

Pruritus in allergy and immunology



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Activity Objectives:

1. To recognize that histaminergic pathways do not completely explain the pathophysiology of chronic itch and that antihistamines are often ineffective.
2. To differentiate the various nonhistaminergic pathways involving monoamines, cytokines, ion channels, intracellular signaling pathways, and receptors on keratinocytes, neurons, and immune cells that are involved in generating the sensation of chronic itch.
3. To compare the shared mechanisms behind itch in allergic (chronic spontaneous urticaria, atopic dermatitis, and allergic contact dermatitis) and nonallergic (chronic pruritus of unknown origin and prurigo nodularis) conditions.
4. To evaluate the mechanisms behind new targeted therapies that are being developed and studied, including those blocking interleukins, histamine H4 receptor, Janus kinases, and neuropeptides.

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Although evolutionarily conserved to expel ectoparasites and aid in the clearance of toxins and noxious environmental stimuli from the host, the type 2 immune response can become pathologic in the setting of a variety of allergic disorders. Itch can be a behavioral extension of type 2 immunity by evoking scratching and, in the setting of disease, can become chronic and thus highly pathologic as well. Classically, our understanding of itch mechanisms has centered around the canonical IgE–mast cell–histamine axis. However, therapies aimed at blocking the histaminergic itch pathway have been largely ineffective, suggesting the existence of nonhistaminergic itch pathways.

Indeed, recent advances in itch biology have provided critical new insight into a variety of novel therapeutic avenues for chronic itch in the setting of a number of allergic disorders. Here we highlight how these new developments will likely inform the problem of pruritus in a variety of well-established and emerging conditions in the field of allergy. (*J Allergy Clin Immunol* 2019;144:353-60.)

Key words: Allergic contact dermatitis, atopic dermatitis, cytokine, eczema, histamine, itch, Janus kinase, mast cell, Mas-related G protein–coupled receptor, neuroimmunology, prurigo nodularis, pruritus

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Abbreviations used

ACD:	Allergic contact dermatitis
AD:	Atopic dermatitis
CPUO:	Chronic pruritus of unknown origin
CSU:	Chronic spontaneous urticaria
FDA:	US Food and Drug Administration
H4R:	Histamine receptor 4
JAK:	Janus kinase
Mrgpr:	Mas-related G protein–coupled receptor
NK-1R:	Neurokinin-1 receptor
Nppb:	Natriuretic peptide B
PN:	Prurigo nodularis
TSLP:	Thymic stromal lymphopoietin

Pruritus, or itch, is a highly conserved sensation that evokes the desire to scratch. In its acute form it aids in the host's ability to expel ectoparasites, toxins, and noxious environmental substances. However, in its chronic form, itch is generally pathologic and underlies a wide variety of medical disorders.

Chronic pruritus, defined as itch lasting greater than 6 weeks, is associated with a number of medical conditions, including inflammatory skin disorders, such as atopic dermatitis (AD); malignancies, including various leukemias and lymphomas; chronic kidney and hepatobiliary disease; endocrine disorders, such as hyperthyroidism and diabetes; and primary neuropathic disorders, such as brachioradial pruritus and postherpetic itch. Despite its association with so many medical disorders and afflicting approximately 15% of the population,^{1,2} efficacious therapies remain very limited. However, recent advances in our understanding of novel itch-sensory pathways, particularly in patients with AD, have brought new insight into how new therapies can be developed to specifically target symptoms of itch in patients.^{3,4}

The purpose of the current review is to highlight how new understanding of the pathophysiology of itch broadens our perspective of how chronic pruritic conditions might fall within the family of allergic disorders. First, starting with our classical understanding of histaminergic itch in patients with urticaria, we delve into how new molecular and cellular insights into the basis of nonhistaminergic itch in patients with AD inform our understanding of itch in the context of the broader field of allergy. Second, we will discuss new and emerging pathways and therapeutics across a number of chronic itch conditions. Finally, throughout the course of this review, we will introduce more recently recognized chronic itch disorders that likely share pathophysiology with well-defined allergic disorders (for more comprehensive reviews on chronic itch, see several previous reviews^{5–8}). Collectively, we highlight and underscore how a variety of chronic itch conditions, both well defined and more recently recognized, fall well within the realm of clinical allergy and immunology.

CLASSICAL HISTAMINERGIC ITCH AND BEYOND

Classically, the most well-defined form of itch is histamine-mediated or histaminergic itch (Fig 1). A defining feature of type I hypersensitivity, histamine is released from mast cells after IgE-mediated activation through its cell-surface high-affinity receptor, FcεRI. Upon degranulation of mast cells in close proximity to itch-sensory nerve fibers in the skin, a

variety of itch-inducing molecules or pruritogens, including histamine, are released and bind their respective receptors on terminal axons. This triggers the opening of nonspecific cation channels, such as transient receptor potential A1 (TRPA1), transient receptor potential V1 (TRPV1), or both, resulting in membrane depolarization and subsequent activation of an action potential by voltage-gated ion channels, such as Na_v1.7 and Na_v1.8. Itch-sensory signals are relayed through unmyelinated and slow-conducting C-fibers to their respective cell bodies in the dorsal root ganglia and subsequently transmitted to the dorsal horn of the spinal cord in the central nervous system and ultimately to the brain, where these signals are perceived as itch. Although the IgE–mast cell–histamine axis has been well understood for decades, this pathway has proved disappointing as a target for most chronic itch disorders.

