The Itch–Scratch Cycle: A Neuroimmune Perspective

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Abstract

Relentless, repetitive itching and scratching is a debilitating feature of many chronic inflammatory skin disorders such as atopic dermatitis. While well known clinically, this itch–scratch cycle has historically lacked in-depth mechanistic understanding. However, recent advances at the interface of itch neurobiology and skin immunology have shed new light on this phenomenon. In this review, we highlight recent advances in our understanding of the neuroimmunology of chronic itch centered around three key points of entry into the itch–scratch cycle: the epithelial barrier, the immune system, and the peripheral nervous system. Furthermore, we explore novel neuro-epithelial-immune interactions that may represent promising therapeutic paradigms.

Chronic Itch: An Emerging Clinical Problem

Itch sensation is highly conserved across mammalian species and is currently hypothesized to be protective by inciting scratching behavior that can repel insects and parasites [1]. While loss-of-function mutations in molecules required for pain sensation can result in devastating trauma, burns, and loss of limbs [2], no loss-of-function mutations in itch-related molecules have yet been identified. However, like pain, when itch becomes chronic it is pathological. Indeed, multiple studies have demonstrated that chronic itch, defined as itch lasting longer than 6 weeks, is highly debilitating and results in an equivalent loss in quality of life as chronic pain [3,4]. Of relevance, chronic itch underlies many skin disorders such as atopic dermatitis (AD) and psoriasis, as well as a wide range of medical disorders including

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chronic kidney disease, liver disease, leukemia, lymphoma, and certain neuropathies. Yet, in contrast to pain, there is not a single FDA-approved medication available for the treatment of chronic itch.

A lack of mechanistic insight into what drives the chronicity of itchy skin diseases is a major barrier to therapeutic intervention. However, recent advances in itch biology are starting to uncover novel interactions between skin-resident populations important for mediating chronic itch states. In this review, we highlight recently described interactions between the **epithelium** (see Glossary), immune system, and sensory nervous system in the skin that may contribute to pathological itch sensation. Additionally, we review current therapeutic efforts underway that aim to target these pathways in human disease.

The Itch–Scratch Cycle

Itch is defined as an uncomfortable sensation on the skin that causes a desire to scratch (Figure 1A, Key Figure). Scratching temporarily relieves the itch sensation through activation of pain-sensory fibers that can inhibit itch sensation at the level of the spinal cord [5,6]. However, chronic itch sensations can drive persistent scratching responses that cause mechanical disruption of the skin. In one mouse study, itchy skin – induced with a combination of acetone, ether, and water (AEW) treatment – exhibited a lower histopathological score and distinct transcriptional profile in areas that were inaccessible to scratching (lower back) compared to accessible areas (nape), indicating that scratching might contribute to disease induction [7]. However, how scratching promotes chronic itch pathology is not well understood. Furthermore, additional factors might contribute to chronic itch disease, such as humidity and inflammation. Our current conceptualization of chronic itch involves crosstalk between multiple host cellular networks, including the stromal, immune, and sensory nervous systems (Figure 1B-D). Indeed, recent findings discussed in this review demonstrate that epithelial cells, immune cells, and neurons can individually promote itch sensation, suggesting that their activation by repetitive scratching can set off a vicious itch–scratch cycle that is a hallmark of chronic skin diseases such as AD [8] and **prurigo nodularis (PN)** [9].

The role of the itch–scratch cycle as a key player in disease pathogenesis is exemplified in AD, a chronic and relapsing inflammatory skin disorder that typically starts in early childhood and presents with red, scaly rashes. The central symptom of AD is chronic itch in which the urge to scratch is often uncontrollable; thus, AD is often referred to as the 'itch that rashes'. However, in AD, the point of entry into the itch–scratch cycle is a matter of debate. Underlying defects in the **skin barrier**, such as loss-of-function mutations in the epidermal barrier protein filaggrin (*FLG*) in humans, have been associated with a heightened risk for developing AD [10,11]. This is often referred to as the 'outside-in hypothesis' [12,13] because barrier breakdown allows for penetration of irritants and epithelial damage that can activate inflammatory cells to initiate disease. For example, mice with mutations that affect epithelial cell differentiation and barrier formation can develop spontaneous AD-like disease [14,15]. In contrast, it is also possible to develop immune dysregulation resulting in AD pathology; this is referred to as the 'inside-out hypothesis' [13], as exemplified by AD mouse models of transgenic overexpression of inflammatory

cytokines interleukin (IL)-4, IL-13, and STAT6 (downstream of IL-4/13) [16]. Accordingly, the recruitment of immune cells that produce type 2 effector cytokines IL-4, IL-5, and IL-13 have been considered to be some of the hallmarks of murine and human AD [17-21]. In either case, both hypotheses suggest that epithelial disruption and inflammation are key mediators of the itch–scratch cycle in AD (Figure 1B).

Beyond AD, the recognition of additional itchy skin disorders with distinct etiologies suggests that inflammation may not always be a necessary component the itch–scratch cycle. Clinically, **dry skin itch** is a condition in which chronic itch develops independently of overt skin inflammation and is thought to be due to physiological changes associated with aging, temperature, and humidity that dry out the skin [22-25] (Figure 1C). In addition, there are several primary chronic itch disorders such as PN, **chronic idiopathic pruritus (CIP**, also known as **generalized pruritus of unknown origin**), as well as neuropathic itch disorders such as brachioradial pruritus [26], notalgia paresthetica [27], and scalp pruritus [28]. The lack of inflammation or visible skin lesions in these diseases suggests that in the case of the itch–scratch cycle, neurogenic itch may be an initiating factor in disease pathogenesis, although further studies are warranted. Taken together, we posit that a complex network of epithelial-neuro-immune interactions might sense and propagate chronic itch states.

