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Why we scratch an itch: the molecules, cells and circuits of itch

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Abstract

Itch is described as an irritating sensation that triggers a desire to scratch. However, this definition hardly seems fitting for the millions of people who suffer from intractable itch. Indeed, the Buddhist philosopher Nāgārjuna more aptly stated, “There is pleasure when an itch is scratched. But to be without an itch is more pleasurable still.” Chronic itch is widespread and very difficult to treat. In this review we focus on the molecules, cells and circuits in the peripheral and central nervous systems that drive acute and chronic itch transmission. Understanding the itch circuitry is critical to developing new therapies for this intractable disease.

Itch is defined as an unpleasant sensation that evokes a desire to scratch. In contrast to acute itch that is transient, chronic itch is a persistent, debilitating condition for which there are few treatment options. Chronic itch accompanies a number of skin diseases and systemic conditions, including eczema, kidney failure, liver cirrhosis and some cancers. A variety of neurological disorders also induce severe, chronic itch; for example, multiple sclerosis, diabetic neuropathy and post-herpetic neuralgia (shingles)[1–3]. Chronic itch, like chronic pain, can occur without injury or disease, serves no apparent biological purpose and has no recognizable endpoint. Although studies have identified a number of essential molecules in primary afferent neurons that transduce acute itch signals, we are only now beginning to uncover the cellular and molecular players that drive chronic itch in both the peripheral and central nervous system.

Primary afferent sensory neurons detect a multitude of sensory stimuli, including touch, temperature, chronic pain and itch. These neurons have cell bodies in dorsal root ganglia (DRG) and trigeminal ganglia (TG) and project axons to target organs, such as the skin, in the periphery. There is considerable apparent overlap in the neuronal cells and circuits that transmit itch and pain. Although these sensations are easily distinguished, they are

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intimately linked in a number of other ways. First, pain inhibits itch, as exemplified by the relief one gets from noxious scratching of itchy skin. Second, some analgesics (for example, opioids) can cause itch. Third, some itch-causing compounds (pruritogens) induce inflammatory pain, and, under certain circumstances, some pain-causing compounds (algogens) induce itch. Finally, there is overlap in some of the signaling molecules that transduce itch and pain[1]. However, whether itch and pain signals are actually transduced by the same populations of DRG neurons remains unknown.

Subsets of primary neurons have been shown to act as sensors for acute and chronic itch stimuli and to promote scratching behaviors. Itch-sensitive neurons are activated by a variety of exogenous pruritogens (itch-causing compounds), as well as pruritogens produced endogenously by epithelial and immune cells (**Fig. 1**). However, whether the plethora of pruritogens activates the same populations of itch-sensitive neurons remains controversial. Adding to this cellular complexity, interactions among immune cells, sensory neurons and epithelial cells also contribute to both acute and chronic itch[1]. Indeed, elucidating both the intercellular and intracellular signaling molecules that drive these sensations is a major goal in the field.

In this review we present our views on some of the most exciting advances in itch research over the past few years. We highlight progress in defining some of the molecules, cells and circuits in the peripheral and central nervous system that drive acute and chronic itch transmission. We also discuss novel candidate signaling molecules in neurons, keratinocytes and immune cells and some of the best chronic itch models for assessing the role of such candidates. Finally, we describe some of the latest therapeutic approaches for treating chronic itch conditions in humans. We refer the readers to reviews that comprehensively cover the itch field[1,4–8].

What molecules mediate acute itch transduction?

Itch-sensitive neurons are often classified according to their sensitivity to histamine, the best-studied pruritogen. Histamine is released from immune cells (mast cells and basophilic granulocytes) and keratinocytes and acts on a subset of sensory neurons that express histamine receptors and the heat- and capsaicin-gated ion channel transient receptor potential cation channel, subfamily V, member 1 (TRPV1; **Fig. 1**). A large body of evidence demonstrates that TRPV1 is a key transduction channel that functions downstream of histamine receptors to induce neuronal excitation and promote itch behaviors; first, TRPV1 antagonists inhibit histamine-evoked signals in DRG neurons; second, patients with allergic rhinitis display increased itch sensations following TRPV1 stimulation; and third, mice lacking TRPV1-expressing neurons or TRPV1 itself display substantially less histamine-induced scratching than wild-type littermates[9,10]. However, histamine-evoked itch is not completely attenuated in TRPV1-deficient mice[10], suggesting that other channel(s) may be required for histaminergic itch[11]. Interestingly, not all histamine-sensitive neurons are capsaicin-sensitive, but whether this subset of histaminergic neurons mediates itch, pain and/or inflammation, is unknown.