Pruriceptors, or itch-specific sensory neurons, are now recognized as a distinct class of neurons that transmit itch signals. Recent discoveries of novel itch-mediating molecules, such as the gastrin-releasing peptide receptor,⁹ Mas-related G protein–coupled receptor (Mrgpr) family,^{10,11} natriuretic peptide B (Nppb),^{12,13} and various itch-mediating cytokine receptors, have generated tremendous interest in understanding how new and emerging pathways can be targeted for the treatment of various chronic itch disorders (Fig 2). Although all of these pathways demonstrate mechanisms independent from other sensations, such as pain, further work is needed to assess how these various pathways might be distinct, interdependent, or synergistic in the context of various chronic itch conditions.

CHRONIC SPONTANEOUS URTICARIA

Urticaria is characterized by pruritic wheals or hives on the skin that typically last for 24 hours or less and often migrate. The causes can be numerous, including allergic reactions (eg, medications), mechanical stimulation, autoimmunity, or simply idiopathic. In the setting of acute urticaria, it is well understood that activation of IgE by putative antigens results in activation of mast cells (and basophils) and release of preformed mediators, the most important being histamine. This process results in elicitation of hives and associated histaminergic itch that is often responsive to antihistamines. However, when urticaria is chronic and occurs for a period of greater than 6 weeks, it is described as chronic spontaneous urticaria (CSU), and its associated chronic itch becomes more difficult to manage.

In contrast to acute urticaria, antihistamines often demonstrate even less efficacy in patients with CSU.¹⁴ These observations provoke the hypothesis that, although histamine is a major component of urticarial itch, there are likely histamine-independent pathways that also mediate chronic itch in this context. Mast cells can also synthesize and release other mediators, including eicosanoids, such as prostaglandin D₂ and leukotriene C₄, D₄, and E₄. Leukotriene receptor antagonists have not been shown to be superior to placebo or antihistamine therapy in the treatment of CSU. However, the combination of a leukotriene receptor antagonist and antihistamines appear to be more effective than antihistamine alone.¹⁵

In the context of CSU, there are also other well-recognized immunologic stimuli that can degranulate mast cells through the IgE receptor, including IgG antibodies to IgE (5% to 10% of patients) or FcεRI (30% to 40% of patients).¹⁶ Whether alternative modes of IgE-mediated activation result in differential

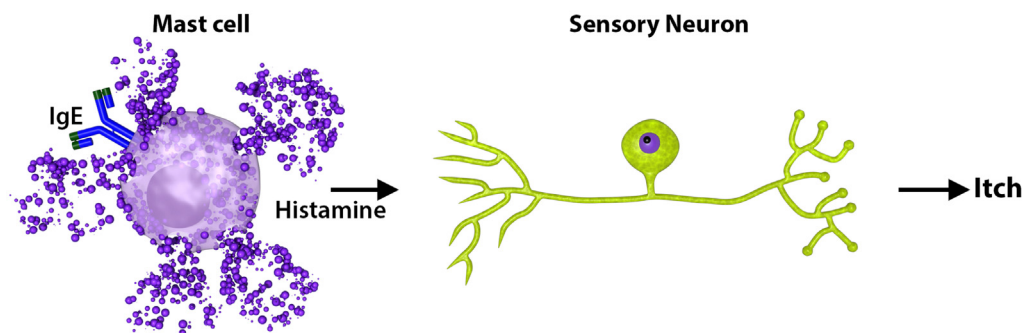


FIG 1. Classic histaminergic itch pathway. Mast cell degranulation through IgE activation of FcεRI releases histamine to activate itch-sensory neurons.

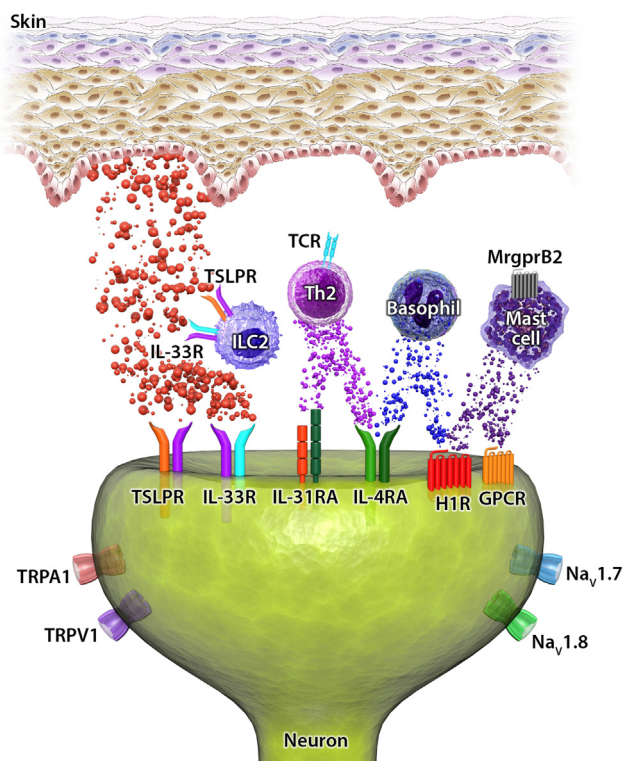


FIG 2. The neuroimmune axis in itch biology. A complex interplay of molecular signals and receptors on immune cells and neurons drives itch. Key immune cells and their associated cytokines include group 2 innate lymphoid cells (ILC2; TSLP and IL-33 responsive), Th2 cells (effector cytokines IL-4/13 and IL-31), basophils (effector molecules IL-4/13 and histamine), and mast cells (effector molecules tryptase, serotonin, and histamine). Activation of cytokine receptors, ion channels, and gastrin-releasing peptide receptors drive itch-specific signals on sensory neurons. The image was created with BioRender. *IL-4RA*, IL-4 receptor A; *IL-31R*, IL-31 receptor; *IL-33R*, IL-33 receptor; *Na_v*, voltage-gated sodium channel; *TRPA1*, transient receptor potential A1; *TRPV1*, transient receptor potential V1; *TSLPR*, thymic stromal lymphopoietin receptor.

release of pruritogens remains to be explored. Additionally, it is important to note that other cell types have also been implicated, as evidenced by the presence of eosinophils, neutrophils, and lymphocytes in urticarial skin lesions on histology. However, their pathogenic roles in patients with CSU have yet to be fully elucidated. In terms of itch, future studies will be required to fully define the pruritogenic pathways that underlie both acute and chronic urticaria.