Neurophysiology of Itch

Whether itch sensation could be defined by distinct molecular pathways, apart from other sensations such as pain and touch, has been a matter of intense debate [29] (Box 1). Thus, the discovery of the G protein-coupled receptor (GPCR) called gastrin-releasing peptide receptor (GRPR), a receptor expressed on spinal cord neurons that specifically transmits itch but not pain signals [30], was a major conceptual advance from the first original identification of GRP (also known as bombesin) itch in 1983 [31]. The functional specificity of GRPR for itch was demonstrated by showing that murine scratching behavior in response to **pruritogens** was diminished in the setting of GRP-GRPR interruption, while behavioral responses to **algogens** were preserved [30]. The discovery of GRPR emboldened the search for other itch-sensory pathways that could represent novel therapeutic targets. For instance, B-type natriuretic peptide (BNP), encoded by the gene *Nppb*, may be one such mediator as *Nppb* deficiency and selective ablation of BNP receptor Npra$^+$ neurons in the murine spinal cord resulted in reduced scratching behaviors in response to a range of pruritogens [32]. While this study found that BNP could function upstream of GRP–GRPR signaling, the precise relationship between these pathways remains to be fully defined [33]. Collectively, these studies have identified novel itch-specific circuits that can relay peripheral signals to the **central nervous system (CNS),** thus mediating itch.

Furthermore, subsets of the Mas-related GPCR (Mrgpr) family, such as MrgprA3, have emerged as critically important receptors for itch and have led to a deeper appreciation for how itch sensation is encoded by the **peripheral nervous system (PNS)** [34]. The Mrgpr family consists of approximately 50 GPCRs in mice and at least four in humans [35-37]; many of which are expressed on sensory neurons. Two notable examples are MrgprA3 (in mice) and MrgprX1 (in humans) [35]. Ablation of MrgprA3$^+$ neurons in mice caused loss of responsiveness to a wide range of pruritogens but had no effect on pain behavior,

and selective activation of MrgprA3^{+} neurons resulted in itch, but not pain responses [36]. Although their endogenous ligands are still under investigation, MrgprX1 is activated by the proenkephalin-derived peptide BAM8-22 [38], and another study recently reported that the neuropeptide substance P (SP) is an endogenous ligand of MrgprA1 in mice [39]. MrgprA3 can also be activated by intradermal injection of the exogenous pruritogen chloroquine [40] or through **optogenetic** approaches [41]; both of which can induce scratching behavior in mice. Of note, some Mrgprs are uniquely expressed by mast cells, and the receptors MrgprB2 (in mice) and MrgprX2 (in humans) can respond to a range of cationic substances including the basic mast cell secretagogue compound 48/80 [35]. Moreover, mice with a loss-of-function mutation in *Mrgprb2* have normal mast cell responses to IgE crosslinking, suggesting that MrgprB2-induced mast cell activation is IgE independent [35]. However, while mast cells have long been associated with itch sensation, the role of MrgprB2/X2 on mast cells in the context of chronic itch has yet to be elucidated. Collectively, the identification of itch-specific receptor–ligand interactions such as GRP–GRPR and neuronal subpopulations such as MrgprA3^{+} pruriceptors opened the door to new insights into itch biology and drug development.

The Skin Barrier and Itch

Skin barrier damage is a common point of entry into the itch–scratch cycle (Figure 1C). Clinical studies in children have demonstrated that early treatment with moisturizers to target skin barrier damage reduces the risk of developing AD [42,43]. Conversely, mice with homozygous mutations in *Tmem79/Matt* (also known as flaky tail mice) are born with skin barrier dysfunction and spontaneously develop AD-like dermatitis over time, despite no intrinsic defects in the immune system [14,44]. This is thought to be mediated in part by keratinocyte damage or stress [45], which may be sensed through changes in osmolarity [46], temperature [47], or cell membrane tension [48]. These changes may feedback directly on the PNS to evoke further itch sensation. For example, the osmosensitive cation channel TRPV4 on keratinocytes was recently shown to be required for histamine and endothelin (ET)-1-induced scratching behavior induced by intradermal injection of these compounds in mice [49]. In addition, *Trpv4*^{−/−} mice presented significantly reduced scratching behavior in the AEW model of dry skin itch relative to wild-type mice [46]. Therefore, keratinocyte-derived mediators may play an important role in the itch–scratch cycle (Figure 2A), although further studies are warranted.

In response to damage or stress, keratinocytes produce a number of key immune mediators. **Kallikreins (KLKs)** are a family of serine proteases produced in the stratum corneum of the skin that regulate **desquamation** in mice and humans [50,51]. However, in AD, they become dysregulated and can promote skin inflammation and barrier disruption through activation of a variety of pathways [52-55]. Of relevance, KLK5 has been reported to be elevated in lesional skin of pediatric AD patients compared to nonlesional or healthy control skin, and overexpression of KLK5 in an *ex vivo* culture model promoted acanthosis, as well as the release of IL-8 and thymic stromal lymphopoietin (TSLP) from keratinocytes [55]. The effects of KLKs are mainly thought to be mediated by cleavage of protease-activated receptors (PARs) in the skin [52]. PAR2, which is cleaved and activated by specific forms of KLKs [53], is expressed on a number of cell types in mice and humans, including sensory

neurons, and for many years has been implicated in mediating itch [56–58]. However, in AD, the key substrates cleaved by KLKs and their relative contributions to chronic itch remain to be fully defined (Figure 2A). Recently, the MrgprC11 receptor in mice was shown to be activated *in vivo* by the endogenous peptide SLIGRL, a tryptase-induced cleavage product of PAR2 [59], as well as by the cysteine protease cathepsin S [60], thus eliciting itch in mice. Furthermore, overexpression of human cathepsin S (*CTSS*) in mice has been shown to drive AD-like pathology [61], and cathepsin S is over-produced by keratinocytes in patients with psoriasis [62] and **seborrheic dermatitis** [63] relative to healthy controls. Taken together, these findings suggest that epidermal proteases such as cathespin S and KLKs might directly stimulate neuronal pathways such as PAR2 and MrgprC11 to trigger itch (Figure 2A). However, future studies will be required to identify whether unique protease–neuron interactions underlie chronic itch disorders.