Many forms of itch are insensitive to antihistamine treatment. As such, much research over the last five years has focused on elucidating the mechanisms of nonhistaminergic itch. The exogenous pruritogens cowhage, chloroquine and imiquimod and the endogenous pruritogens serotonin, endothelin-1, thymic stromal lymphopoietic protein (TSLP) and bovine adrenal medulla peptide (BAM) 8–22 signal via distinct histamine-independent molecular pathways and evoke robust scratching behaviors in TRPV1-deficient mice[4,6,10,12–14] (**Table 1**). However, the pharmacologic or genetic silencing of TRPV1-expressing neurons attenuates the itch behaviors induced by all of these pruritogens[10,12,13]. These data suggest that TRPV1-positive afferents mediate itch in response to diverse pruritogens and express a wide variety of itch receptors, signaling molecules and transduction channels.

The Mas-related G protein–coupled receptor (Mrgpr) family has emerged as a novel class of histamine-independent itch receptors[6,15]. MrgprA3 is a receptor for the antimalarial drug chloroquine, which has a side effect of itch[15]; but the endogenous agonist(s) that activate MrgprA3 *in vivo* to induce itch is not known. MrgprC11 is a receptor for the mast cell amide BAM. MrgprD is a receptor for β-alanine, which induces itch, mild prickling, tingling and burning sensations[16]. The MrgprD neurons are distinct from other classes of itch neurons in that they do not all express TRPV1 or TRPA1 ion channels and have been linked to pain, suggesting a more complex role for these neurons in somatosensation[17–21]. Chloroquine- and BAM-evoked itch also requires the irritant receptor TRPA1, which acts as the primary transduction channel downstream of MrgprA3 and MrgprC11. TRPA1 is required for both chloroquine- and BAM-evoked depolarization of somatosensory neurons as well as chloroquine- and BAM-evoked scratching in mice[14]. Interestingly, although signaling downstream of these two itch receptors converges on TRPA1, MrgprC11 signals through phospholipase C (PLC) and MrgprA3 via GβY (ref. 14). These studies highlight a potential role for Mrgprs and TRPA1 channels as mediators of chronic itch.

Patients with a variety of chronic itch conditions display high levels of proteases in their skin, which can activate protease receptors, including protease activated receptor 2 (PAR2)[22]. PAR2 is expressed in both keratinocytes and DRG neurons and is proposed to promote acute and chronic itch[22–24]. A direct role for PAR2 in neuronal itch signaling was suggested by studies using the ligand Ser-Leu-Ile-Gly-Arg-Leu (SLIGRL), which was proposed to act as a mimetic of the PAR2 ligand that is generated by proteolytic cleavage of the tethered peptide in the amino-terminal extracellular domain of PAR2 (ref. 24). When injected intradermally, SLIGRL induces neuronal excitability and robust itch behaviors in rodents. However, a recent study showed that SLIGRL also activates the MrgprC11 receptor, and scratch responses triggered by this peptide are abolished in Mrgpr-null animals but not affected in PAR2-deficient mice[25]. However, there is strong evidence for a role of PAR2 in human and mouse models of chronic itch. For example, tryptase and cathepsin S activate PAR2 by cleaving the N terminus, and their proteolytic products are increased in the skin of patients with atopic dermatitis[23,26]. Interestingly, the endogenous generation of PAR2 agonist by tryptase triggers robust itch behaviors that are attenuated in PAR2-deficient mice[12]. Unlike SLIGRL, tryptase does not activate rodent MrgprC11 or human MrgprX1, suggesting that SLIGRL is not equivalent to the natural tethered ligand *in vivo*[12].

In fact, PAR2 activation by SLIGRL, tryptase or cathepsin S also promotes the release of the cytokine, thymic stromal lymphopoietin (TSLP) from keratinocytes, indicating that intricate multicellular pathways may underlie chronic itch[12,27]. TSLP is a robust pruritogen associated with atopic dermatitis that activates a subset of neurons expressing TRPA1- and TSLP receptor (TSLPR) (**Fig. 1**). Indeed, TRPA1-deficient mice display significantly reduced itch behaviors after TSLP injection[12]. The broad expression of PAR2 and TSLPR in neurons, epithelial cells and immune cells, suggests that the analysis of tissue-specific knockouts is needed to elucidate the relative contributions of these cell types to itch.

Recent studies have implicated Toll-like receptors (TLRs) in neuronal itch signaling[28–30]. TLRs are best known for their role in innate immune responses. These membrane proteins act as sentinels for components of foreign organisms such as lipopolysaccharides, lipoproteins, flagellin, double- and single-stranded RNA and CpG DNA, and they also bind endogenous compounds released by necrosis or tissue remodeling[31]. TLRs are broadly expressed and are associated with pathological inflammatory conditions[32,33]. A number of reports suggest that TLRs have a key role in itch. First, tissue profiling suggests that sensory neurons express TLR3, TLR4, TLR7 and TLR9, but different studies describe distinct expression profiles[34]. Second, TLR agonists promote activation of sensory neurons, but whether they act directly on TLRs has not been settled, making the exact mechanism by which these receptors function in itch unclear[13,28,35]. However, TLRs remain intriguing candidates, as there are links between TLR polymorphisms and susceptibility to chronic itch disorders[36,37]. Owing to the broad expression of TLRs in keratinocytes, neurons and immune cells, tissue-specific knockout of candidate genes is required to establish the exact roles of TLRs in chronic itch.