Notwithstanding our limited understanding of itch in patients with urticaria, H1 antagonist antihistamines remain a first-line treatment. Of the 4 histamine receptors, histamine receptor 1 and, more recently, histamine receptor 4 (H4R) have been implicated in itch.¹⁷ Although H1 antihistamines are used for both acute urticaria and CSU, the presence of other receptors on sensory neurons, such as H4R, suggests that there might be additional mechanisms by which histamine can mediate itch in patients with urticaria.¹⁸ Furthermore, H4R is also expressed on mast cells, indicating that there might be additional indirect mechanisms by which mast cells can be stimulated to release pruritogens. Indeed, a recent clinical trial with an H4 antagonist demonstrated significant reduction in histamine-induced pruritus with no effect on wheal formation (JNJ 39758979).¹⁹ Thus, future studies with newer-generation antihistamines (ie, H4R antagonists) will be required to better determine the role of histamine in urticarial itch.

Although H1 antihistamines are first-line therapy in the treatment of urticaria, many patients do not respond and have persistent hives and itching. In this setting, patients with CSU will often require additional mast cell–targeted therapy, namely omalizumab, which blocks IgE and prevents its binding to FcεRI on mast cells and basophils.^{20–23} Although this likely results in reduced histamine release, the observation that omalizumab improves symptoms in many patients who are refractory to antihistamines suggests that other mast cell–derived factors might also be involved in mediating histamine-independent itch. Additionally, patients with CSU treated with omalizumab show differential response patterns characterized into “fast” responders (60% to 70% of patients who demonstrate a complete response in 3–7 days), “slow” responders (10% to 20% of patients who respond in 3–5 months), and nonresponders (10% to 20% of patients), suggesting different pathogenic mechanisms in CSU.²⁴ Furthermore, recent seminal work uncovering the role of Mrgprb2 as a key receptor that mediates IgE-independent mast cell activation suggests that other modalities can also be important in mediating urticarial itch.^{25–27} However, future studies will be required to determine the precise role of Mrgprb2 in patients with urticaria and CSU.

AD

AD is a common chronic and relapsing inflammatory skin disorder characterized by intense pruritus and scaly red rashes involving classic locations (cheeks and extensor extremities in infants and flexural sites in children and adults). It typically

presents during infancy and can persist into adulthood.²⁸ In addition to localized skin lesions, patients with AD can exhibit systemic immune dysregulation, as demonstrated by peripheral eosinophilia and increased serum IgE levels.^{29,30} Furthermore, AD is a clear risk factor for the development of asthma and food allergy. Like these other atopic disorders, AD is associated with increased expression of epithelial cell–derived cytokines, such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) from the epithelial barrier, and enhanced adaptive T_H2 cell and innate basophil, eosinophil, mast cell, and group 2 innate lymphoid cell responses.³¹ Collectively, these processes result in increased production of the effector cytokines IL-4, IL-5, and IL-13, which orchestrate the overall allergic cutaneous immune response in patients with AD.

Beyond skin inflammation, recent studies have begun to unveil how the immune system interacts with the sensory nervous system to evoke symptoms of itch. Although AD is associated with enhanced mast cell activation and histamine release, H1 antihistamines are largely ineffective for the treatment of AD-associated itch. Thus, clinical trials are currently underway to investigate the effects of H4 antihistamines for the treatment of AD and its resulting itch (NCT03517566). Notwithstanding this, the first cytokine to be identified as a pruritogen was found to be produced by T_H2 cells in the context of AD, namely IL-31.³² Indeed, phase 2 clinical trials with nemolizumab, an anti-IL-31 receptor (IL-31 receptor A) blocking mAb, have recently demonstrated antipruritic efficacy in patients with AD.³³ Additionally, epithelial cell–derived cytokines, such as TSLP and IL-33, which are upstream of type 2 cellular responses, have also been shown to directly stimulate itch-sensory neurons *in vivo*,^{34,35} and anti-TSLP (tezepelumab) and anti-IL-33 (etokimab) mAbs are also being explored in clinical trials for AD.³⁶ Collectively, these studies will provide novel insight into the antipruritic properties of blocking specific signals at the skin-neuroimmune interface.

Dupilumab is the first US Food and Drug Administration (FDA)–approved mAb for the treatment of AD and targets IL-4 receptor α to block both IL-4 and IL-13 signaling.³⁷ We recently identified that IL-4 receptor α is expressed on sensory neurons and critically regulates itch responses *in vivo* in a murine model of AD-like disease. In contrast to IL-31 and TSLP, rather than acting as pruritogens, it appears that IL-4 and IL-13 regulate itch on neurons by promoting neuronal hypersensitivity to a variety of pruritogens.³⁸ Beyond dupilumab, clinical trials are underway for anti-IL-13 mAbs, including tralokinumab and lebrikizumab, with tralokinumab significantly improving AD-associated itch.^{39,40} Ultimately, it remains to be determined which cytokines are the most potent targets for selectively targeting AD-associated itch, and this will be revealed in ongoing clinical investigations.

