Journal of Dermatological Research

Online Submissions: http://www.ghrnet.org/index./jdr/
doi:10.17554/j.issn.2413-8223.2022.07.60

J. of Dermatological Res. 2022 June; **7(1)**: 225-231
ISSN 2413-8223

REVIEW

Role of Histamine on Itch Sensation Induced by Interleukin-31

Masahiro Seike, MD, Ph D

1 Department of Food and Nutrition Science, Sagami Women's Junior College, 2-1-1 Bunkyo Minami-ku Sagamihara Kanagawa 252-0383 Japan.

Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Correspondence to: Masahiro Seike, Department of Food and Nutrition Science, Sagami Women's Junior College, 2-1-1 Bunkyo Minami-ku Sagamihara Kanagawa 252-0383 Japan
Email: seike_masahiro@isc.sagami-wu.ac.jp
Telephone: +81-42-749-4784

Received: July 19, 2021
Revised: August 31, 2021
Accepted: September 2, 2021
Published online: May 30, 2022

ABSTRACT

Chronic allergic dermatitis, including atopic dermatitis and chronic allergic contact dermatitis, is characterized by an itch sensation and eczematous lesions, along with T helper (Th) 2 cell and granulocyte infiltration. Th2 cells, mast cells and eosinophils secrete interleukin (IL)-31, inducing intense itching in allergic dermatitis. Regulatory T cells (Tregs) inhibit the infiltration of these cells. Histamine induces the development of eczematous lesions in patients with chronic allergic dermatitis. In these eczematous lesions, histamine induces cell infiltration and inhibits Treg infiltration via histamine H1 and H4 receptors. Therefore, histamine may aggravate the itch sensation during chronic allergic dermatitis by increasing IL-31 levels.

Key words: Allergic dermatitis; Itch sensation; IL-31; Histamine

Seike M. Role of Histamine on Itch Sensation Induced by Interleukin-31. *Journal of Dermatological Research* 2022; **7(1)**: 225-231 Available from: URL: http://www.ghrnet.org/index.php/jdr/article/view/3187

INTRODUCTION

Chronic allergic dermatitis, such as atopic dermatitis (AD) and chronic allergic contact dermatitis (CACD), is characterized by pruritus and eczematous lesions accompanied by T helper (Th) 2 cell infiltration. Interleukin (IL)-31 is primarily secreted by Th2 cells[1]. Granulocytes are an additional source of IL-31[2-5]. Patients with AD, chronic spontaneous urticaria, CACD, prurigo nodularis, primary cutaneous lymphoma or mastocytosis exhibit increased levels of IL-31 protein and elevated IL-31 mRNA in the skin[6]. IL-31 is regulated by exposure to allergens[7]. IL-31 signals are mediated via a heterodimeric receptor complex comprising IL-31 receptor A (IL-31RA) and oncostation M receptor (OSMR)[8-10]. The IL-31 receptor is expressed in macrophages, dendritic cells, basophils, cutaneous neurons and keratinocytes[11-17]. Furthermore, small-diameter neurons in the dorsal root ganglia (DRG) express IL-31RA[11]. IL-31 may act directly on peripheral nerves, causing pruritus associated with AD[18].

EXPRESSION OF IL-31

Notably, Th2 cells primarily secrete IL-31[1]. IL-31 expression is dependent on autocrine IL-4 expression. IL-31 can induce proinflammatory genes, such as CC chemokine ligand 2 (CCL2) and granulocyte colony-stimulating factor[19]. Signal transducer and activator of transcription 6 (STAT6) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) are central players mediating IL-31 expression induced by IL-4 and IL-33. In contract, transforming growth factor (TGF)-β1 attenuates IL-31 secretion by Th2 cells[20]. IL-31RA induces STAT signaling, with the presence of a functional JAK-binding box within IL-31RA considered an essential prerequisite for functional IL-31-mediated STAT3 signaling. Suppressor of cytokine signaling-3 (SOCS3) acts as a potent feedback inhibitor of IL-31-inducing signaling[21]. In human keratinocytes, IL-31RA levels are upregulated by interferon-γ and a toll-like receptor

(TLR) 2/TLR1 agonists, but not by IL-4[15]. IL-31RA levels are low in human macrophages, whereas they are upregulated by staphylococcal enterotoxin B or staphylococcal α-toxin[15,16].

Although Th2 cells remain the primary source of IL-31, granulocytes are an additional IL-31 source[7, 13, 22, 23]. IL-31 is robustly expressed in the skin of patients with chronic spontaneous urticaria and is released from isolated basophils following anti-IgE, IL-31, or N-formylmethionyl-leucyl-phenylalanine stimulation[13]. IL-31RA and OSMR are expressed in human basophils.

Human β-defensins (hBDs) and cathelicidin LL-37 enhance IL-31 gene expression, as well as IL-31 protein production and release, in the human mast cell line LAD2 and peripheral blood-derived mast cell cultures. IL-31 expression is found to be elevated in psoriatic skin mast cells. hBD-2-4 and LL-37 activate the phosphorylation of mitogen-activated protein kinases, p38, ERK, and INK, which are required for IL-31 production and release[22]. Elevated serum levels of IL-31 can be observed in patients with myeloproliferative disorders, known to be characterized by pruritus. Additionally, mast cells of patients exhibit increased IL-31 secretion[24].

Human eosinophils can release IL-31, which is significantly more intense in eosinophils from patients with AD than in those from normal volunteers. IL-31 affects eosinophil functions by inducing chemotaxis, Ca2+ mobilization, CCL26 release, and reactive oxygen species generation[25]. IL-31RA, OSMR-β and IL-33 receptor component ST2 are expressed on the surface of eosinophils. A co-culture of eosinophils and fibroblasts was found to induce IL-6 and AD-related chemokines C-X-C motif chemokine ligand 1 (CXCL1), CXCL10, CCL2 and CCL5. The induction is further enhanced by IL-31 and IL-33 stimulation[4, 5].