Are itch neurons a homogeneous or heterogeneous population?

The number of itch-neuron subtypes remains enigmatic. Studies using the plant-derived pruritogen cowhage were the first to propose that there are histamine-dependent and histamine-independent itch pathways in the periphery[4]. Consistent with this model, many forms of chronic itch are insensitive to antihistamine treatment. Recent ablation studies also support a model with at least two subtypes of itch neuron. Genetic ablation of MrgprA3-expressing neurons attenuates mouse itch behaviors evoked by many pruritic compounds; responses to chloroquine, a direct MrgprA3 agonist, were nearly abolished, and itch behaviors to other pruritogens were partially reduced[38]. Likewise, genetic ablation of calcitonin gene–related peptide (CGRP)-expressing sensory neurons (which includes the MrgprA3 subgroup) resulted in a near complete loss of chloroquine- and histamine-evoked itch behaviors[39]. These results suggest that MrgprA3-positive neurons have an important function in itch but that additional neuronal subsets also detect pruritic stimuli (**Fig. 1**). Finally, pharmacological silencing of distinct subsets of neurons also suggests that itch-sensitive neurons are heterogeneous, with partially overlapping populations of histamine- and chloroquine-responsive cells[40].

The existence of separate itch and pain pathways is also controversial. Indeed, there has been a longstanding debate over how input from somatosensory neurons gives rise to the distinct sensations of itch and pain, leading to a number of models. First, the intensity model

suggests that itch neurons are polymodal and mediate sensations of both itch and pain; itch sensations are triggered when these neurons are weakly activated, whereas pain sensations are elicited when neurons are strongly activated. Second, the spatial-contrast model suggests that itch and pain neurons are polymodal but can be distinguished by their differential localization in the skin. Third, the labeled-line model proposes that itch and pain pathways are functionally and anatomically segregated in the PNS and CNS. Finally, the selectivity model posits that itch and pain neurons are polymodal, with itch sensations occurring when selective subsets of itch neurons are activated alone and pain sensations dominating when itch and pain neurons are activated together.

A number of studies support models in which itch neurons are polymodal. All itch-sensitive neurons also respond to classical algogenic stimuli, such as heat and capsaicin[6]. Likewise, high doses of pruritogens, such as histamine, induce pain, and low doses of algogens, such as capsaicin, evoke itch[6]. In further support of this model, electrophysiological recordings show that many peripheral and central neurons respond to both itch and pain stimuli[41–43]. The selectivity theory is supported by evidence that blocking pain transmission through deletion of the gene encoding vesicular glutamate transporter 2 (VGLUT2) in a subset of nociceptors triggers spontaneous itch behaviors[44,45]. However, whether the acute block of pain transmission also unmasks itch circuit activity is unknown.

A number of studies also support the existence of a selective subpopulation of itch neurons (**Table 2**). First, spinal neurons that express gastrin-releasing peptide receptor (GRPR) and the natriuretic polypeptide receptor subtype A (NPRA) are required for histamine-dependent and histamine-independent itch behaviors but not pain behaviors[46–48]. Second, a population of dorsal horn inhibitory interneurons expressing the basic helix-loop-helix B5 (Bhlhb5) transcription factor suppress itch but not pain-signal transmission[5]. Third, mice lacking MrgprA3-positive neurons display attenuated itch behaviors but normal pain sensitivity[38]. Fourth, mice expressing TRPV1 solely in MrgprA3-positive neurons exhibit scratching, but no pain behaviors when challenged with the TRPV1 agonist capsaicin[38]. Lastly, the pharmacological silencing of itch- sensitive neurons has no effect on pain behavior[40]. Overall, these experiments suggest that detection of itch and pain stimuli at the periphery occur through distinct classes of neurons and that the itch circuit is, at least in part, separate from the pain circuit.

Among these studies, there are some discrepancies in the percentages of cells required for itch responses as well as in the exact molecular identity of the cells responsible for itch (**Table 2**). Such differences may be due to varying experimental conditions or age of animals, incomplete ablation of neuronal subtypes or the timing of ablation or silencing relative to experimentation. Likewise, a number of unanswered questions about peripheral itch transduction persist, including the mechanisms by which itch is induced by the pruritogens serotonin, endothelin-1 and imiquimod (**Table 1**). Future studies will more precisely define the molecules and diverse populations of neurons required for itch detection.

How are itch signals transmitted to the spinal cord?