Beyond proteases, keratinocytes produce a number of other factors in response to damage or stress. β-Defensin is an antimicrobial peptide produced from epithelial cells that was recently shown to also promote scratching behavior in mice via Toll-like receptor (TLR) 4 signaling in macrophages [64]. Notably, the epithelial cell-derived cytokines IL-25, IL-33, and TSLP are potent stimulators of allergic type 2 inflammation [65]. However, despite their proinflammatory effects on skin-resident immune cells such as mast cells and group 2 innate lymphoid cells (ILC2), recent studies in mice have demonstrated that both IL-33 and TSLP can directly stimulate itch-sensory neurons [66,67]. In these studies, intradermal injection of TSLP led to acute scratching behavior in mice; however, IL-33 has not been reported to act as an acute pruritogen in mice or humans. Rather, this 2016 study demonstrated that the IL-33 receptor ST2 was present on pruriceptive neurons and that anti-IL-33 and anti-ST2 blocking antibodies could inhibit scratching behavior in a mouse model of poison-ivy-induced **allergic contact dermatitis (ACD)** [66]. Thus, the precise role of these epithelial cell-derived cytokines in itch has not been formally tested and remains to be determined in both mice and in humans. Furthermore, the role of IL-25 in itch remains entirely unexplored. Nevertheless, reports that such epithelial cell-derived cytokines and proteases can activate pruriceptive neurons and modulate itch behaviors are suggestive of an itch–scratch cycle in which skin damage could directly lead to sensations of itch via a variety of mechanisms (Figure 2A).

Skin Inflammation, Immunity, and Itch

Mast cells have traditionally been associated with itch behavior in allergic reactions. When activated, either by IgE crosslinking or innate receptor stimulation such as via TLRs, mast cells release their intracellular granules containing histamine, which can act on pruriceptors to induce itch [68]. However, recent studies have added additional complexity to this classical paradigm [69]. In addition to mast cells, the numbers of basophils – which also release histamine in response to IgE activation – are elevated in mouse and human AD and appear to have a critical role in the development of AD-like dermatitis [20,70]. Specifically, basophil depletion in BaS-DTR mice treated with diptheria toxin resulted in reduced ILC2 expansion and reduced histopathological features in AD-like skin [70]. Despite the clear role of histamine in acute itch sensation, antihistamines have traditionally been ineffective in the treatment of chronic itch, especially in the setting of AD [71].

However, while conventional antihistamines only target the histamine receptor 1 (H1R), new antihistamines in development such as JNJ-3975879 [72] and ZPL-3893787 (ZPL-389) (www.clinicaltrials.gov) can selectively target H4R, which has shown promise in preclinical animal models such as those of FITC-induced contact dermatitis [73] (Figure 2B). Immune cells can also secrete serine proteases such as tryptase, which has been shown to trigger itch through the activation PAR2 in mice [74] (Figure 2B). Furthermore, individuals with additional copies of the gene encoding α-tryptase (*TSAB1*) have a high incidence of pruritus and **flushing** [75], suggesting that mast cells, basophils, and their constituent tryptase might be mediators of pruritus in multiple itch pathologies, though the precise mechanisms are yet undetermined.

Apart from granulocytes such as mast cells and basophils [69,76,77], recent studies have also implicated both innate and adaptive lymphocytes in mediating inflammatory itch. As previously discussed, as part of the **epithelial stress response**, the epithelial cell-derived cytokines IL-25, IL-33, and TSLP robustly activate ILC2s and recruit Th2 cells into the skin [17,19,78,79]. ILC2s and Th2 cells are also rich sources of the type 2 cytokines IL-4, IL-5, and IL-13, which can initiate and perpetuate allergic skin inflammation by recruiting basophils and eosinophils and promoting immunoglobulin class switching to IgE [16]. It is thus possible that the pruritogenic capacity of certain cytokines can position immune cells such as ILC2s to act as itch-promoting effector cells in addition to their proinflammatory properties (Figure 2B).

The first cytokine that was recognized to mediate itch by acting directly on sensory neurons is the Th2 cell-associated cytokine IL-31, originally discovered in 2004 [80,81]. Meanwhile, single-cell RNA sequencing studies in mice have also revealed a previously unrecognized diversity in receptor expression on sensory neuron populations [82,83]. These studies led to the hypothesis that other proinflammatory mediators, such as certain type 2 effector cytokines, might act as pruritogens. A recent study documented the expression and function of the receptor subunit for both IL-4 and IL-13 (IL-4Rα) on murine and human sensory neurons [84]. However, in contrast to IL-31, acute intradermal injection of IL-4 or IL-13 did not elicit substantial scratching behavior in a murine cheek injection model [84]. Despite this, deletion of IL-4Rα in **Nav1.8$^+$ sensory neurons** critically disrupted scratching behavior in a murine model of AD. Furthermore, pretreatment of murine dorsal root ganglia (DRG) neurons with IL-4 evoked more robust calcium responses to a variety of pruritogens than those pruritogens alone and co-injection of IL-4 with histamine amplified histamine-induced scratching behavior in mice [84]. Together, these findings implicated type 2 cytokines such as IL-4 as being able to promote hypersensitivity within pruriceptors in mouse models of chronic itch (Figure 2B).

