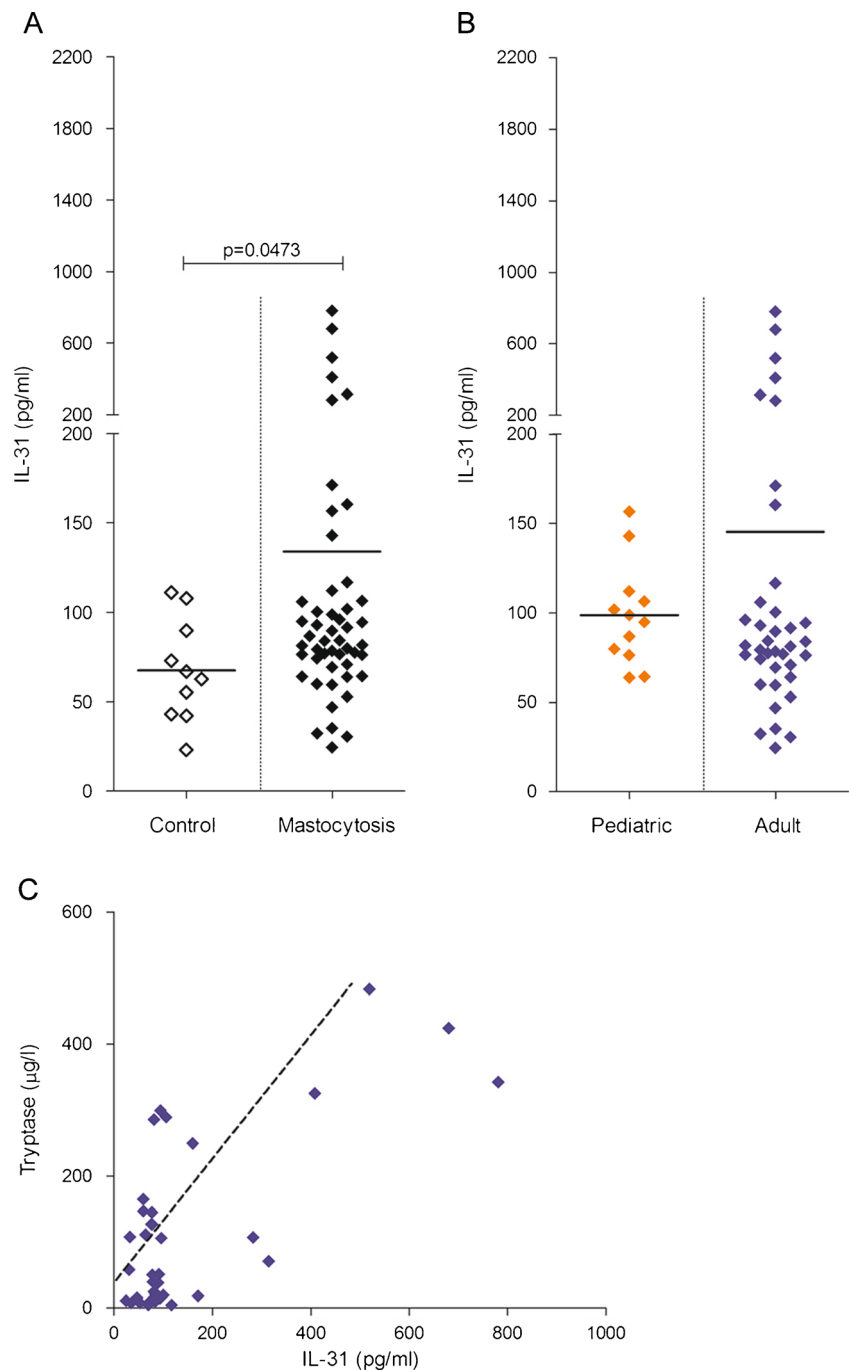
Szegedi et al. observed that in atopic dermatitis the number of IL-31-producing T-cells is increased and that IL-31 levels in the blood of these patients correlated with IL-31-producing CD4+T-cell frequencies as well as with the severity of the disease [36]. Interestingly, in co-culture experiments with direct interaction of eosinophils and fibroblasts, the release of the atopic dermatitis-related chemokines CXCL1, CXCL8, CXCL10, CCL2 and CCL5 as well as of the proinflammatory cytokine IL-6 was significantly induced and further enhanced by IL-31 stimulation [16]. Recently, patients with atopic dermatitis were challenged with IL-31 by skin prick testing [37•]. Of note, IL-31 failed to induce an immediate itch response in this study. This observation led to the conclusion that IL-31 exerts its pruritic effect indirectly via keratinocytes and secondary mediators rather than through stimulation of its receptors on cutaneous nerves [37•].

IL-31 in Other Diseases

Cutaneous Diseases

In addition to atopic dermatitis, patients with chronic spontaneous urticaria, prurigo nodularis and primary cutaneous

Fig. 1 **a** IL-31 serum levels are significantly ($p=0.0473$) elevated in patients with mastocytosis (Mastocytosis) compared to healthy controls (Control). **b** Adult patients show increased IL-31 levels compared to pediatric patients. Data are presented as scatter dot plots with means. **c** Tryptase serum levels (y -axis) positively correlate with IL-31 levels (x -axis) in all adult patients with mastocytosis (Spearman's $r=0.4167$, $p=0.0093$)



lymphoma were reported to express increased levels of serum IL-31 and IL-31 mRNA in the skin. Patients with cutaneous T-cell lymphoma exhibited increased levels of serum IL-31 compared to healthy controls [38•]. Serum IL-31 levels also reflected the severity of cutaneous T-cell lymphoma and were therefore implicated to play a role in causing pruritus in these patients [38•], as has been reported for patients with atopic dermatitis [1, 8, 30, 39]. Another study confirmed that IL-31 mRNA is increased in cutaneous T-cell lymphoma and also showed a significant correlation between IL-31 and patients

experiencing marked pruritus at the time of sample collection [40]. Additionally, 53 % of pruritic cutaneous T-cell lymphoma patients had detectable serum IL-31 levels, whereas only 8 % of non-pruritic patients showed serum IL-31 protein [40].