A number of exciting advances have been made in characterizing and identifying itch neurotransmitters. Glutamate was originally thought to be the main neurotransmitter released by primary itch neurons. Recent studies have suggested that gastrin releasing peptide (GRP), B-type natriuretic peptide (BNP; also called naturietic polypeptide B (NPPB)) and neuromedin B (NMB) may act as itch transmitters in conjunction with glutamate[46–49]. Whether NMB is a selective neurotransmitter is unknown; one study showed a role for NMB in itch[50], whereas another showed that NMB mediates pain but not itch transmission[49]. However, GRP and BNP are thought to function as itch-specific transmitters.

Evidence for glutamate acting as co-transmitter came from studies in which glutamate transmission was abolished in sensory neurons through deletion of the gene encodingVGLUT2 in TRPV1-expressing neurons[44,45]. Mice lacking VGLUT2 showed enhanced itch responses, suggesting that an additional neurotransmitter(s) is used at the first itch synapse in the absence of glutamate, and that glutamate-mediated transmission is required for disinhibition of itch (discussed below).

GRP has emerged as a key mediator of itch transmission. Ablation of dorsal horn interneurons that express GRPR attenuates itch behaviors in response to a variety of pruritogens, with no change in pain behaviors[47]. This seminal study suggested that itch and pain signals are transmitted via distinct circuits. However, whether GRP acts as a peripheral or central neurotransmitter remains controversial. Several lines of evidence support a model wherein GRP acts as a peripheral itch neurotransmitter that signals to second-order GRPR-expressing neurons in the spinal cord (**Fig. 2**, model 1). First, a number of studies have shown GRP expression in a subset of primary afferent sensory neurons and GRPR staining in dorsal spinal neurons[46,47,51]. Second, MrgprA3-positive primary afferent nerve terminals colocalize with synapsin and GRPR-expressing cells in the dorsal horn of the spinal cord[38]. Third, GRP expression was significantly increased in primary afferents in mice that display enhanced spontaneous and evoked itch behaviors due to constitutive activity of BRAF kinase in nociceptors[52]. However, a number of studies have reported little or no GRP staining in primary afferents[48,49,51] but robust GRP expression in dorsal horn neurons[48,51,53]. Indeed, GRP was first described in a microarray screen to identify dorsal horn–enriched genes[54]. Despite the contradictory evidence of GRP expression in peripheral tissue and the unresolved role of GRP in spinal cord neurons, GRP clearly has a key function in itch transmission, as mice deficient in GRPR do not scratch in response to a variety of pruritogens; however, these mice display normal itch responses to histamine, endothelin-1 and serotonin, suggesting the existence of multiple itch transmitters[46].

Recent studies have implicated BNP, a neurohormone secreted by the cardiac ventricles in response to volume expansion and pressure overload[55], in itch and pain transmission[48,56]. BNP is the modified product of the gene *Nppb* and targets the receptor NPRA. BNP is expressed in a subset of primary afferent neurons, and intrathecal injection of BNP triggers robust itch in mice and attenuation of inflammatory pain in rats. Mice lacking BNP display a loss of itch behaviors to a wide variety of pruritogens. Likewise, ablation of NPRA-

expressing interneurons eliminated BNP- and histamine-evoked itch behaviors. Overall these experiments demonstrate a key role for BNP in itch transmission.

What is the relationship between the GRP and BNP signaling pathways? Two findings support a model whereby BNP release by primary afferent neurons triggers the release of GRP by spinal cord interneurons (**Fig. 2**, model 2). First, NPRA is expressed in a subset of spinal interneurons that also express GRP. Second, mice lacking NPRA-expressing interneurons display normal GRP-evoked itch. Nevertheless, these experiments do not exclude the possibility that GRP may act in parallel with BNP to transmit signals from the PNS to the CNS (**Fig. 2**, model 3). Distinguishing between these three models will be an essential next step in understanding itch signal transmission.

How are itch signals modulated by spinal interneurons?

Some noxious mechanical (for example, scratching) and thermal stimuli (cold) inhibit the sensation of itch, whereas light stroking potentiates itch. Indeed, recent studies have shed light on our understanding of how spinal inhibitory interneurons contribute to itch sensations and how spinal thalamic tract (STT) neurons integrate multiple signals.

Excitatory pathways

Recent studies have identified three excitatory itch-interneuron subsets that express morphine receptors, the transcription factor T cell leukemia homeobox 3 (Tlx3) or the testicular orphan nuclear receptor (TR4). The analgesic morphine produces a side effect of intense itch, which can be reversed with μ-opioid receptor antagonists[57]. Several studies suggest that morphine-evoked itch and analgesia are mediated by two independent mechanisms. First, genetic analyses revealed that itch responses are dependent on MOR1D, a splice variant of the μ-opioid receptor, whereas analgesia requires the canonical form, MOR1 (ref. 57). The MOR1D variant is coexpressed with GRPR, suggesting that these receptors may form heterodimers that mediate morphine-evoked itch in a subset of morphine-sensitive interneurons. Second, electrophysiological analyses of trigeminothalamic tract neurons revealed that morphine increases the activity of pruriceptive interneurons and decreases activity of nociceptive interneurons[58].