Our evolving understanding of how soluble mediators from the immune system in the skin can influence the itch-sensory nervous system has opened an exciting new field of inquiry in which epithelial cells, innate immune cells, and adaptive immune cells might work in concert to shape the scope and intensity of itch. These newly uncovered pathways may provide a molecular framework to further our understanding of the **neuroimmune axis** within the itch–scratch cycle.

Neurogenic Inflammation and Itch

While we are now beginning to understand how various proinflammatory factors contribute to the propagation of itch [85] (Figure 2B), how neurogenic activation and itch may directly promote the itch–scratch cycle is a new area of inquiry. A model of neurogenic itch was recently developed in which mice expressed the constitutively active form of the serine/threonine kinase B-Raf in $Na_V1.8^+$ sensory neurons (BRAF$^{Nav1.8}$) (Box 1). These mice gradually develop spontaneous scratching behavior that leads to skin lesions and worsening itch over time [86]. On a molecular level, sensory neurons from BRAF$^{Nav1.8}$ mice exhibited ectopic expression of GRPR and MrgprA3 in the spinal cord and DRG neurons, respectively, as well as heightened scratching responses to the pruritogens histamine, chloroquine, and ET-1 compared to littermate controls [86]. Although the mechanisms by which such **neural hypersensitivity** occurs are unclear, mice that experienced dinitrofluorobenzene-induced ACD and dry skin itch exhibited activation of MrgprA3$^+$ DRG neurons as in the BRAF$^{Nav1.8}$ mouse model, suggesting that these might be conserved signaling pathways, although further studies are warranted [86]. Such murine models serve as a proof of concept that the itch–scratch cycle may start with neuronal activation and itch, and consequently, that putative therapies to treat itch might require multiple points of intervention to curb the cycle.

Other studies have demonstrated that sensory neurons critically regulate cutaneous inflammation in the context of psoriasis and antifungal immunity (Table 1). Denervation of cutaneous nerve fibers reduced **acanthosis** and inflammatory infiltrate compared to normally innervated skin in a murine model of psoriasis, which could be reversed by addition of the neuropeptide calcitonin-gene related peptide (CGRP) [87]. Similarly, another study found that denervation lessened psoriasiform pathology in murine psoriasis [88]. This study also showed that production of IL-23 from dermal dendritic cells (DCs) was required for psoriasiform ear thickening and was lost when TRPV1+ neurons were ablated with resiniferatoxin treatment [88]. This implicated sensory neurons in the promotion of pruritic skin inflammation. A similar neuron-DC interaction promoting the production of IL-23 was shown to be protective against *Candida albicans* infection in mouse skin [89]. In the lungs, exogenous administration of the neuropeptide neuromedin U (NMU) amplified IL-25- and house dust mite allergen-induced ILC2 activation and allergic airway inflammation in mice [90]. Similarly, two additional studies found that Nmur$^{-/-}$ mice were unable to clear the intestinal helminth *Nippostrongylus brasiliensis*, suggesting that the NMU–ILC2 axis was important for type 2 immunity in the gut [91,92].

Collectively, these studies have led to the hypothesis that neuropeptides derived from sensory neurons might also be able to promote inflammation contributing to or exacerbating the itch–scratch cycle (Figure 3). It is also reasonable to speculate that if certain proinflammatory cytokines act as pruritogens, itch or neuronal stimulation might directly promote inflammatory itch independently from scratching. However, robust studies will be required to unveil these additional and provocative possibilities to the itch–scratch cycle.

Therapeutic Considerations

Many cytokines and their associated signaling pathways, including IL-4, IL-13, IL-31, IL-33, and TSLP have emerged as some of the most promising targets for the treatment of AD (Table 2). One such treatment is dupilumab, an anti-IL-4rα monoclonal antibody (mAb) that blocks both IL-4 and IL-13 signaling and is FDA-approved for the treatment of moderate-to-severe AD. In addition to limiting skin inflammation, it has demonstrated unprecedented improvement of itch in clinical trials for AD [93-95]. Thus, we speculate that dupilumab may have neuromodulatory effects based on the recent identification of IL-4rα functionality on sensory neurons [84]. Two anti-IL-13 mAbs, lebrikizumab and tralokinumab, are also in clinical trials for the treatment of AD and may have similar effects on itch as dupilumab, although this remains to be determined. Moreover, in a recent phase 2 clinical trial of nemolizumab (anti-IL-31RA mAb), where AD-associated pruritus was the primary outcome, the drug demonstrated significant antipruritic effects [96]. Finally, both anti-IL-33 and anti-TSLP mAbs are also being explored in phase 2 clinical trials for AD. Remarkably, inhibitors of cytokines most recently shown to activate itch-sensory neurons are either available or actively being explored for possible use in various patient populations. Future studies will aim to determine which of these therapeutics can have the most robust and specific effect on clinical itch.