MECHANISM OF ITCH SENSATION

Itch sensation emanates from the activity of itch-specific nerve fibers in the epidermis and can be attributed to mechano-insensitivity, low condition velocities, large innervation territories, and high transcutaneous electrical thresholds[26]. These nerve fibers extend to the stratum granulosum of the epidermis. It is well established that keratinocytes are predominant cells in the epidermis and release pruritogenic molecules (opioids, proteases, substance P, nerve growth factor [NGF], neurotrophin4, endocannabinoids) expressing various receptors involved in itch sensation, including, but not limited to, protease activated receptor (PAR) 2, vanilloid, transient receptor potential vanilloid (TRPV) ion channels, TrkA, TrkB, cannabinoid receptor 1, IL-31 receptor, and μ- and κ-opioid receptors. Keratinocytes act as initiators of the itch sensation and are responsible for communicating the itch signal to the cutaneous sensory nerves[27].

Cytokines play a crucial role in mediating mechanisms underlining itch. Thymic stromal lymphopoietin (TSLP) is a cytokine long implicated as a critical mediator of T-lymphocyte maturation and activation. TSLP directly promotes itch by activating cutaneous sensory neurons[28]. This TSLP-induced itch requires TRPA1, and the expression of keratinocyte-derived TSLP depends on the ORAI1/NFAT calcium signaling pathway[28]. Intradermal IL-2 injection induces itch sensation in patients with AD or healthy individuals[29]. On utilizing intravenous IL-2 for cancer therapy, severe pruritus is a known side effect of treatment[30-32]. In patients with AD, cyclosporine downregulated IL-2 synthesis and decreased pruritus [33]. Notably, IL-4 and IL-13 are necessary for the development, initiation, and maintenance of the Th2 subset of cells. IL-4 and IL-13 are associated with eosinophilic infiltration and the production of NGF and TrkA[34-36]. Pruritus was observed in transgenic mice overexpressing IL-4 and IL-13[37, 38]. IL-13 is a potent stimulator of pruritus in AD and appears to be involved in TRPV1 signaling[39]. Dupilmab, a monoclonal antibody targeting IL-4 and IL-13, demonstrated a 55.7% reduction in pruritus severity[40].

Gastrin-releasing peptide (GRP) is a neuropeptide involved in the itch sensation, as intradermal injections of GRP elicit scratching in mice[41]. GRP is released by neurons in the DRG[42-45] and activates dorsal spinal cord neurons expressing the GRP receptor, which, in turn, transmits the itch signal to higher-order neurons[46]. Severe pruritus in patients with AD positively corelated with serum GRP levels[47].

Acetylcholine (ACh) stimulates histaminergic and nonhistaminergic cutaneous sensory nerve C fibers[48, 49]. Intradermal ACh injection induced axonal reflexive flare response similar to that noted in histaminergic itch[50]. Patients with AD are more sensitive to intradermal ACh injections than to histamine[51]. Intradermal injections of ACh induced pain in healthy subjects, whereas itch sensation was observed in patients with AD[52].

Glucocorticoids stimulate the upregulation of cytokines that mediate Th2 responses, such as IL-4 and IL-13[53]. As IL-4 and IL-13 are implicated in the pathogenesis of itch, glucocorticoid secretion in response to psychological stress can be implicated as a mediator of itch[27].

Histamine is released from immune cells in response to tissue inflammation or allergen-induced stimulation[54-56]. Direct application of histamine to human skin induces itching and subsequent axonal reflexive vasodilation and flare[57]. There are four established histamine receptors (H1 receptor [H1R]-H4 receptor [H4R])[50]. H1R and H4R have been identified as potential mediators of pruriception[56]. H1R is expressed in the DRG, and H1R inhibitors can completely suppress histamine-induced itch in human skin[56, 57]. Thus, H1R is an important mediator of histamine-induced itch reactions. However, a recent study showed that H4R inhibitors blocked itching in a murine allergic contact dermatitis (ACD) model[58]. Moreover, the concomitant blockage of H1R and H4R was more effective at reducing itch than either receptor alone[59].

Substance P (SP) is a neuropeptide involved in afferent neuronal signal transduction[60]. Activation of sensory neurons in the skin causes the release of SP[32, 61]. SP binds to neurokinin receptors on mast cells, keratinocytes, and cutaneous nerve ending, resulting in the release of additional itch mediators[48, 61]. In humans, intradermal injection of SP induced mast cell activation and histamine release, associated with a wheal and flare reaction[62-65]. Mast cells activated by SP reportedly release inflammatory mediators such as leukotriene B4, prostaglandin D2, and tumor necrosis factor-alpha[66-69]. Moreover, SP triggers the release of pruritogenic compounds from keratinocytes, endothelial cells, and immune cells[70, 71]. Notably, skin lesions in patients with AD and prurigo nodularis are characterized by increased SP-positive sensory neurons[72, 73]. Elevated serum SP levels have been detected in patients with AD and corelate with itch intensity[74].

Furthermore, histamine released from mast cells increases levels of NGF[75]. NGF is a neurotrophin that modulates the development of the peripheral nervous system, including cutaneous innervation, which induces pruritus. NGF is thought to precipitate neurohyperplasia in the skin lesion of patients with AD[76, 77]. Additionally, NGF upregulates SP and calcitonin gene-related peptide (CGRP)[78], both of which are related to neurogenic inflammation and hypersensitization of itch pruriceptors[67]. Eosinophils are the primary source of NGF, and the release of NGF can be associated with increased TRPV receptor 1 and intracellular calcium, which, in turn, release SP and CGRP via SNARE/synaptogoin/synaptobrevin mechanisms. Both SP and CGRP increase eosinophil chemotaxis, activation, and survival, thus, propagating a vicious itch cycle[27].