In lymphocytes, a number of AD-associated cytokines are dependent on Janus kinase (JAK)–signal transducer and activator of transcription signaling for their effects on cellular transcription and activation.⁴¹ Indeed, a number of both topical and systemic JAK inhibitors are in development for the treatment of AD and related conditions. Phase 2 clinical trials with topical tofacitinib (JAK1/3 inhibitor), JTE-052 (pan-JAK inhibitor), and ruxolitinib (JAK1/2 inhibitor) have demonstrated efficacy, with rapid effects on the resolution of itch.^{42–45} In recent studies we have identified that neuronal JAK1 signaling is a critical regulator of AD-associated itch *in vivo* and that JAK inhibitors likely have neuromodulatory properties.³⁸ In addition to the studies with topical JAK inhibitors, oral JAK1-selective inhibitors

(upadacitinib and PF-04965842) are in clinical trials for the treatment of AD and are demonstrating potent anti-itch effects as well (NCT02780167).⁴⁶ Baricitinib, a JAK1/2 inhibitor, was also able to improve AD rash in addition to AD-associated pruritus in a phase 2 trial.⁴⁷ Collectively, these studies are rapidly paving the way for the development of FDA-approved JAK inhibitors for the treatment of AD and already demonstrating the unique antipruritic properties of these agents.

In contrast to urticaria, it is well established now that AD-associated itch is largely nonhistaminergic in nature. Indeed, a number of cytokines, mostly those associated with the type 2 immune response (eg, IL-4, IL-13, IL-31, IL-33, and TSLP), have been implicated in mediating both inflammation and neurophysiologic itch in the context of AD. Recent advances in our understanding of the neuroimmune basis of AD-associated itch have emboldened the development of new treatments for AD and also provoked the hypothesis that other immunologically related disorders might also be amenable to similar therapeutic interventions.

PRURIGO NODULARIS

Prurigo nodularis (PN) is classically described as a neurodermatosis, meaning that the underlying itch is believed to drive the development of the rash, which is typically characterized by multiple dome-shaped hyperkeratotic nodules. These nodules are distributed symmetrically on extensor surfaces of the extremities and areas of the torso where one can reach and scratch (hence the midback is commonly spared); however, the flexural surfaces, palms, soles, face, and groin are rarely affected (Fig 3). Intense pruritus and chronic repetitive scratching, rubbing, or picking are observed.⁴⁸

PN presents in the context of a number of systemic diseases, including chronic kidney disease and HIV, but can also manifest independently.^{49–51} Strikingly, 50% of patients with PN exhibit atopy as a comorbid entity.

Although exhibiting distinct clinical features, even in the context of AD, PN has demonstrated similar pathologic features to AD. First, both conditions are associated with histologic features of hyperkeratosis and a mixed dermal inflammatory infiltrate commonly composed of lymphocytes, neutrophils, mast cells, and occasional eosinophils.⁵² Second, both conditions have been associated with increased expression of IL-31 within the lesions.⁵³ Third, as in patients with AD, PN lesions are noted to have increased density of nerve fibers innervating the skin.^{54,55}

Although a distinct clinical entity, given the common copresentation with AD and its shared pathologic features, it is likely that PN will respond to a number of therapeutics that are currently being explored or used in the setting of AD. Indeed, as with AD, a phase 2 clinical trial with nemolizumab was recently completed (NCT03181503), and clinical trials are currently underway with KPL-716 (NCT03816891), an oncostatin M receptor β antagonist, which would also limit IL-31 signaling by disrupting oncostatin M receptor β –IL-31 receptor A interactions. Furthermore, a recent case series using dupilumab to treat PN demonstrated a reduction in pruritus and prurigo lesion sizes after 12 weeks in all 3 patients who underwent treatment.⁵⁶ Taken together, these developments suggest that a number of AD-associated therapies will likely be directed at PN in the near future.

Notwithstanding the shared characteristics between the 2 conditions, there is empiric evidence to suggest that PN might



FIG 3. PN. Itchy hyperkeratotic nodules distributed on the extensor forearm (*right*), classically described as a neurodermatosis.

be more of a neurodermatosis than AD. Indeed, the neurokinin-1 receptor (NK-1R) antagonist serlopitant, which blocks binding of substance P to NK-1R on a variety of neurons, has been found in phase 2 clinical trials to be effective in the context of PN, whereas both primary and secondary end points were not met in patients with AD.⁵⁷ Taken together, these findings suggest that the neuromodulatory effects of NK-1R antagonism preferentially affect PN rather than AD. Thus, future studies will be required to define what features are truly similar and divergent between patients with PN and those with AD.

CHRONIC PRURITUS OF UNKNOWN ORIGIN

Chronic pruritus of unknown origin (CPUO), also referred to as chronic idiopathic pruritus or pruritus of the elderly, presents as generalized pruritus with no clearly defined cause. These patients typically do not exhibit a rash but are widely believed to have a type 2 immune profile.⁵⁸ Indeed, we have shown that these patients can have increased eosinophils in the dermis and in the blood, and can also exhibit mild increases in serum IgE levels.⁵⁹ Additionally, transcriptional profiling of CPUO skin demonstrated a distinct but similar profile to lesional AD skin.³⁸ However, in contrast to AD, although patients with CPUO exhibit a type 2 immune profile, they are believed to have milder systemic inflammation and do not typically have a history of atopic disease. Furthermore, similar to PN, no FDA-approved medications exist for the treatment of CPUO.

It is hypothesized that patients with CPUO have sensory neuronal dysfunction that potentiates the effects of type 2 inflammation to drive itch. Based on this hypothesis we examined whether patients who are refractory to conventional anti-inflammatory or immunosuppressive treatments would respond to the neuromodulatory properties of JAK inhibitors.