It is tempting to postulate that behavioral responses and sensory dysfunction in other tissues such as the meninges (migraine headaches), cochlear and vestibular apparatus (tinnitus and vertigo), airway (asthma and cough), gut (irritable bowel syndrome), and bladder (interstitial cystitis) may involve a similar neuroimmune interplay as in the itch–scratch cycle. The breadth of clinical indications for itch-modulating drugs support this notion: dupilumab (anti-IL-4rα) is also being used to treat asthma [97,98] and CGRP antagonists are now indicated for migraine headaches [99] (Table 1). Similarly, SP receptor (NK-1R) antagonists are in development for chronic pruritus and PN [100], as well as Sézary syndrome, a cutaneous T cell lymphoma that is highly pruritic [101]. Ultimately, recent advances informing the itch–scratch cycle elicit the broader hypothesis that previously unrecognized inflammatory circuits might underlie the perpetuation of a variety of sensory disorders.

Concluding Remarks

Although itch has been closely associated with inflammatory skin disorders for many decades, recent advances in our understanding of both disease pathogenesis – especially AD – and itch neurobiology have brought new mechanistic insight to this association. It is now clear that the immune system acts as a sentinel by relaying signals from the skin barrier to the PNS that can be dysregulated in chronic itch states and even affected by scratching behavior. Although numerous questions remain to be addressed (see Outstanding Questions), we are beginning to understand how epithelial cells, immune cells, and neurons might communicate at the molecular level to drive the pathophysiology of the itch–scratch cycle.

First, future studies are needed to determine which immune pathways most critically regulate specific chronic itch diseases. To do this, the development of additional mouse

models will be required for conditions such as PN and CIP. Second, evidence is accumulating that the epithelium itself releases proteases and cytokines that may directly stimulate subsets of pruriceptive neurons. However, additional work is needed to determine whether these epithelial–neuronal connections are alone sufficient to drive chronic itch states, and to test whether they can be disrupted to break the itch–scratch cycle. Third, intrinsic dysregulation of the nervous system itself can initiate scratching behaviors and, ultimately, the formation of skin lesions. The growing evidence of neurogenic inflammation as a key neuroimmune process highlights that the nervous system itself could initiate the itch–scratch cycle and potentiate a secondary inflammatory process. However, which neurogenic pathways regulate itch sensation in the setting of neuropathic itch disorders, and whether these also contribute to inflammatory skin diseases in humans, remains to be explored.

In conclusion, this review highlights an emerging paradigm in which epithelial and immune cells in the skin act as sentinels for the sensory nervous system by communicating through various factors such as cytokines and proteases. In turn, afferent sensory neurons appear to have critically important roles in sending efferent signals to the epithelium and immune system through various neuropeptides. Thus, there appears to be a bidirectional circuit between the nervous system and the skin that, when dysregulated, may represent a highly pathological cycle of barrier dysfunction and neuroinflammation. Finally, although the itch–scratch cycle is a phenomenon that is exclusive to the skin, whether similar pathological sensory-reflex arcs exist at other barrier surfaces such as the lung (cough), gut (dysmotility), and beyond remains to be determined.

Acknowledgments

Glossary

Acanthosis
epidermal hyperplasia/thickening of the epidermis

Algogen
a molecule that activates pain-sensory neurons and pain sensations/behavior.

Allergic contact dermatitis (ACD)
a skin reaction caused by contact with a specific allergen to which an individual has been previously sensitized. An erythematous, itchy rash develops within minutes to hours of exposure.

Central nervous system (CNS)
the components of the nervous system located within the brain and spinal cord.

Chronic idiopathic pruritus (CIP) (also known as generalized pruritus of unknown origin (GPUO)

chronic itch (lasting >6 weeks) in the absence of a visible skin rash or evidence of other cutaneous or systemic causes of pruritus. Frequently associated with immune dysregulation and aging.

Desquamation

the process of shedding the outermost layer of skin, comprising terminally differentiated keratinocytes.

Dry skin itch

itch secondary to dry skin, often associated with aging or seasonal changes.

Epithelial stress response

in response to cellular damage or inflammatory cytokines, epithelial cells such as keratinocytes undergo a stress response that includes changes in antimicrobial peptide production, synthesis of TSLP and IL-25, release of IL-33, and changes in their differentiation process.

Epithelium

a layer of embryonically related stromal cells located at the interface between the mammalian host and the environment.

Flushing

a vascular dilation response that results in redness and edema in the skin.

Group 2 innate lymphoid cells (ILC2)

innate lymphocytes derived from the common lymphoid progenitor that have similar effector functions to Th2 cells without rearranged T cell receptors. Instead, ILC2s are tissue-resident cells that respond to epithelial cell-derived cytokines IL-33, IL-25, and TSLP.

Kallikreins (KLK)

a family of 15 (in humans) trypsin- and chymotrypsin-like serine proteases that show tissue-specific expression profiles throughout the body. In the skin, KLK5 and KLK7 have been attributed to regulating desquamation.

Nav1.8$^+$ sensory neurons

the major nociceptive population within the dorsal root ganglia, including pruriceptive fibers.

Neural hypersensitivity

a state of heightened responsiveness of neurons caused by a change in the resting membrane potential and/or a change in the intracellular signaling pathways related to sensing stimuli.

Neuroimmune axis

the direct molecular communication between cells of the immune system and the nervous system. This can occur both centrally in the brain as well as peripherally in organs such as the skin.

Optogenetics

targeted expression of light-sensitive ion channels to selectively activate (or inhibit) neuronal subpopulations.

Peripheral nervous system (PNS)

the collection of neurons and neuronal support cells and tissues located outside of the spinal cord and brain. The somatic branch of PNS relays sensory information as well as voluntary motor functions. The autonomic branch regulates basal homeostatic functions like blood pressure and respiration.

Pruriceptor

a neuron capable of firing in response to a pruritogen and, when activated, evokes itch sensation/scratching behavior.

Prurigo nodularis (PN)

a disease of unknown etiology characterized by highly pruritic excoriated nodules on the skin; often associated with other chronic itch conditions such as atopic dermatitis, lichen planus, and bullous pemphigoid.