The deletion of TR4 eliminates a subset of superficial dorsal horn neurons, which leads to a profound unresponsiveness to pruritogens[53]. Neurons that express both GRP and NPRA and neurons that express GRPR are missing in TR4-deficient mice. In contrast, the number of inhibitory dorsal horn neurons, primary afferent neurons and projection neurons are normal in TR4- deficient mice. Likewise, mice that lack Tlx3 in dorsal horn excita-tory neurons have major pruriceptive deficits owing to a loss of excitatory neurons that express somatostatin, preprotachykinin 1, GRP and/or GRPR[59]. Overall, these studies show that distinct subsets of dorsal horn neurons are required for itch transmission. However, these experiments do not address the issue of itch specificity in the CNS, as TR4- and Tlx3-deficient mice also display defects in pain behaviors.

Inhibitory pathways

Genetic ablation studies suggest that tonic activity of the itch circuit is inhibited by activation of the pain circuit. The genetic deletion of VGLUT2 in nociceptors abolishes pain transmission and leads to robust spontaneous itch behaviors[44,45]. Similarly, mice lacking a subset of inhibitory dorsal spinal neurons owing to the conditional deletion of the Bhlhb5 transcription factor[5] also display spontaneous itch behaviors. In addition to spontaneous scratching, both VGLUT2- and Bhlhb5-deficient mice display augmented pruritic responses to itch-inducing agents[5,44,45]. Together, these studies support a model of cross-inhibition, whereby glutamatergic pain afferents activate Bhlhb5-expressing interneurons, which in turn inhibit the itch circuitry (**Fig. 2**). This cross-inhibition model is also supported by the observation that activity-dependent silencing of neurons expressing TRPA1 or TRPV1 switches the behavioral response to mustard oil or capsaicin application from pain to itch[40]. The roles of known neurotransmitters[60] and other signaling mechanisms in cross-inhibition remain unknown. However, the κ-opioid receptor agonist nalfurafine inhibits scratching, suggesting that κ-opioid receptor–expressing neurons may form part of the inhibitory pathway for itch[61].

How are itch signals sent to and processed by the brain?

Electrophysiological itch studies of spinal thalamic tract (STT) neurons have examined the effects of cowhage and histamine on excitability. These studies show that cowhage and histamine elicit responses in separate populations of neurons, suggesting that different pruritogens activate distinct central pathways[4,43,62]. In addition, these studies show there is a convergence of itch and pain signals before the STT neurons. For example, itch-evoked firing of STT neurons in primates is enhanced by stroking, and inhibited by scratching, the skin[40].

Like STT recordings, brain imaging shows that cowhage and histamine activate distinct brains regions as well as some overlapping areas[63]. How this anatomical segregation affects the perception of itch is unclear. Future studies will define the brain regions that process itch sensations and may help explain the paradoxical convergence of itch and pain signals and apparent segregation of different pruriceptive stimuli.

What molecules and cells contribute to chronic itch?

Studies on acute itch have led to the identification of candidate molecules and cell types that may represent good targets for treating chronic itch. A number of chronic itch models have recently been developed to probe the function of transgenic mice lacking such candidates. The different models mimic distinct human itch disorders and fall into three broad categories: chemically induced itch, genetically induced itch or chronic itch that develops naturally in some inbred mouse strains (**Table 3**).

The discovery of MrgprA3, MrgprC11 and TRPA1 as histamine-independent itch transducers led to a number of studies examining the roles of these receptors in chronic itch. The importance of MrgprA3-positive neurons was examined in both the acetone ether water (AEW) dry skin–evoked model of itch and the ovalbumin-induced allergic contact

dermatitis model[38]. In the AEW model, mice deficient for these neurons exhibited a dramatic decrease in itch behaviors, to levels similar to that observed in untreated mice[38]. Loss of MrgprA3-positive neurons also led to a 50% decrease in allergic itch behaviors, suggesting that these neurons contribute at least partially to allergic itch[38]. The different outcomes of these chronic itch models is not surprising, as distinct forms of chronic itch in humans respond to different treatments and thus are hypothesized to involve distinct mediators. Mice lacking TRPA1 also displayed significantly decreased itch behaviors in both the AEW and allergic itch models[34]. In addition to decreased itch behaviors, loss of TRPA1 attenuated epidermal thickening and changes in gene expression in both neurons and skin that normally accompany the itch-scratch cycle[34]. In the allergic model, loss of TRPA1 decreased skin edema, immune cell infiltration and inflammatory cytokine levels[64]. These studies highlight a role for TRPA1 in both itch signal transmission and in the pathophysiological changes that occur within the skin to promote and/or maintain chronic itch.