IL-31 AND ITCH SENSATION

Notably, IL-31 transgenic mice, as well as those treated with IL-31, exhibited scratching behavior and AD-like skin lesions. Moreover, IL-31 induced an increase in cutaneous nerve fiber density in the skin lesions of these mice[79]. Murine DRG cultures treated with IL-31 demonstrated increased neuronal elongation. Therefore, IL-31 promotes sensitivity to pruritus in AD, and the IL-31 nerve axis may play a role in the skin hypersensitivity, a well-known characteristic of AD[79].

Cutaneous and intradermal injections of IL-31 evoke intense itching, with markedly increased concentrations detected in murine AD-like skin. Human and mouse DRG neurons express IL-31RA, mainly in neurons that express TRPV1. IL-31-induced itching behavior was shown to be significantly reduced in TRPV1-deficient and transient receptor channel potential cation channel ankyrin subtype 1-deficient mice[11]. Pretreatment with an anti-IL-31 RA antibody inhibited scratching behavior induced by IL-31 injection. In contrast, a non-sedative antihistamine (terfenadine), immunosuppressants (dexamethasone and tacrolimus), or a µ-opioid receptor antagonist (naloxone) failed to significantly suppress scratching behavior. Anti-IL-31RA antibodies reduced ear swelling and dermatitis scores in a chronic pruritus-inducing AD-like murine model[80]. Transgenic mice overexpressing IL-31 were found to develop severe pruritus. IL-31R expression is increased in diseased tissues derived from an animal model of airway hypersensitivity[81]. Administration of an anti-mouse IL-31 antibody ameliorated scratching behavior in NC/Nga mice with AD-like skin lesion[82]. *Il-31* transgenic mice or mice supplemented with an iso-osmotic pump containing IL-31 developed AD-like skin lesions with scratching[83], with the lesioned skin presenting hyperinnervation. Accordingly, IL-31 promotes nerve fiber elongation and branching of murine small-diameter DRG neurons, which are abrogated in DRG neurons from *Il-31ra*-deficient mice[83]. IL-31 binds to IL-31RA on the sensory nerve and evokes itch sensation via TRPV1 and TRPA1 ion channel activation. Additionally, IL-31 promotes the elongation and branching of IL-31RA+ sensory nerve fibers, which might self-aggravate itch sensation[84].

Cacine IL-31induces pruritic behaviours in dogs and can be detected in most dogs with naturally occurring AD[85]. IL-31 delivery elicited a scratching response immediately after IL-31 administration, persisting for at least 3 h in cynomolgus monkeys. Treatment with IL-31 monoclonal antibody inhibited the IL-31-mediated scratching response[86]. In cynomolgus monkeys, a single subcutaneous injection of nemolizumab, an anti-human IL-31RA monoclonal antibody, suppressed IL-31-induced scratching for approximately 2 months [87]. Furthermore, nemolizumab was efficacious and well-tolerated for up to 64 weeks in patients with moderate-to-severe AD inadequately controlled by topical therapy[88]. Nemolizumab rapidly and sustainably improved cutaneous signs of inflammation and pruritus in patients with AD, with the maximal efficacy observed at 30mg[89]. The use of subcutaneous nemolizumab, in addition to topical agents for AD, resulted in a greater reduction in pruritus than with the use of placebo plus topical agents. The incidence of injection-related reactions was 8% with nemolizumab and 3% with placebo[89]. Nemolizumab reduced pruritus and skin lesion severity in patients with prurigo nodularis. However, nemolizumab has been associated with gastrointestinal symptoms (abdominal pain and diarrhea) and musculoskeletal symptoms[89].

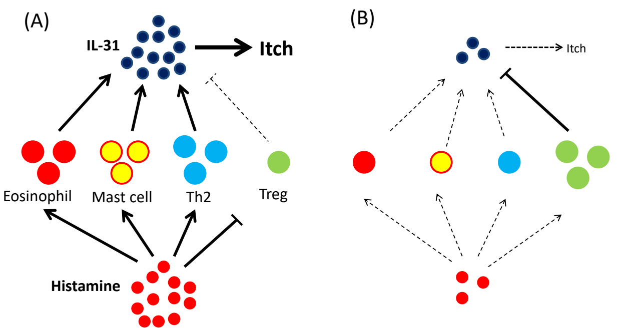

Figure 1 Roles of histamine on IL-31 secretion and itch sensation. (A) Histamine levels increase in eczematous lesions of allergic dermatitis. Histamine induces eosinophil, mast cell and Th2 cell infiltration. Conversely, histamine inhibits the infiltration of Tregs, which suppresses cell infiltrations. An Increase in infiltrated eosinophils, mast cells and Th2 cells induces an increase in IL-31 levels. Consequently, an increase in IL-31 levels evokes an intense itch sensation in skin lesions. (B) A decrease in histamine levels inhibits the infiltration of eosinophils, mast cells and Th2 cells and induces Treg infiltration in eczematous lesions. A decrease in IL-31 levels ameliorates itch sensation.

HISTAMINE AND IL-31

Histamine-deficient histidine decarboxylase (HDC, -/-) mice were used to investigate the role of histamine in the extent of CACD induced by repeated application of contact sensitizing agent. CACD was induced following the daily application of diphenylcyclopropenone (DCP). Histological examination of the skin revealed that mice displayed mast cell, eosinophil, and CD4+ T-cell infiltration. The magnitude of cell infiltration was more significant in HDC (+/+) mice than HDC (-/-) ones[90, 91]. Histamine mediates chemotaxis of mast cells and eosinophils via H1R or H4R in allergic tissues[91, 92]. Therefore, histamine plays a vital role in the development of eczematous lesions in patients with chronic allergic dermatitis. As human mast cells and eosinophils secrete IL-31, histamine may increase IL-31 levels and induce itch sensation in CACD via H1R and H4R in these cells. IL-4 levels were increased in HDC (+/+) mice when compared with that in HDC (-/-) mice; this increased IL-4 was ameliorated by H1R and H4R antagonist[90-92]. Moreover, as IL-4 induces the release of IL-31 from Th2 cells, histamine could increase IL-31 levels and induce itch sensation by increasing IL-4 levels. Moreover, these effects were induced by H1R and H4R.