Pruritogen

a molecule that evokes activation of itch-sensory neurons and scratching behavior.

Seborrheic dermatitis

a scaly, greasy skin rash primarily found on the scalp that can cause dandruff and pruritus.

Skin barrier

the physical and chemical barrier created by the keratinocytes and their secreted factors such as keratins and antimicrobial peptides that protect the host from dehydration, penetration of irritants, and infection.

T helper type 2 (Th2) cells

effector T cell population that develops in the presence of IL-4 and promotes allergic inflammation through production of additional IL-4, IL-5, IL-13, and IL-9; also thought to be the main source of IL-31.

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Box 1.

Activation of Peripheral Sensory Neurons

The PNS relays signals from the skin to the CNS. To elicit a distinct sensation, unique receptors are stimulated at the nerve terminals and neurons become depolarized in a graded potential through opening of a family of nonselective cation channels called transient receptor potential (TRP) channels such as TRPV1 and TRPA1 [102]. Upon reaching a critical threshold of depolarization, an action potential (AP) is triggered, which is relayed to the spinal cord and on to the brain. The APs are triggered by voltage-gated sodium channels including $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$ on the neuronal membrane [103]. Collectively, this sequence of events can apply to any sensation being relayed from the PNS, including pain and itch [104]. However, the specific receptor expression profile and spinal cord synapses of an individual neuron dictate its cellular identity as well as the sensory modalities it transmits.

Highlights

Keratinocyte-derived mediators such as thymic stromal lymphopoietin, cathepsin S, and kallikreins can induce itch sensation.

Inflammatory cytokines IL-31, IL-4, and IL-13 can directly activate itch-sensory neurons in mice and humans and mediate scratching behavior in mice.

Neurogenic activation of B-Raf signaling in mice can trigger itch, inflammation, and tissue damage.

Activation of immune cells at barrier surfaces by neuropeptides can regulate psoriatic dermatitis in mice.

Neuroimmune mediators of the itch–scratch cycle such as IL-31 and TSLP are currently considered prime therapeutic targets for atopic dermatitis.

Outstanding Questions

Which molecular pathways are necessary or sufficient to propagate the itch–scratch cycle? Which of these can be effectively applied to new therapeutic approaches for human itch disorders?

To what degree does scratching contribute to inflammation and/or itch? How can this be measured?

How is neural hypersensitivity encoded in the setting of chronic itch?

What are the endogenous ligands of Mrgprs? What are their roles in complex itch disorders and can they be therapeutically targeted for itch relief?

Are specific pathways that promote the itch–scratch cycle also able to propagate chronic sensory dysfunction at other mucosal surfaces such as the airway and gut?
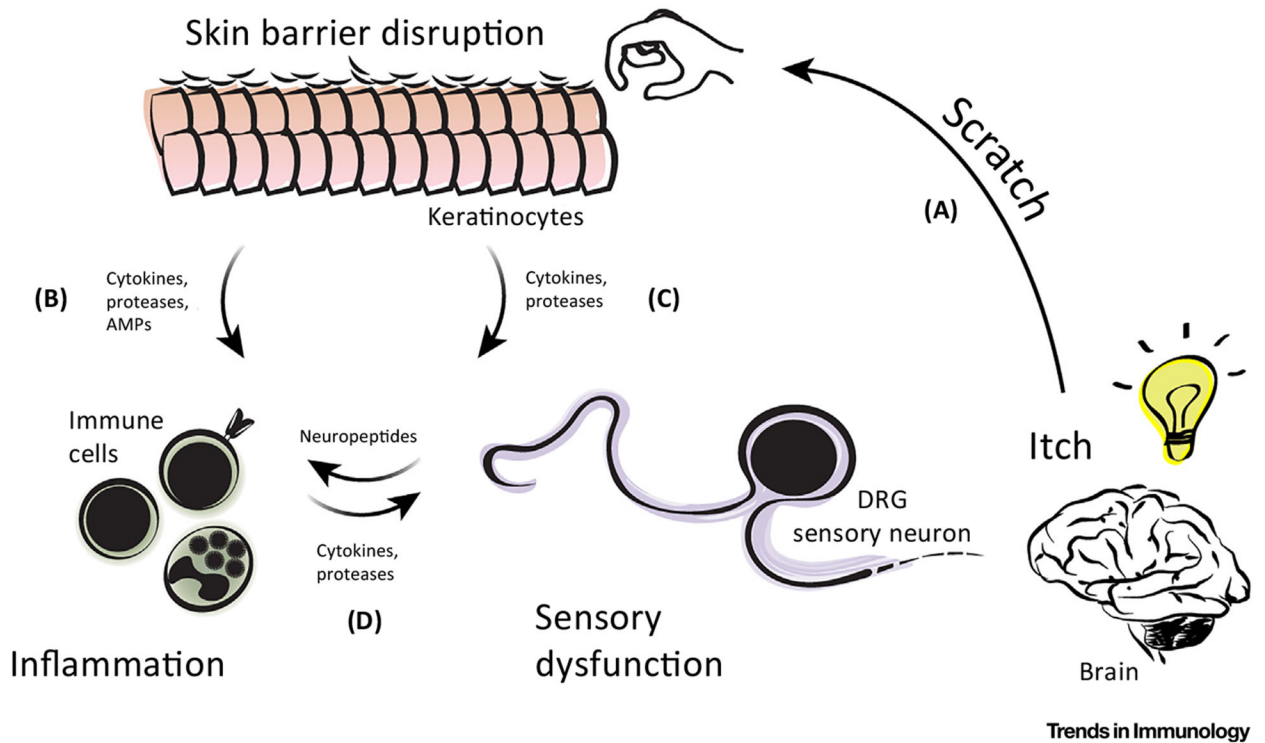
Figure 1. Key Figure. The Itch–Scratch Cycle