In patients with chronic spontaneous urticaria, serum IL-31 levels were significantly increased compared to non-atopic healthy controls, although levels were significantly lower compared to patients with atopic dermatitis [41]. In this study, no correlation between IL-31 serum levels and the urticarial wheal score was found [41]. Serum concentrations of IL-31

were also measured in a group of 59 patients with psoriasis vulgaris, either untreated or treated with narrow band ultraviolet B irradiations [42]. In these psoriatic patients, a significantly increased concentration of IL-31 was found compared to healthy control subjects, and additionally, narrow band ultraviolet B exposures caused a significant decrease in IL-31 levels [42]. In a Chinese population of 65 patients with systemic lupus erythematosus, serum levels of IL-31 did not significantly differ from healthy controls [43].

Furthermore, IL-31 mRNA was expressed at significantly higher levels in prurigo compared to psoriatic and normal skin, and a significant correlation was found between the expression levels of IL-4 and IL-31 in patients with prurigo [44], similar as seen in atopic dermatitis. Also in primary cutaneous amyloidosis (PCA), an itchy skin disease common in South America and Southeast Asia, a link between IL-31 signaling and the pathogenesis of amyloidosis was suggested [45].

Using a human three-dimensional organotypic skin model with either primary keratinocytes or HaCaT keratinocytes with inducible IL-31RA, it was shown that IL-31 interferes with keratinocyte differentiation, associated with reduced epidermal thickness, disturbed epidermal constitution, altered alignment of the stratum basale and poor development of the stratum granulosum [46].

Allergic Rhinitis and Asthma

IL-31 is not only important in the skin; it also seems to play a crucial role in allergic rhinitis and asthma. Following nasal allergen challenge, IL-31 was released into nasal secretions in patients with allergic rhinitis [7•]. Furthermore, IL-31 levels showed a trend to correlate with the symptoms and severity of allergic rhinitis [7•]. On the other hand, local IL-31 levels did not correlate with itching after a single nasal allergen challenge, which contrasts with the described link between IL-31 and itching in atopic dermatitis [1, 47], suggesting other functions of IL-31 in allergic rhinitis [7•]. IL-31, detected especially in the submucosal tissue, and IL-31RA, primarily localized in submucosal glands, were upregulated in patients with allergic rhinitis, which implicates an important role for IL-31 in mucus overproduction in nasal allergic inflammation [48]. IL-31 production was also demonstrated for pollen antigen-induced PBMC responses in patients with allergic rhinitis [7•, 49]. Around two thirds of PBMCs produced detectable levels of IL-31 in response to pollen allergens *in vitro* in association with the severity of allergic rhinitis [49].

Additionally, IL-31 was reported as a potential indicator in patients with allergic asthma [50, 51]. Furthermore, IL-31-induced activation of human bronchial epithelial cells was investigated [51]. IL-31 significantly induced gene and protein expressions of epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and monocyte

chemoattractant protein-1 (MCP-1/CCL2) of human bronchial epithelial cells in a time- and dose-dependent manner [51]. Moreover, serum concentrations of IL-31 in patients with allergic asthma and mRNA levels in PBMCs were significantly increased compared to normal control subjects [50].

IL-31 in Animal Models

The role of IL-31 and IL-31 receptor expression has also been studied in animal models. For example, IL-31 receptor expression was found to be increased in tissues derived from an animal model of airway hypersensitivity [1]. Besides, in a mouse model for atopic dermatitis, high IL-31 mRNA expression was associated with intensive scratching behavior [39]. Transgenic mice overexpressing IL-31 developed dermatitis resembling human atopic dermatitis with severe pruritus, alopecia and eczematous skin lesions [1, 52]. Interestingly, anti-IL-31 antibodies significantly inhibited the development of scratching activities in a mouse model for atopic dermatitis [47], indicating again that IL-31 plays an important role in the regulation of itch. In line with these observations, a single intradermal injection of IL-31 induced continuous scratching in mice [53•].

Moreover, in 57 % of dogs with naturally occurring atopic dermatitis, significant serum levels of IL-31 were detectable [54], and injection of IL-31 into laboratory beagle dogs caused transient episodes of pruritic behavior [54].

Conclusions

IL-31 serum and mRNA levels have been studied intensively in different diseases, especially in allergic diseases. While expression of IL-31 was first mainly associated with pruritus, it became increasingly evident that IL-31 also carries out additional important functions. In most diseases investigated so far, such as mastocytosis, atopic dermatitis, allergic contact dermatitis, primary cutaneous T-cell lymphoma and allergic rhinitis, IL-31 levels significantly correlated with disease severity, but not necessarily with pruritus. In other diseases, including psoriasis, primary cutaneous amyloidosis and asthma, correlations between IL-31 levels and disease severity have been suggested, but not proven, whereas diseases such as chronic spontaneous urticaria and lupus erythematosus failed to demonstrate associations between IL-31 and severity. Taken together, current data suggest exploiting IL-31 serum and mRNA levels as potential diagnostic markers of severity of allergic diseases. Moreover, therapeutic strategies targeting IL-31 could be a novel promising approach for treatment of allergic diseases.

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Compliance with Ethics Guidelines

Conflict of Interest Karin Hartmann has served as a speaker for ALK-Abello, Novartis and Shire; is a consultant in a Novartis trial; and has received research grants from Novartis.

Anja Rabenhorst declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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