Many studies using chronic itch models have focused on the communication between skin cells and the immune cells that promote itch and inflammation. Indeed, the use of immune cell inhibitors that target mast cells, basophils or T lymphocytes have been effective at treating antihistamine-insensitive chronic itch conditions. For example, in a clinical trial, monoclonal anti-IgE antibodies provided relief from the debilitating itch caused by idiopathic urticaria[65]. Likewise, a recent study using anti IL-31 antibodies was successful in treating inflammatory responses in atopic dermatitis[66]. Importantly, these trials highlight a key role for the immune system in mediating chronic itch. In addition to immune cells, sensory neuron terminals and epithelial cells also release inflammatory mediators that contribute to a complex network of multi-directional communication between cell types. For example, sensory neurons release substance P, which promotes immune cell chemoattraction and activation[67]. Similarly, sensory neurons and epithelial cells express receptors for inflammatory mediators[28,29,34]. Future studies using diverse itch models and tissue-specific knockout mice will help define the roles of each of these cell types in chronic itch.

Where do we go from here?

A number of key questions remain to be addressed to understand the development and maintenance of chronic itch. First, whether the molecules and cells that mediate acute itch, chronic itch and pain are the same remains controversial. Second, the changes in gene expression and somatosensory circuitry that occur during the development and maintenance of chronic itch have yet to be discovered. Third, it is unknown whether modulation of dorsal horn interneurons in the itch circuit promotes neuropathic itch. Fourth, the signaling mechanisms and relative contributions of epithelial cells, immune cells and sensory neurons in chronic itch must be elucidated. Finally, candidate mechanisms must be validated in a variety of different human itch disorders and translated to the clinic so that effective therapeutic strategies can alleviate a variety of human itch disorders. Identifying the molecules and cells that are shared and those that are unique to the itch and pain pathways may lead to the development of drugs and therapies to treat itch without affecting pain and to alleviate pain without triggering itch. The dramatic progress in recent molecular and clinical studies suggests better therapies for chronic itch are close at hand.

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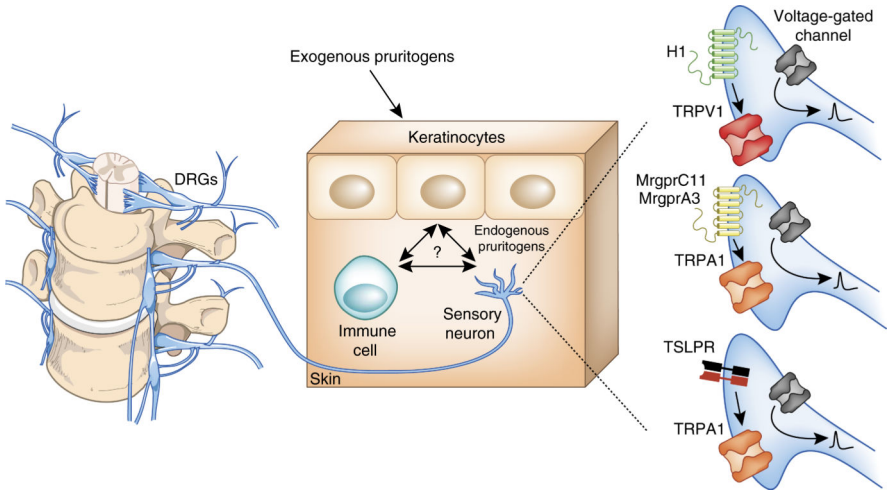

Figure 1.

Schematic depicting the cell types involved in the detection of diverse itch stimuli. DRG neurons (blue; left) innervate the skin and can be activated directly by exogenous or endogenous itch-inducing agents (pruritogens) released by keratinocytes, immune cells or neighboring neuronal afferent endings. However, many of these endogenous compounds also activate keratinocytes and various immune cells. In addition, cross-talk between all three cell types, via release of secreted compounds (for example, via neurogenic inflammation), can further modulate cellular responsiveness and itch pathway output. Distinct subsets of sensory neuron afferents innervate the skin and mediate itch signaling (right). The pruritogen histamine activates neurons via the histamine receptor 1 (H1) that leads to the opening of TRPV1 ion channels (red; top right). The pruritogens BAM8–22 and chloroquine activate neurons via MrgprC11 and MgprA3, respectively, leading to opening of TRPA1 channels (red; middle right). The cytokine TSLP activates neurons via TSLPR, which leads to the opening of TRPA1 channels (red; bottom right). The activation of TRPV1 or TRPA1 leads to neuronal depolarization, action potential firing and the transmission of itch signals from the periphery to the CNS. See Table 1 for a complete list of pruritogens and receptors implicated in itch.