(A) Chronic itch sensations and associated scratching behaviors are components of a dynamic pathological process known as the itch–scratch cycle. Scratching behaviors exacerbate itch sensation through damage to skin epithelial cells. (B) The epithelial stress response releases cytokines, proteases, and AMPs that can activate immune cells to promote inflammation. (C) Keratinocytes may also activate itch-sensory neurons directly through soluble mediators such as cytokines and proteases. (D) Release of neuropeptides from neurons can also cause neurogenic inflammation. In contrast, cytokines and proteases produced by immune cells interface with the sensory nervous system to mediate itch. Abbreviations: AMP, antimicrobial peptide; DRG, dorsal root ganglion.
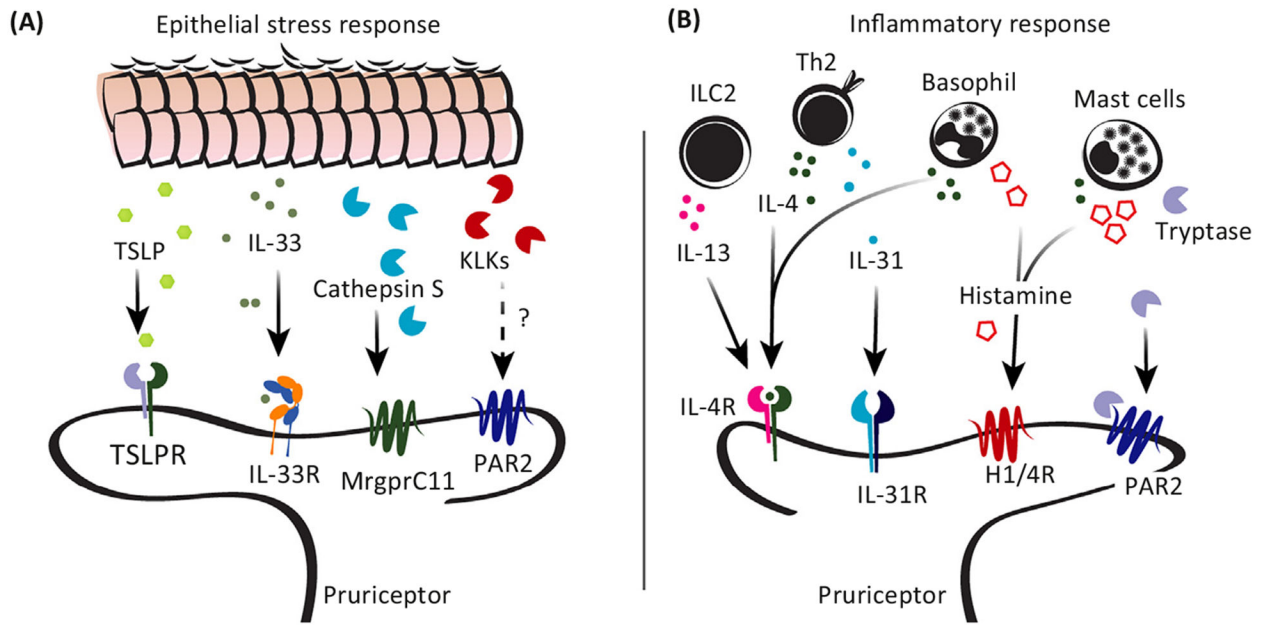
Figure 2. Known Molecular Mediators of Epithelial and Inflammatory Itch.
(A) Skin damage from dry skin, genetic lesions, or chronic scratching causes release of epithelial cell-derived cytokines such as TSLP and IL-33, which can directly activate itch-sensory neurons (pruriceptors). Keratinocyte-derived proteases such as KLKs and cathepsin S can also trigger itch through cleavage-based activation of the PAR2 and MrgprC11; however, whether KLKs activate neuronal PAR2 directly is not yet clear. (B) Immune cells may modulate itch-sensory neurons through expression of certain cytokines, such as IL-4 from Th2 cells, mast cells, and basophils, which can exacerbate the itch sensation in atopic dermatitis. IL-31 from Th2 cells can directly trigger scratching in mice. Histamine and tryptase from mast cells and basophils can activate G-protein-coupled receptors such as H1/4R as well as PAR2. While the receptor–ligand interactions shown here have been linked to itch, and immune cells are known to produce these ligand mediators, the precise cellular sources in the context of specific itch disorders is still under investigation. Abbreviations: H1/4R, histamine 1/4 receptor; IL, interleukin; ILC2, group 2 innate lymphoid cells; KLK, kallikrein; PAR2, protease activated receptor 2; Th2, T helper type 2; TSLP, thymic stromal lymphopoietin.
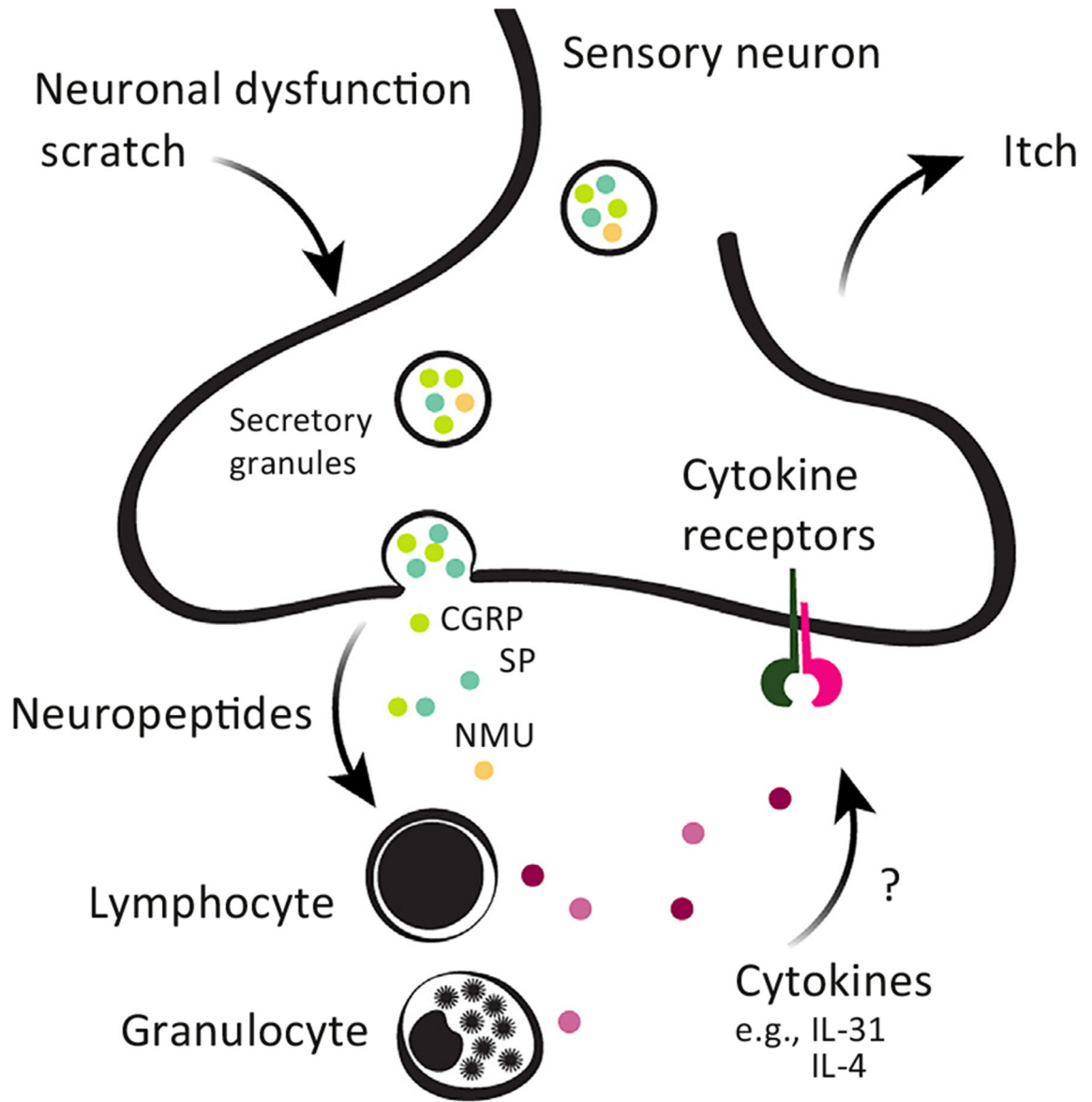
Figure 3. Neurogenic Inflammation and Itch.