Regulatory T cells (Tregs) are a subset of T cells known to regulate effector T cells, leading to immune tolerance to reduce allergic reactions, and play a role in maintaining immunological self-tolerance by actively suppressing self-reactive lymphocytes[93]. Tregs suppress effector T cells and ameliorate ACD[94]. TGF-β is one of the central regulators of Treg recruitment in allergic lesions[95]. As the level of TGF-β1 and number of Tregs in eczematous lesions is higher in HDC (-/-) mice than in HDC (+/+) mice, histamine suppresses Tregs mediated by TGF-β1 in skin lesions[96]. This suppression was found to be improved by H1R or H4R antagonist[96]. Furthermore, TGF-β1 attenuates IL-31 secretion by Th2 cells; accordingly, histamine may increase IL-31 levels and itch sensation by decreasing TGF-β1. Moreover, these effects were induced via H1R and H4R. Experimentally, scratching behavior was observed in HDC (+/+) mice but not in HDC (-/-) mice after DCP application[97]. Furthermore, scratching behavior was ameliorated in mice treated with H1R and H4R antagonist[98]. The roles of histamine in IL-31 and itch are summarized in Figure 1.

CONCLUSION

Chronic allergic dermatitis can be characterized by pruritus and eczematous lesions, accompanied by Th2 cell and granulocyte infiltration. These inflammatory cells secrete IL-31, which induces an itch sensation. Histamine promotes cell infiltration and inhibits Treg infiltration in allergic dermatitis via H1R and H4R. Finally, histamine may aggravate itch sensation in allergic dermatitis by increasing IL-31 levels.

ACKNOWLEDGEMENT

I would like to thank Editage (www.editage.com) for English language editing.