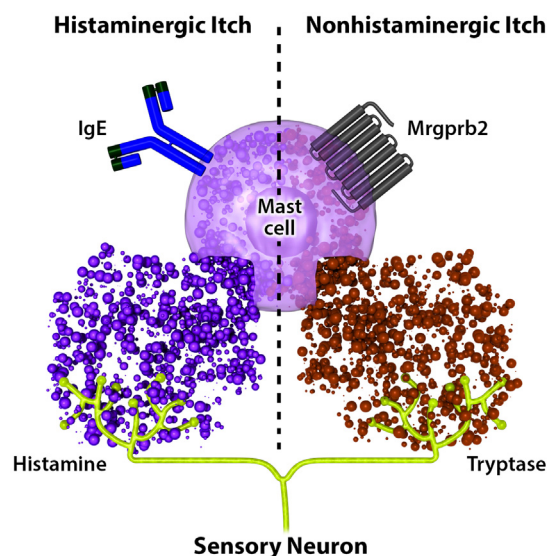


FIG 4. Histamine-dependent and histamine-independent itch pathways of mast cells. Mast cells can be activated by classic IgE-mediated release of histamine (*left*) or by Mrgprb2 activation and subsequent release of distinct effector molecules (eg, tryptase; *right*). The image was created with BioRender.

Indeed, in a nonrandomized proof-of-concept study we found that patients with CPUO responded to systemic tofacitinib.³⁸ Thus, larger randomized studies will be required to fully establish the efficacy of these agents in patients with CPUO. Beyond JAK inhibition, based on the success of serlopitant for chronic pruritus,⁶⁰ a phase 2 clinical trial is currently underway for its use in CPUO (NCT03841331). Given that patients with CPUO often present with disproportionate itch relative to skin inflammation, it will be interesting to see how such neuro-modulators influence itch in this context. Due to the highly unmet nature of this condition, additional insight into its pathogenesis is urgently needed to better address current treatment gaps.

ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis (ACD) is an itchy eczematous reaction of the skin that occurs hours to days after coming into contact with an allergen. Unlike irritant contact dermatitis, which results from an irritant chemical causing a direct toxic effect on the skin, ACD is a delayed type IV hypersensitivity reaction to a hapten or antigen.⁶¹ Unlike other hypersensitivity reactions, ACD is not dependent on antibodies but relies on a T_H1 response to an antigen presented by an antigen-presenting cell. It is dependent on 2 phases: the induction phase, whereby the immune system is sensitized to an antigen, and the elicitation phase, whereby the immune response is triggered on rechallenge of the allergen.⁶² Common allergens include metals (eg, nickel), plants (eg, poison ivy), topical medications (eg, neomycin), and household products (eg, formaldehyde and fragrance mix). Although irritant contact dermatitis and ACD are often difficult to distinguish from each other, patch testing is the gold standard test to determine culprit allergens that favor a diagnosis of ACD.^{62,63}

The mainstay of ACD treatment is allergen avoidance, which is often challenging given that minute amounts of allergen exposure can be enough to trigger a reaction. After complete avoidance of an allergen, resolution might take 6 weeks or longer because the

TABLE I. Emerging therapeutics for chronic pruritus in patients with allergic skin disorders

Target	Source	Therapeutics (target)	Disorder
IL-4	T _H 2 cells, basophils, MCs, ILC2s	Dupilumab (IL-4RA)	AD
IL-13	T _H 2 cells, basophils, ILC2s	Dupilumab (IL-4RA) Tralokinumab (IL-13) Lebrikizumab (IL-13)	AD
IL-33	KCs	Etokimab (IL-33)	AD ACD
TSLP	KCs	Tezepelumab (TSLP)	AD
IL-31	T _H 2 cells	Nemolizumab (IL-31RA)	AD PN
IgE	Plasma cells	Omalizumab (IgE)	CSU
JAK	Lymphocytes, neurons	Tofacitinib (JAK1/3) Ruxolitinib (JAK1/2) Baricitinib (JAK1/2) Upadacitinib (JAK1) PF-04965842 (JAK1) JTE-052 (pan-JAK)	AD
NK-1R	Neurons	Serlopitant (NK1R)	PN CPUO
Histamine	Basophils, MCs, KCs	JNJ 39758979 (H4R) ZPL-389 (H4R)	AD CSU
MrgprX2	MCs	N/A	CSU

Disorders are shown in boldface when the therapeutic is FDA approved.

ILC2, Group 2 innate lymphoid cell; IL-4RA, IL-4 receptor A; IL-31RA, IL-31 receptor A; KC, keratinocyte; MC, mast cell.

allergen can be present in the skin for up to 3 weeks.⁶⁴ Furthermore, the culprit allergen is often not identified and frequently remains elusive.

Systemic and topical steroids are effective in the short term for symptomatic relief, but they are not appropriate for long-term use. In the event that longer-term therapy is required, other agents used include topical calcineurin inhibitors and/or systemic cyclosporine, mycophenolate mofetil, and light therapy. Similar to many other chronic itch disorders, antihistamines are largely ineffective for ACD.⁶⁵ Strikingly, the precise mechanisms that broadly underlie the development of itch in patients with ACD remain poorly defined.