Activation of sensory neurons through scratching or neuronal dysfunction can trigger release of neuropeptides such as CGRP, SP, and NMU. These neuropeptides can activate immune cells such as innate and adaptive lymphocytes and granulocytes that can lead or contribute to neurogenic inflammation. New findings describing the modulation of sensory neurons by cytokines such as IL-4 and IL-31 suggests that neurogenic inflammation may itself regulate itch. Abbreviations: CGRP, calcitonin gene-related peptide; IL, interleukin; NMU, neuromedin U; SP, substance P.

Table 1.

Examples of Regulatory Neuropeptides in Immune Cells and Potential Therapeutic Targets

Neuropeptide	Receptor	Immune cell targets	Therapeutics (target)	Diseases
SP	NK-1R	MC, basophil, eosinophil	Tradipitant (NK-1R)	AD, Chronic pruritus
			Serlopitant (NK-1R)	Chronic pruritus
			Aprepitant (NK-1R)	Sézary syndrome, Prurigo nodularis
CGRP	CGRPR	DC, macrophage, Th2, MC	Telcagepant (CGRPR)	Migraine
			Fremanezumab (CGRP)	Migraine
			Erenumab (CGRPR)	Migraine
NMU	NMUR1	ILC2	?	–

Table 2.

Itch-Modulating Factors as Potential Targets for AD Patients

Ligand	Receptor	Source	Therapeutics (target)
IL-4	IL-4Rα/IL-2Rγ	Th2, basophil, MC, ILC2	Dupilumab (IL-4Rα)
			Pitrakinra (IL-4/13)
IL-13	IL-4Rα/IL-13Rα1	Th2, ILC2	Dupilumab (IL-4Rα)
			Tralokinumab (IL-13)
			Lebrikizumab (IL-13)
			Pitrakinra (IL-4/13)
IL-33	ST2/IL-1RAcP	KC	ANB020 (IL-33)
TSLP	TSLPR/IL-7Rα	KC	Tezepelumab (TSLP)
IL-31	IL-31Rα/OsmR	Th2	Nemolizumab (IL-31Rα)
			BMS-981164 (IL-31)
Histamine	H1/4R	MC, basophil	ZPL389 (H4R)
Tryptase	PAR1/2	MC, basophil	?
Kallikreins	PAR1/2	KC	?
BAM8-22, others?	MrgprX1	?	?