REFERENCE

1. Dillon SR, Sprecher C, Hammond A, Bilsborough J, Rosenfeld-Franklin M, Presnell SR, Haugen HS, Maurer M, Harder B, Johnston J, Bort S, Mudri S, Kuijper JL, Bukowski T, Shea P, Dong DL, Dasovich M, Grant FJ, Lockwood L, Levin SD, LeCiel C, Waggie K, Day H, Topouzis S, Kramer J, Kuestner R, Chen Z, Foster D, Parrish-Novak J, Gross JA. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol*. 2004; **5** :752-60. [PMID: 15184896]
2. Raap U, Gehring M, Kleiner S, Rüdrich U, Eiz-Vesper B, Haas H, Kapp A, Gibbs BF. Human basophils are a source of - and are differentially activated by - IL-31. *Clin Exp Allergy*. 2017; **47**: 499-508. [PMID: 2800095]
3. Niyonsaba F, Ushio H, Hara M, Yokoi H, Tominaga M, Takamori K, Kajiwara N, Saito H, Nagaoka I, Ogawa H, Okumura K. 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. [PMID: 20190140]
4. Wong C, Leung KM, Qiu H, Chow JY, Choi AO, Lam CY. Activation of eosinophils interacting with dermal fibroblasts by pruritogenic cytokine IL-31 and alarmin IL-33: implications in atopic dermatitis. *PLoS One*. 2012; **7**:e29815. [PMID: 22272250]
5. 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. [PMID: 20410259]
6. Rabenhorst A, Hartmann K. Interleukin-31: a novel diagnostic marker of allergic diseases. *Curr Allergy Asthma Rep*. 2014; **14**:423. [PMID: 24510535]
7. Sonkoly E, Muller A, Lauerma AI, Pivarcsi A, Soto H, Kemeny L, Alenius H, Dieu-Nosjean MC, Meller S, Rieker J, Steinhoff M, Hoffmann TK, Ruzicka T, Zlotnik A, Homey B. IL-31: a new link between T cells and pruritus in atopic skin inflammation. *J Allergy Clin Immunol*. 2006; **117**:411-7. [PMID: 16461142]
8. 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. [PMID: 18926762]
9. Diveu C, Lak-Hal AH, Froger J, Ravon E, Grimaud L, Barbier F, Hermann J, Gascan H, Chevalier S. Predominant expression of the long isoform of GP130-like (GPL) receptor is required for interleukin-31 signaling. *Eur Cytokine Netw*. 2004; **15**: 291-302. [PMID: 15627637]
10. 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. [PMID: 15194700]
11. Cevikbas F, Wang X, Akiyama T, Kempkes C, Savinko T, Antal A, Kukova G, Buhl T, Ikoma A, Buddenkotte J, Soumelis V, Feld M, Alenius H, Dillon SR, Carstens E, Homey B, Basbaum A, Steinhoff M. 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. [PMID: 24373353]
12. Kato A, Fujii E, Watanabe T, Takahashi Y, Matsushita H, Furuhashi T, Morita A. Distribution of IL-31 and its receptor expressing cells in skin of atopic dermatitis. *J Dermatol Sci*. 2014; **74**: 229-35. [PMID: 2466709]
13. Raap U, Gehring M, Kleiner S, Rüdrich U, Eiz-Vesper B, Haas H, Kapp A, Gibbs BF. Human basophils are a source of - and are differentially activated by - IL-31. *Clin Exp Allergy*. 2017; 47: 499-508. [PMID: 28000952]
14. Dai X, Okazaki H, Hanakawa Y, Murakami M, Tohyama M, Shirakata Y, Sayama K. Eccrine sweat contains IL-1α, IL-1β and IL-31 and activates epidermal keratinocytes as a danger signal. *PLoS One*. 2013; **8**: e67666. [PMID: 23874436]
15. Kasraie S, Niebuhr M, Baumert K, Werfel T. Functional effects of interleukin 31 in human primary keratinocytes. *Allergy*. 2011; 66: 845-52. [PMID: 21261663]
16. Kasraie S, Niebuhr M, Werfel T. Interleukin (IL)-31 activates signal transducer and activator of transcription (STAT)-1, STAT-5 and extracellular signal-regulated kinase 1/2 and down-regulates IL-12p40 production in activated human macrophages. *Allergy*. 2013; **68**: 739-47. [PMID: 23621408]
17. Horejs-Hoeck J, Schwarz H, Lamprecht S, Maier E, Hainzl S, Schmittner M, Posselt G, Stoecklinger A, Hawranek T, Duschl A. Dendritic cells activated by IFN-γ/STAT1 express IL-31 receptor and release proinflammatory mediators upon IL-31 treatment. J Immunol. 2012; **188**: 5319-26. [PMID: 22539792]
18. Nakashima C, Otsuka A, Kabashima K. Interleukin-31 and interleukin-31 receptor: New therapeutic targets for atopic dermatitis. *Exp Dermatol*. 2018; **27**: 327-331. [PMID: 29524262]
19. 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. [PMID: 23694808]
20. Maier E , Werner D , Duschl A, Bohle B , Horejs-Hoeck J. Human Th2 but not Th9 cells release IL-31 in a STAT6/NF-κB-dependent way. *J Immunol*. 2014; **193**: 645-54. [PMID: 24943220]
21. Maier E, Mittermeir M, Ess S, Neuper T, Schmiedlechner A, Duschl A, Horejs-Hoeck J. Prerequisites for Functional Interleukin 31 Signaling and Its Feedback Regulation by Suppressor of Cytokine Signaling 3 (SOCS3). *J Biol Chem*. 2015; **290**: 24747-59. [PMID: 26306032]
22. Niyonsaba F, Ushio H, Hara M, Yokoi H, Tominaga M, Takamori K, Kajiwara N, Saito H, Nagaoka I, Ogawa H, Okumura K. 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. [PMID: 20190140]
23. Raap U, Wichmann K, Bruder M, Ständer S, Wedi B, Kapp A, Werfel T. Correlation of IL-31 serum levels with severity of atopic dermatitis. *J Allergy Clin Immunol*. 2008; **122**: 421-3. [PMID: 18678344]
24. Ishii T , Wang J, Zhang W, Mascarenhas J, Hoffman R, Dai Y, Wisch N, Xu M. Pivotal role of mast cells in pruritogenesis in patients with myeloproliferative disorders. *Blood*. 2009; **113**: 5942-50. [PMID: 19196660]
25. Nikola Kunsleben, Urda Rüdrich, Manuela Gehring, Natalija Novak , Alexander Kapp, Ulrike Raap. 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. [PMID: 25789701]
26. Schmelz M, Schmidt R, Weidner C, Hilliges M, Torebjork HE, Handwerker HO. Chemical response pattern of different classes of C-nociceptors to pruritogens and algogens. *J Neurophysiol*. 2003; **89**: 2441-8. [PMID: 12611975]
27. Mollanazar NK, Smith PK, Yosipovitch G. Mediators of Chronic Pruritus in Atopic Dermatitis: Getting the Itch Out? *Clin Rev Allergy Immunol*. 2016; **51**: 263-292. [PMID: 25931325]
28. Moniaga CS, Jeong SK, Egawa G, Nakajima S, Hara-Chikuma M, Jeon JE, Lee SH, Hibino T, Miyachi Y, Kabashima K. Protease