Although classically defined as a type IV hypersensitivity reaction mediated by T_H1 and/or cytotoxic T cells, recent studies are demonstrating novel T cell-independent mechanisms as key players in ACD-associated itch. In a murine model of poison ivy-induced dermatitis, neuronal IL-33 receptor signaling was found to be a key mediator of itch, indicating that epithelial cell-derived IL-33 can directly stimulate itch-sensory neurons in this context.³⁴ Although somewhat controversial, mast cells have been implicated in modulating ACD-associated inflammation as well.⁶⁶⁻⁶⁹

Along these lines, we sought to investigate the role of novel mast cell-associated Mrgprb2 (MRGPRX2 in humans) in the setting of ACD-related itch and identified that proadrenomedullin peptide, an endogenous activator of Mrgprb2/X2, was critically upregulated in lesional human ACD skin. In addition to eliciting itch in an Mrgprb2- and mast cell-dependent manner, its activity was entirely independent of histamine. In contrast to IgE-mediated activation of mast cells, which resulted in large

amounts of histamine release, Mrgprb2-elicited activation resulted in smaller amounts of histamine release but greater release of tryptase (Fig 4). Strikingly, ACD-associated itch was dependent on Mrgprb2 across multiple models of ACD in mice.²⁶ Along these lines, Solinski et al⁷⁰ recently showed that chemogenetic activation of mast cells results in the release of serotonin, leukotriene C₄, and sphingosine-1-phosphate. Notably, Nppb neurons were found to express receptors for these molecules, which activate itch along the gastrin-releasing peptide–spinal cord pathway. Collectively, these studies demonstrate unique itch mechanisms in the context of ACD and heterogeneous pathways by which mast cells can be activated to mediate itch beyond histamine.

CONCLUSIONS

Although it has long been recognized that chronic pruritus is not solely driven by histaminergic processes, treatments have been historically limited to antihistamines and nonspecific immunosuppressive therapies such as corticosteroids. Recent advances in neuroimmunology and itch biology have yielded critical new insight into how the skin transmits itch signals through a complex interplay of molecular signals mediated by monoamines, cytokines, ion channels, and various receptors expressed by keratinocytes, immune cells, and neurons. These studies have emboldened the development of new targeted therapeutics, such as dupilumab, tralokinumab, lebrikizumab, neurokinin receptor antagonists, Mrgpr antagonists, and JAK inhibitors, which will likely have a major effect on chronic itch disorders within allergy and immunology in the next decade (Table I).

We thank members of the Kim laboratory for insightful discussions.

What do we know?

- Chronic pruritus is highly debilitating and a major component of many allergic diseases.
- The classical IgE–mast cell–histamine axis is a poor therapeutic target in many patients with chronic itch disorders.
- A number of nonhistaminergic itch-sensory pathways have been uncovered with the discovery of the gastrin-releasing peptide, Mrgpr, and Nppb circuits.
- AD-associated itch is histamine independent.
- Recent studies indicate neuronal IL-4, IL-13, IL-31, TSLP, and JAK1 signaling as critical targets for itch in this context.
- Mrgprb2 is a novel target for mast cell-associated itch.

What is still unknown?

- Which newly identified itch-specific pathways underlie various forms of allergic itch?
- How conserved are various itch targets across multiple allergic conditions?
- Does activation of the Mrgprb2/MRGPRX2 pathway underlie refractory forms of urticaria?
- What are the key IgE-independent mast cell-derived pruritogens?