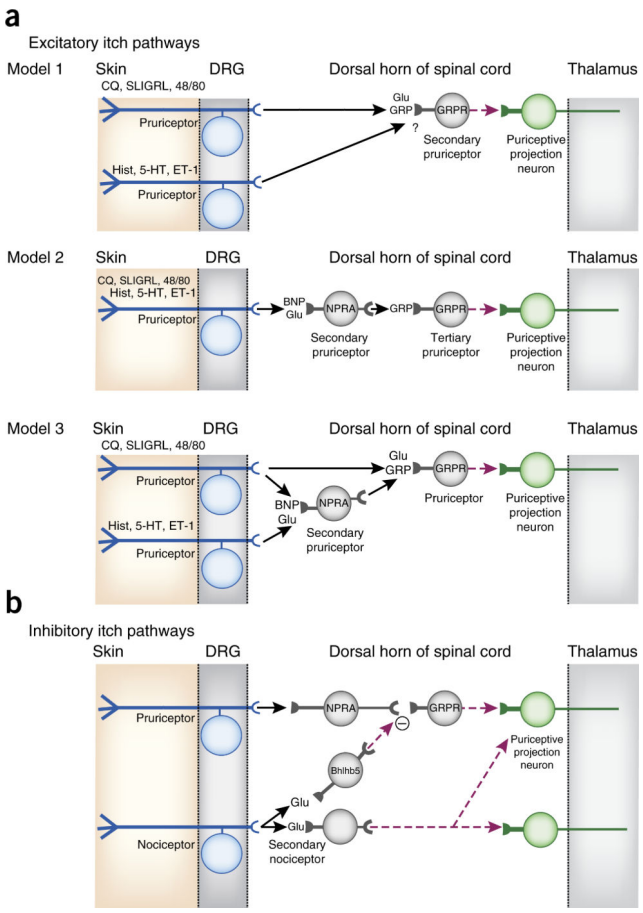

Figure 2.

Models of peripheral and spinal itch circuitry. (**a**) Excitatory itch pathways. Sensory neurons have cell bodies in the DRG (blue) and project primary afferents to the skin, where a variety of transduction molecules reside and detect itch, touch and pain stimuli. These neurons also send projections to the dorsal horn of the spinal cord, where they synapse with secondary neurons (gray). Second-order spinal neurons connect with other dorsal horn interneurons and/or spinal thalamic projection neurons (green). Model 1 proposes that GRP is a peripheral itch transmitter that activates GRPR on secondary pruriceptors. Chloroquine, SLIGRL and the mast-cell degranulating compound 48/80 (48/80) all require functional GRP signaling to evoke itch. Histamine (Hist), 5-hydroxytryptamine (5-HT) and endothelin-1 induce itch independent of GRP signaling. Model 2 proposes that BNP serves as a peripheral itch transmitter that activates secondary pruriceptors that express NPRA and GRP. These neurons then activate tertiary GRPR-expressing pruriceptors. Model 3 is a combination of models 1 and 2, in which BNP and GRP act in parallel as peripheral itch transmitters. GRP can be released by DRG neurons and NPRA-positive spinal neurons. BNP activates NPRA-expressing spinal interneurons, and GRP activates GRPR-expressing spinal interneurons. (**b**) Model for the inhibitory inputs of the itch pathway whereby tonic activity is inhibited by paired activation of the pain circuitry. A subset of VGLUT2-expressing nociceptors in the DRG and a subset of dorsal horn inhibitory interneurons expressing

Bhlhb5 specifically suppress itch signal transmission. Connections that are unknown or controversial are shown as dashed magenta arrows. CQ, chloroquine.

Table 1

Receptors and channels that mediate itch transduction in sensory neurons

	Receptor	Agonists	Type
Peripheral	Histamine receptor 1 (ref. 68)	Histamine	GPCR
	MrgprA3 (ref. 15)	Chloroquine	GPCR
	MrgprCll (MrgprX1 in humans)[15]	BAM, SLIGRL	GPCR
	MrgprD[16]	β-Alanine	GPCR
	Endothelin-1 (refs. 69-71)	Endothelin	GPCR
	5-HT receptors 1-7 (ref. 72)	Serotonin, 12(S)-HPETE	GPCR
	Protease-activated receptor 2 (refs. 24,26,73-75)	Tryptase, trypsin, SLIGRL, SLIGR, LIGRLO	GPCR
	TRL3 (ref. 29)	Poly(I:C)	Cytokine
	TLR7 (ref. 28)	Imiquimod	Cytokine
	TSLPR (in complex with IL-7Ra)[12]	TSLP	Cytokine
	IL-31R[66]	IL-31	Cytokine
	TRPA1 (ref. 14)	Allyl isothiocyanate, cinnamaldehyde (reviewed in ref. 76)	Ion channel
	TRPV1 (refs. 9,10)	Capsaicin (reviewed in ref. 77)	Ion channel
Central	GRPR[46,47]	GRP	GPCR
	Npra[48]	BMP (NPPB)	Receptor GC
	MOR1D[57]	Opioids	GPCR