activity enhances production of thymic stromal lymphopoietin and basophil accumulation in flaky tail mice. *Am J Pathol.* 2013; **182**: 841-51. [PMID: 23333753]
29. Wahlgren CF, Tengvall Linder M, Hägermark O, Scheynius A. Itch and inflammation induced by intradermally injected interleukin-2 in atopic dermatitis patients and healthy subjects. *Arch Dermatol Res.* 1995; 287: 572-80. [PMID: 7487145]
30. Gaspari AA, Lotze MT, Rosenberg SA, Stern JB, Katz SI. Dermatologic changes associated with interleukin 2 administration. *JAMA*. 1987; **258**: 1624-9. [PMID: 3306005]
31. Lee RE, Gaspari AA, Lotze MT, Chang AE, Rosenberg SA. Interleukin 2 and psoriasis. *Arch Dermatol.* 1988; **124**: 1811-5. [PMID: 3263840]
32. Kremer AE, Feramisco J, Reeh PW, Beuers U, Oude Elferink RP. Receptors, cells and circuits involved in pruritus of systemic disorders. *Biochim Biophys Acta.* 2014; 1842: 869-92. [PMID: 24568861]
33. Wahlgren CF, Scheynius A, Hägermark O. Antipruritic effect of oral cyclosporin A in atopic dermatitis. *Acta Derm Venereol*. 1990; **70**: 323-9. [PMID: 1977258]
34. Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. *J Clin Invest*. 2004; **113**: 651-7. [PMID: 14991059]
35. Hamid Q, Boguniewicz M, Leung DY. Differential in situ cytokine gene expression in acute versus chronic atopic dermatitis. *J Clin Invest.* 1994; **94**: 870-6. [PMID: 8040343]
36. Simon D, Braathen LR, Simon HU. Eosinophils and atopic dermatitis. *Allergy*. 2004; 59: 561-70. [PMID: 15147438]
37. Chan LS, Robinson N, Xu L. Expression of interleukin-4 in the epidermis of transgenic mice results in a pruritic inflammatory skin disease: an experimental animal model to study atopic dermatitis. *J Invest Dermatol*. 2001; 117: 977-83. [PMID: 11676841]
38. Zheng T, Oh MH, Oh SY, Schroeder JT, Glick AB, Zhu Z. Transgenic expression of interleukin-13 in the skin induces a pruritic dermatitis and skin remodeling. *J Invest Dermatol*. 2009; **129:** 742-51. [PMID: 18830273]
39. Oh M, Oh SY, Lu J, Lou H, Myers AC, Zhu Z, Zheng T. TRPA1-dependent pruritus in IL-13-induced chronic atopic dermatitis. *J Immunol.* 2013; **191**: 5371-82. [PMID: 24140646]
40. Beck LA, Thaçi D, Hamilton JD, Graham NM, Bieber T, Rocklin R, Ming JE, Ren H, Kao R, Simpson E, Ardeleanu M, Weinstein SP, Pirozzi G, Guttman-Yassky E, Suárez-Fariñas M, Hager MD, Stahl N, Yancopoulos GD, Radin AR. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med.* 2014; **371**:130-9. [PMID: 25006719]
41. Andoh T, Kuwazono T, Lee J, Kuraishi Y. Gastrin-releasing peptide induces itch-related responses through mast cell degranulation in mice. *Peptides* 2011; **32**: 2098-103. [PMID: 21933692]
42. Liu X, Wan L, Huo F, Barry DM, Li H, Zhao Z, Chen Z. B-type natriuretic peptide is neither itch-specific nor functions upstream of the GRP-GRPR signaling pathway. *Mol Pain* 2014; **10**: 4. [PMID: 24438367]
43. Sun YG, Zhao ZQ, Meng XL, Yin J, Liu XY, Chen ZF. Cellular basis of itch sensation. *Science.* 2009; **325**: 1531-4. [PMID: 19661382]
44. Sun YG, Chen ZF. A gastrin-releasing peptide receptor mediates the itch sensation in the spinal cord. *Nature.* 2007; **448**: 700-3. [PMID: 17653196]
45. Mishra SK, Hoon MA. The cells and circuitry for itch responses in mice. *Science*. 2013**; 340**: 968-71. [PMID: 23704570]
46. Akiyama T, Tominaga M, Takamori K, Carstens MI, Carstens E. Role of spinal bombesin-responsive neurons in nonhistaminergic itch. *J Neurophysiol.* 2014; **112**: 2283-9. [PMID: 25122701]
47. Kagami S, Sugaya M, Suga H, Morimura S, Kai H, Ohmatsu H, Fujita H, Tsunemi Y, Sato S. Serum gastrin-releasing peptide levels correlate with pruritus in patients with atopic dermatitis. *J Invest Dermatol.* 2013; **133**: 1673-5. [PMID: 23353988]
48. Schmelz M, Schmidt R, Bickel A, Handwerker HO, Torebjörk HE. Specific C-receptors for itch in human skin. *J Neurosci*. 1997; **17**: 8003-8. [PMID: 9315918]
49. Twycross R, Greaves MW, Handwerker H, Jones EA, Libretto SE, Szepietowski JC, Zylicz Z. Itch: scratching more than the surface. *QJM*. 2003; **96**: 7-26. [PMID: 12509645]
50. Benarroch EE, Low PA. The acetylcholine-induced flare response in evaluation of small fiber dysfunction. *Ann Neurol*. 1991; **29**: 590-5. [PMID: 1892361]
51. Rukwied R, Lischetzki G, McGlone F, Heyer G, Schmelz M. Mast cell mediators other than histamine induce pruritus in atopic dermatitis patients: a dermal microdialysis study. *Br J Dermatol.* 2000; **142**: 1114-20. [PMID: 10848733]
52. Heyer GR, Hornstein OP. Recent studies of cutaneous nociception in atopic and non-atopic subjects. *J Dermatol.* 1999; **26**: 77-86. [PMID: 10091477]
53. Elenkov I. Glucocorticoids and the **Th1**/**Th2** balance. *J.Ann N Y Acad Sci.* 2004; **1024**: 138-46. [PMID: 15265778]
54. Shim WS, Tak MH, Lee MH, Kim M, Kim M, Koo JY, Lee CH, Kim M, Oh U. TRPV1 mediates histamine-induced itching via the activation of phospholipase A2 and 12-lipoxygenase. *J Neurosci.* 2007; **27**: 2331-7. [PMID: 17329430]
55. Benditt EP, Bader S, Lam KB. Studies of the mechanism of acute vascular reactions to injury. I. The relationship of mast cells and histamine to the production of edema by ovomucoid in rats. *AMA Arch Pathol.* 1955; **60**: 104-15. [PMID: 14387365]
56. Simons FE, Simons KJ. Histamine and H1-antihistamines: celebrating a century of progress. *J Allergy Clin Immunol*. 2011; **128**: 1139-1150. [PMID: 22035879]
57. Han SK, Mancino V, Simon MI. Phospholipase Cbeta 3 mediates the scratching response activated by the histamine H1 receptor on C-fiber nociceptive neurons. *Neuron*. 2006; **52**: 691-703. [PMID:17114052]
58. Rossbach K, Wendorff S, Sander K, Stark H, Gutzmer R, Werfel T, Kietzmann M, Bäumer W. Histamine H4 receptor antagonism reduces hapten-induced scratching behaviour but not inflammation. *Exp Dermatol* 2009; **18**: 57-63. [PMID: 18647342]
59. Cowden JM, Zhang M, Dunford PJ, Thurmond RL. The histamine H4 receptor mediates inflammation and pruritus in Th2-dependent dermal inflammation. *J Invest Dermatol*. 2010; **130**: 1023-33. [PMID: 19907432]
60. Felipe CD, Herrero JF, O'Brien JA, Palmer JA, Doyle CA, Smith AJ, Laird JM, Belmonte C, Cervero F, Hunt SP. Altered nociception, analgesia and aggression in mice lacking the receptor for substance P. *Nature.*1998; **392**:394-7. [PMID: 953732]
61. Church MK, Okayama Y, el-Lati S. Mediator secretion from human skin mast cells provoked by immunological and non-immunological stimulation. *Skin Pharmacol.*1991; **4** Suppl 1:15-24. [PMID: 1722414]
62. Hägermark O, Hökfelt T, Pernow B. Flare and itch induced by substance P in human skin. *J Invest Dermatol.*1978; **71**: 233-5. [PMID: 81243]
63. Fjellner B, Hägermark O. Studies on pruritogenic and histamine-releasing effects of some putative peptide neurotransmitters. *Acta Derm Venereol.* 1981; **61**: 245-50. [PMID: 6167109]
64. Jorizzo JL, Coutts AA, Eady RA, Greaves MW. Vascular responses of human skin to injection of substance P and mechanism of action. *Eur J Pharmacol.* 1983; **87**: 67-76. [PMID: 6188619]
65. van der Kleij HP, Ma D, Redegeld FA, Kraneveld AD, Nijkamp FP, Bienenstock J. Functional expression of neurokinin 1 receptors on mast cells induced by IL-4 and stem cell factor. *J Immunol.* 2003; **171**: 2074-9. [PMID: 12902513]
66. Luger TA. Neuromediators--a crucial component of the skin immune system. *J Dermatol Sci.* 2002; **30**: 87-93. [PMID: 12413763]
67. Steinhoff M, Ständer S, Seeliger S, Ansel JC, Schmelz M, Luger