REFERENCES

- Ständer S, Schäfer I, Phan NQ, Blome C, Herberger K, Heigel H, et al. Prevalence of chronic pruritus in Germany: results of a cross-sectional study in a sample working population of 11,730. *Dermatology* 2010;221:229-35.
- Matterne U, Apfelbacher C, Loerbroks A, Schwarzer T, Büttner M, Ofenloch R, et al. Prevalence, correlates and characteristics of chronic pruritus: a population-based cross-sectional study. *Acta Derm Venereol* 2011;91:674-9.
- Werfel T, Allam J-P, Biedermann T, Eyerich K, Gilles S, Guttman-Yassky E, et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol* 2016;138:336-49.
- Leonard A, Guttman-Yassky E. The unique molecular signatures of contact dermatitis and implications for treatment. *Clin Rev Allergy Immunol* 2019;56:1-8.
- Trier AM, Kim BS. Cytokine modulation of atopic itch. *Curr Opin Immunol* 2018;54:7-12.
- Mack MR, Kim BS. The itch-scratch cycle: a neuroimmune perspective. *Trends Immunol* 2018;39:980-91.
- Oetjen LK, Kim BS. Interactions of the immune and sensory nervous systems in atopy. *FEBS J* 2018;285:3138-51.
- Erickson S, Nahmias Z, Rosman IS, Kim BS. Immunomodulating agents as antipruritics. *Dermatol Clin* 2018;36:325-34.
- Sun Y-G, Chen Z-F. A gastrin-releasing peptide receptor mediates the itch sensation in the spinal cord. *Nature* 2007;448:700-3.
- McNeil B. Treatment XD-IM and, 2014 undefined. 12 Mrgprs as itch receptors. Available at: <https://books.google.com/books?hl=en&lr=&id=tXSBQAAQBAJ&oi=fnd&pg=PA213&ots=wEvLqUuC9g&sig=ib5MV7NKXpnZ7ePqFDGN5Bvgxec>. Accessed May 5, 2019.
- Liu Q, Tang Z, Surdenikova L, Kim S, Patel KN, Kim A, et al. Sensory neuron-specific GPCR Mrgprs are itch receptors mediating chloroquine-induced pruritus. *Cell* 2009;139:1353-65.
- Liu X-Y, Wan L, Huo F-Q, Barry DM, Li H, Zhao Z-Q, et al. B-type natriuretic peptide is neither itch-specific nor functions upstream of the GRP-GRPR signaling pathway. *Mol Pain* 2014;10:4.
- Mishra SK, Hoon MA. The cells and circuitry for itch responses in mice. *Science* 2013;340:968-71.
- Kaplan AP. Chronic spontaneous urticaria: pathogenesis and treatment considerations. *Allergy Asthma Immunol Res* 2017;9:477-82.
- de Silva NL, Damayanthi H, Rajapakse AC, Rodrigo C, Rajapakse S. Leukotriene receptor antagonists for chronic urticaria: a systematic review. *Allergy Asthma Clin Immunol* 2014;10:24.
- Eckman JA, Hamilton RG, Gober LM, Sterba PM, Saini SS. Basophil phenotypes in chronic idiopathic urticaria in relation to disease activity and autoantibodies. *J Invest Dermatol* 2008;128:1956-63.
- Thurmond RL, Kazerouni K, Chaplan SR, Greenspan AJ. Antihistamines and itch. Berlin: Springer; 2015:257-90.
- Schneider EH, Seifert R. The histamine H4-receptor and the central and peripheral nervous system: a critical analysis of the literature. *Neuropharmacology* 2016;106:116-28.
- Kollmeier A, Francke K, Chen B, Dunford PJ, Greenspan AJ, Xia Y, et al. The histamine H₄ receptor antagonist, JNJ 39758979, is effective in reducing histamine-induced pruritus in a randomized clinical study in healthy subjects. *J Pharmacol Exp Ther* 2014;350:181-7.
- Chang T, Shiung Y. Anti-IgE as a mast cell-stabilizing therapeutic agent. *J Allergy Clin Immunol* 2006;117:1203-12.
- Maurer M, Rosén K, Hsieh H-J, Saini S, Grattan C, Giménez-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013;368:924-35.
- Saini SS, Bindslev-Jensen C, Maurer M, Grob J-J, Bülbül Baskan E, Bradley MS, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol* 2015;135:67-75.
- Beck LA, Marcotte GV, MacGlashan D, Togias A, Saini S. Omalizumab-induced reductions in mast cell FcεRI expression and function. *J Allergy Clin Immunol* 2004;114:527-30.
- Gericke J, Metz M, Ohanyan T, Weller K, Altrichter S, Skov PS, et al. Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. *J Allergy Clin Immunol* 2017;139:1059-61.e1.
- Gaudenzio N, Sibillano R, Marichal T, Starkl P, Reber LL, Cenac N, et al. Different activation signals induce distinct mast cell degranulation strategies. *J Clin Invest* 2016;126:3981-98.
- Meixiong J, Anderson M, Limjunyawong N, Sabbagh MF, Hu E, Mack MR, et al. Activation of mast-cell-expressed Mas-related G-protein-coupled receptors drives non-histaminergic itch. *Immunity* 2019;50:1163-71.e5.
- McNeil BD, Pundir P, Meeker S, Han L, Undem BJ, Kulka M, et al. Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature* 2015;519:237-41.
- Wollenberg A, Oranje A, Deleuran M, Simon D, Szalai Z, Kunz B, et al. ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *J Eur Acad Dermatol Venereol* 2016;30:729-47.
- Jenerowicz D, Czarnecka-Operacz M, Silny W. Peripheral blood eosinophilia in atopic dermatitis. *Acta Dermatovenereol Alp Pannonica Adriat* 2007;16:47-52.
- Liu F-T, Goodarzi H, Chen H-Y. IgE, mast cells, and eosinophils in atopic dermatitis. *Clin Rev Allergy Immunol* 2011;41:298-310.
- Kim BS. Innate Lymphoid Cells in the Skin. *J Invest Dermatol* 2015;135:673-8.
- 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.e7.
- 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.
- Liu B, Tai Y, Achanta S, Kaelberer MM, Caceres AI, Shao X, et al. IL-33/ST2 signaling excites sensory neurons and mediates itch response in a mouse model of poison ivy contact allergy. *Proc Natl Acad Sci U S A* 2016;113:E7572-9.
- Wilson SR, Thé L, Batia LM, Beattie K, Katibah GE, McClain SP, et al. The epithelial cell-derived atopic dermatitis cytokine TSLP activates neurons to induce itch. *Cell* 2013;155:285-95.
- Parnes JR, Sullivan JT, Chen L, Dias C. Pharmacokinetics, safety, and tolerability of tezepelumab (AMG 157) in healthy and atopic dermatitis adult subjects. *Clin Pharmacol Ther* 2019[Epub ahead of print].
- Guttman-Yassky E, Bissonnette R, Ungar B, Suárez-Fariñas M, Ardeleanu M, Esaki H, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. *J Allergy Clin Immunol* 2019;143:155-72.
- Oetjen LK, Mack MR, Feng J, Whelan TM, Niu H, Guo CJ, et al. Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. *Cell* 2017;171:217-28.e13.
- Wollenberg A, Howell MD, Guttman-Yassky E, Silverberg JI, Kell C, Ranade K, et al. Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. *J Allergy Clin Immunol* 2019;143:135-41.
- Simpson EL, Flohr C, Eichenfield LF, Bieber T, Sofen H, Taieb A, et al. Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: a randomized, placebo-controlled phase II trial (TREBLE). *J Am Acad Dermatol* 2018;78:863-71.e11.
- Bao L, Zhang H, Chan LS. The involvement of the JAK-STAT signaling pathway in chronic inflammatory skin disease atopic dermatitis. *JAK-STAT* 2013;2:e24137.
- Bissonnette R, Papp KA, Poulin Y, Gooderham M, Raman M, Mallbris L, et al. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. *Br J Dermatol* 2016;175:902-11.
- Levy LL, Urban J, King BA. Treatment of recalcitrant atopic dermatitis with the oral Janus kinase inhibitor tofacitinib citrate. *J Am Acad Dermatol* 2015;73:395-9.
- Nakagawa H, Nemoto O, Igarashi A, Nagata T. Efficacy and safety of topical JTE-052, a Janus kinase inhibitor, in Japanese adult patients with moderate-to-severe atopic dermatitis: a phase II, multicentre, randomized, vehicle-controlled clinical study. *Br J Dermatol* 2018;178:424-32.
- Owens S, Howell MD. Ruxolitinib cream suppresses Th2 inflammation in adult patients with atopic dermatitis [abstract]. *J Allergy Clin Immunol* 2019;143:AB128.
- Beck L, Hong C, Hu X, Chen S, Calimlim B, Teixeira H, et al. Upadacitinib effect on pruritus in moderate-to-severe atopic dermatitis; from a phase 2b randomized, placebo-controlled trial. *Ann Allergy Asthma Immunol* 2018;121(suppl):S21.
- Guttman-Yassky E, Silverberg JI, Nemoto O, Forman SB, Wilke A, Prescilla R, et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. *J Am Acad Dermatol* 2019;80:913-21.e9.
- Zeidler C, Yosipovitch G, Ständer S. Prurigo nodularis and its management. *Dermatol Clin* 2018;36:189-97.
- Iking A, Grundmann S, Chatzigeorgakidis E, Phan NQ, Klein D, Ständer S. Prurigo as a symptom of atopic and non-atopic diseases: aetiological survey in a consecutive cohort of 108 patients. *J Eur Acad Dermatol Venereol* 2013;27:550-7.
- Matthews SN, Cockerell CJ. Prurigo nodularis in HIV-infected individuals. *Int J Dermatol* 1998;37:401-9.
- Lotti T, Buggiani G, Prignano F. Prurigo nodularis and lichen simplex chronicus. *Dermatol Ther* 2008;21:42-6.
- Weigelt N, Metze D, Ständer S. Prurigo nodularis: systematic analysis of 58 histological criteria in 136 patients. *J Cutan Pathol* 2010;37:578-86.