Table 2

The cellular specificity of itch

	Loss of behavioral responses						
	Response to somatosensory stimuli						
Subset of sensory neurons ablated or silenced	**Histamine**	**Chloroquine**	**PAR2**	**β-Alanine**	**Heat**	**Pain**	**Touch**
Capsaicin-induced ablation of all TRPV1 neurons[10,18]	Complete loss	Complete loss	Complete loss	ND	Complete loss	Complete loss	Normal
Molecular genetic ablation of all CGRP-expressing neurons: ~50% of TRPV1 neurons eliminated[39]	Complete loss	Complete loss	ND	ND	Complete loss	Complete loss	Normal
Molecular genetic ablation of all MrgA3-expressing neurons: ~20% TRPV1 neurons eliminated[38]	Partial loss	Complete loss	Partial loss	ND	Normal	Normal	Normal
QX314-evoked silencing of chloroquine/PAR2-sensitive neurons[40]	Normal	Complete loss	Complete loss	ND	Normal	Normal	Normal
QX314-evoked silencing of histamine-sensitive neurons[40]	Complete loss	Normal	Normal	ND	ND	Normal	Normal

These studies demonstrate that particular subsets of neurons are required for the detection of the itch-inducing compounds histamine, chloroquine and PAR2 and other somatosensory behaviors, including touch, heat and pain. Complete loss, complete loss of a somatosensory behavior; partial loss, partial elimination; normal, no change; ND, not determined (modality was not tested).

Table 3

Chronic itch models in rodents that recapitulate human chronic itch disorders

	Itch assay or mouse line	Human disease model	Species	Genetic modification
Chemical	AEW[78,79]	Dry skin	Mouse	*Trpa1*$^{-/-}$, *Mrgpra3* ablation
	Ovalbumin sensitization[80]	Allergy	Mouse	*Trpa1*$^{-/-}$, Mrgpra3 ablation
	Oxazolone[80]	Irritant contact dermatitis	Mouse	None
	Ethynylestradiol[60]	Cholestasis	Rat	None
	Diphenylcyclopropenone[81]	Contact dermatitis	Mouse	None
	2,4,6-Trinitro-1-chlorobenzene[80]	Contact dermatitis	Mouse	None
	Dorsal horn quisqualate injection[82]	Neuropathic itch	Rat	None
	Streptozotocin[83]	Diabetes	Rat	None
	Dermatophagoides pteronyssinus [84]	Allergy; asthma	Mouse	None
Genetic	K5 IL-13 (IL-13 overexpression in skin)[85]	Atopic dermatitis	Mouse	None
	K14 human chymotryptase overexression[86]	Psoriasis	Mouse	None
	K5 IL-4 overexpression[80]	Atopic dermatitis	Mouse	None
	Cathepsin S overexpression[80]	Atopic dermatitis	Mouse	*Par2*$^{-/-}$
	K5IL-18Tg (IL-18 overexpression in skin)[87]	Atopic dermatitis	Mouse	None
	KCASP1Tg (caspase 1 overexpression in skin)[87]	Atopic dermatitis	Mouse	None
	Spink5$^{-/-}$ (ref. 88)	Netherton syndrome	Mouse	None
	TLR4-deficient mice and 3-week *Aspergillus fumigatus* allergen[89]	Atopic dermatitis	Mouse	None
	Stat6VT and vitamin D[90]	Atopic dermatitis	Mouse	None
	SPT-cKO mice (knockout of serine palmitoyltransferase, critical for ceramide biosynthesis)[91]	Psoriasis	Mouse	None
	IL-31 overexpression[80]	Atopic dermatitis	Mouse	None
	TSLP overexpression[80,92,93]	Atopic dermatitis	Mouse	None
	IL-18 overexpression[80]	Atopic dermatitis	Mouse	None
	RelB$^{-/-}$ (ref. 80)	Atopic dermatitis	Mouse	None
	Ctse$^{-/-}$ (ref. 80)	Atopic dermatitis	Mouse	None
	Msx2-cre Rbpj$^{-/-}$ (DNA-binding partner of Notch)[93]	Barrier disruption	Mouse	None
	K5-TSLP[80]	Atopic dermatitis	Mouse	None
	K5-tTA-Tight-IL-13 (IL-13 overexpression in skin)[94]	Atopic dermatitis	Mouse	*Trpa1*$^{-/-}$
Inbred strain	DAbg/bg[80]	Spontaneous dermatitis; atopic dermatitis	Rat	None
	NC/Tnd mice/NGA[80]	Atopic dermatitis	Mouse	None
	SJL/J mice[95]	Chronic inflammatory liver disease	Mouse	None
	Flaky tail mice[80]	Atopic dermatitis	Mouse	None
	Naruto Research Institute Otsuka Atrichia (NOA) mice[80]	Atopic dermatitis	Mouse	None

	Itch assay or mouse line	Human disease model	Species	Genetic modification
Other	Bile duct ligation[96]	Liver disease	Rat	None
	Scratching[97]	Scratching; itch-scratch cycle	Mouse	None
	Wire-brush scratching[98]	Barrier disruption	Mouse	None