T. Modern aspects of cutaneous neurogenic inflammation. *Arch Dermatol*. 2003; **139**: 1479-88. [PMID: 14623709]
68. Paus R, Theoharides TC, Arck PC. Neuroimmunoendocrine circuitry of the 'brain-skin connection'. *Trends Immunol.* 2006; 27: 32-9. [PMID: 16269267]
69. Furutani K, Koro O, Hide M, Yamamoto S. Substance P- and antigen-induced release of leukotriene B4, prostaglandin D2 and histamine from guinea pig skin by different mechanisms in vitro. *Arch Dermatol Res*. 1999; **291**: 466-73. [PMID: 10482019]
70. Bíró T, Tóth BI, Marincsák R, Dobrosi N, Géczy T, Paus R. TRP channels as novel players in the pathogenesis and therapy of itch. *Biochim Biophys Acta.* 2007; **1772**: 1004-21. [PMID: 17462867]
71. Kulka M, Sheen CH, Tancowny BP, Grammer LC, Schleimer RP. Neuropeptides activate human mast cell degranulation and chemokine production. *Immunology*. 2008; **123**: 398-410. [PMID: 17922833]
72. Abadía Molina F, Burrows NP, Jones RR, Terenghi G, Polak JM. Increased sensory neuropeptides in nodular prurigo: a quantitative immunohistochemical analysis. *Br J Dermatol.* 1992; **127**: 344-51. [PMID: 1419754]
73. Järvikallio A, Harvima IT, Naukkarinen A. Mast cells, nerves and neuropeptides in atopic dermatitis and nummular eczema. *Arch Dermatol Res*. 2003; **295**: 2-7. [PMID: 12709813]
74. Salomon J, Baran E. The role of selected neuropeptides in pathogenesis of atopic dermatitis. *J Eur Acad Dermatol Venereol.* 2008; **22**: 223-8. [PMID: 18211417]
75. Kanda N, Watanabe S. Histamine enhances the production of nerve growth factor in human keratinocytes. *J Invest Dermatol.* 2003; **121**: 570-7. [PMID: 12925217]
76. Dou YC, Hagströmer L, Emtestam L, Johansson O. Increased nerve growth factor and its receptors in atopic dermatitis: an immunohistochemical study. *Arch Dermatol Res*. 2006; **298**: 31-7. [PMID: 16586073]
77. Nockher WA, Renz H. Neurotrophins in allergic diseases: from neuronal growth factors to intercellular signaling molecules. *J Allergy Clin Immunol.* 2006; **117**: 583-9. [PMID: 16522457]
78. Verge VM, Richardson PM, Wiesenfeld-Hallin Z, Hökfelt T. Differential influence of nerve growth factor on neuropeptide expression in vivo: a novel role in peptide suppression in adult sensory neurons. *J Neurosci.* 1995; **15**: 2081-96. [PMID: 7534343]
79. Feld M, Garcia R, Buddenkotte J, Katayama S, Lewis K, Muirhead G, Hevezi P, Plesser K, Schrumpf H, Krjutskov K, Sergeeva O, Müller HW, Tsoka S, Kere J, Dillon SR, Steinhoff M, Homey B. The pruritus- and TH2-associated cytokine IL-31 promotes growth of sensory nerves. *J Allergy Clin Immunol.* 2016; **138**: 500-508. [PMID: 27212086]
80. Kasutani K, Fujii E, Ohyama S, Adachi H, Hasegawa M, Kitamura H, Yamashita N. Anti-IL-31 receptor antibody is shown to be a potential therapeutic option for treating itch and dermatitis in mice. *Br J Pharmacol*. 2014; **171**: 5049-58. [PMID: 24946165]
81. Dillon SR, Sprecher C, Hammond A, Bilsborough J, Rosenfeld-Franklin M, Presnell SR, Haugen HS, Maurer M, Harder B, Johnston J, Bort S, Mudri S, Kuijper JL, Bukowski T, Shea P, Dong DL, Dasovich M, Grant FJ, Lockwood L, Levin SD, LeCiel C, Waggie K, Day H, Topouzis S, Kramer J, Kuestner R, Chen Z, Foster D, Parrish-Novak J, Gross JA. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. *Nat Immunol*. 2004; **5**: 752-60. [PMID: 15184896]
82. Grimstad O, Sawanobori Y, Vestergaard C, Bilsborough J, Olsen UB, Grønhøj-Larsen C, Matsushima K. Anti-interleukin-31-antibodies ameliorate scratching behaviour in NC/Nga mice: a model of atopic dermatitis. *Exp Dermatol.* 2009; **18**: 35-43. [PMID: 19054054]
83. Feld M, Garcia R, Buddenkotte J, Katayama S, Lewis K, Muirhead G, Hevezi P, Plesser K, Schrumpf H, Krjutskov K, Sergeeva O, Müller HW, Tsoka S, Kere J, Dillon SR, Steinhoff M, Homey B. The pruritus- and TH2-associated cytokine IL-31 promotes growth of sensory nerves. *J Allergy Clin Immunol.* 2016; **138**: 500-508. [PMID: 27212086]