53. 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.
54. Liang Y, Jacobi HH, Reimert CM, Haak-Frendscho M, Marcusson JA, Johansson O. CGRP-immunoreactive nerves in prurigo nodularis—an exploration of neurogenic inflammation. *J Cutan Pathol* 2000;27:359-66.
55. Haas S, Capellino S, Phan NQ, Böhm M, Luger TA, Straub RH, et al. Low density of sympathetic nerve fibers relative to substance P-positive nerve fibers in lesional skin of chronic pruritus and prurigo nodularis. *J Dermatol Sci* 2010;58:193-7.
56. Beck KM, Yang EJ, Sekhon S, Bhutani T, Liao W. Dupilumab treatment for generalized prurigo nodularis. *JAMA Dermatol* 2019;155:118.
57. Ständer S, Kwon P, Hirman J, Perlman AJ, Weisshaar E, Metz M, et al. Serlopitant reduced pruritus in patients with prurigo nodularis in a phase 2, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2019;80:1395-402.
58. Berger TG, Steinhoff M. Pruritus in elderly patients—eruptions of senescence. *Semin Cutan Med Surg* 2011;30:113-7.
59. Xu AZ, Tripathi SV, Kau AL, Schaffer A, Kim BS. Immune dysregulation underlies a subset of patients with chronic idiopathic pruritus. *J Am Acad Dermatol* 2016;74:1017-20.
60. Yosipovitch G, Ständer S, Kerby MB, Larrick JW, Perlman AJ, Schnipper EF, et al. Serlopitant for the treatment of chronic pruritus: results of a randomized, multicenter, placebo-controlled phase 2 clinical trial. *J Am Acad Dermatol* 2018;78:882-91.e10.
61. Kostner L, Anzengruber F, Guilloid C, Recher M, Schmid-Grendelmeier P, Navarini AA. Allergic contact dermatitis. *Immunol Allergy Clin North Am* 2017;37:141-52.
62. Kimber I, Basketter DA, Gerberick GF, Dearman RJ. Allergic contact dermatitis. *Int Immunopharmacol* 2002;2:201-11.
63. Usatine RP, Riojas M. Diagnosis and management of contact dermatitis. *Am Fam Physician* 2010;82:249-55.
64. Mowad C, Marks J. Allergic contact dermatitis. In: Bologna J, Jorizzo J, Schaffer J, editors *Dermatology*. 3rd ed. Philadelphia: Elsevier Saunders; 2012.
65. Kamo A, Negi O, Tengara S, Kamata Y, Noguchi A, Ogawa H, et al. Histamine H4 receptor antagonists ineffective against itch and skin inflammation in atopic dermatitis mouse model. *J Invest Dermatol* 2014;134:546-8.
66. Askenase PW, Van Loverent H. Delayed-type hypersensitivity: activation of mast cells by antigen-specific T-cell factors initiates the cascade of cellular interactions. *Immunol Today* 1983;4:259-64.
67. Dudeck A, Dudeck J, Scholten J, Petzold A, Surianarayanan S, Köhler A, et al. Mast cells are key promoters of contact allergy that mediate the adjuvant effects of haptens. *Immunity* 2011;34:973-84.
68. Gimenez-Rivera V-A, Siebenhaar F, Zimmermann C, Siiskonen H, Metz M, Maurer M. Mast cells limit the exacerbation of chronic allergic contact dermatitis in response to repeated allergen exposure. *J Immunol* 2016;197:4240-6.
69. Grimbaldston MA, Nakae S, Kalesnikoff J, Tsai M, Galli SJ. Mast cell-derived interleukin 10 limits skin pathology in contact dermatitis and chronic irradiation with ultraviolet B. *Nat Immunol* 2007;8:1095-104.
70. Solinski HJ, Kriegbaum MC, Tseng PY, Earnest TW, Gu X, Barik A, et al. Nppb neurons are sensors of mast cell-induced itch. *Cell Rep* 2019;26:3561-73.e4.