84. Furue M, Yamamura K, Kido-Nakahara M, Nakahara T, Fukui Y. Emerging role of interleukin-31 and interleukin-31 receptor in pruritus in atopic dermatitis. *Allergy*. 2018; **73**: 29-36. [PMID: 28670717]
85. Gonzales AJ, Humphrey WR, Messamore JE, Fleck TJ, Fici GJ, Shelly JA, Teel JF, Bammert GF, Dunham SA, Fuller TE, McCall RB. Interleukin-31: its role in canine pruritus and naturally occurring canine atopic dermatitis. *Vet Dermatol.* 2013; **24**: 48-53. [PMID: 23331679]
86. Lewis KE, Holdren MS, Maurer MF, Underwood S, Meengs B, Julien SH, Byrnes-Blake KA, Freeman JA, Bukowski TR, Wolf AC, Hamacher NB, Rixon MW, Dillon SR. 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**: 142-150. [PMID: 27501029]
87. Oyama S, Kitamura H, Kuramochi T, Higuchi Y, Matsushita H, Suzuki T, Goto M, Adachi H, Kasutani K, Sakamoto A, Iwayanagi Y, Kaneko A, Nanami M, Fujii E, Esaki K, Takashima Y, Shimaoka S, Hattori K, Kawabe Y. Cynomolgus monkey model of interleukin-31-induced scratching depicts blockade of human interleukin-31 receptor A by a humanized monoclonal antibody. *Exp Dermatol*. 2018; **27**: 14-21. [PMID: 27714851]
88. Kabashima K, Furue M, Hanifin JM, Pulka G, Wollenberg A, Galus R, Etoh T, Mihara R, Nakano M, Ruzicka T. Nemolizumab in patients with moderate-to-severe atopic dermatitis: Randomized, phase II, long-term extension study. *J Allergy Clin Immunol*. 2018; **142**: 1121-1130. [PMID: 29753033]
89. Silverberg JI, Pinter A, Pulka G, Poulin Y, Bouaziz JD, Wollenberg A, Murrell DF, Alexis A, Lindsey L, Ahmad F, Piketty C, Clucas A. Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus. *J Allergy Clin Immunol.* 2020; **145**: 173-182. [PMID: 31449914]
90. Seike M, Takata T, Ikeda M, Kodama H, Terui T, Ohtsu H. Histamine helps development of eczematous lesions in experimental contact dermatitis in mice. *Arch Dermatol Res.* 2005; **297**: 68-74. [PMID: 15902480]
91. Seike M, Furuya K, Omura M, Hamada-Watanabe K, Matsushita A, Ohtsu H. Histamine H4 receptor antagonist ameliorates chronic allergic contact dermatitis induced by repeated challenge. *Allergy*. 2010; **65**: 319-326. [PMID: 19886918]
92. Matsushita A, Seike M, Okawa H, Kadawaki Y, Ohtsu H. Advantages of histamine H4 receptor antagonist usage with H1 receptor antagonist for the treatment of murine allergic contact dermatitis. *Exp Dermatol.* 2012; **21**: 714-5. [PMID: 22897580]
93. Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. Science 2003; **299**: 1057-1061. [PMID: 12522256]
94. Ring S, Schäfer SC, Mahnke K, Lehr HA, Enk AH. CD4+CD25+ regulatory T cells suppress contact hypersensitivity reactions by blocking influx of effector T cells into inflamed tissue. *Eur J Immunol,* 2006:**36**: 2981-2992. [PMID: 17048272]
95. Fantini MC, Becker C, Monteleone G, Pallone F, Galle PR, Neurath MF. Cutting edge: TGF-beta induces a regulatory phenotype in CD4+CD25- T cells through Foxp3 induction and down-regulation of Smad7. *J Immuno, l* 2004; **172**: 5149-5153. [PMID: 15100250]
96. Tamaka K, Seike M, Hagiwara T, Sato A, Ohtsu H. Histamine suppresses regulatory T cells mediated by TGF-β in murine chronic allergic contact dermatitis. *Exp Dermatol*, 2015; **24**: 280-284. [PMID: 25651189]
97. Seike M, Ikeda M, Kodama H, Terui T, Ohtsu H. Inhibition of scratching behavior caused by contact dermatitis in histidine decarboxylase gene knockout mice. *Exp Dermatol*,14; 2005: 169-175. [PMID: 15740588]
98. Köchling H, Schaper K, Wilzopolski J, Gutzmer R, Werfel T,

Bäumer W, Kietzmann M, Rossbach K. Combined treatment with H1 and H4 receptor antagonists reduces inflammation in a mouse model of atopic dermatitis. *J Dermatol Sci,* 2017; **87**: 130-137. [PMID: 28495120]