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Invited Review Article

Peripheral itch sensitization in atopic dermatitis

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ABSTRACT

Atopic dermatitis is a skin disorder caused by skin dryness and barrier dysfunction, resulting in skin inflammation and chronic itch (or pruritus). The pathogenesis of atopic dermatitis is thought to be initiated by a lowering of the itch threshold due to dry skin. This lowering of the itch threshold is at least partially due to the increase in intraepidermal nerve fibers and sensitization of sensory nerves by interleukin (IL)-33 produced and secreted by keratinocytes. Such skin is easily prone to itch due to mechanical stimuli, such as rubbing of clothing and chemical stimuli from itch mediators. In patients with atopic dermatitis, once itch occurs, further itch is induced by scratching, and the associated scratching breaks down the skin barrier. Disruption of the skin barrier allows entry into the epidermis of external foreign substances, such as allergens derived from house dust mites, leading to an increased induction of type 2 inflammatory responses. As a result, type 2 cytokines IL-4, IL-13, and IL-31 are mainly secreted by Th2 cells, and their action on sensory nerve fibers causes further itch sensitization. These sequences of events are thought to occur simultaneously in patients with atopic dermatitis, leading to a vicious itch-scratch cycle. This vicious cycle becomes a negative spiral that leads to disease burden. Therefore, controlling itch is essential for the treatment of atopic dermatitis. In this review, we summarize and discuss advances in the mechanisms of peripheral itch sensitization in atopic dermatitis, focusing on skin barrier-neuro-immune triadic connectivity.

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Introduction

Itch (or pruritus) is defined as an unpleasant sensation that causes a desire to scratch. Two possible physiological reasons have been proposed for itching. One is activation of the self-defense system against external foreign substances, while the other is an alarm reaction that signals abnormalities throughout the body, including the skin.^{1–4}

Four organs, the skin, dorsal root ganglia (DRG), spinal cord, and brain, are greatly involved in the formation of itch transmission and perception (Fig. 1). Sensory nerves, classified as A-, B-, and C-fibers, project from the DRG to the skin. Sensory nerves associated with itch are mainly C-fibers, which have no myelin sheath and therefore transmit information at a slower rate.^{5–7} A recent human study demonstrated that some A-fibers were involved in itch induced by

intradermal insertion of spicules from the cowhage plant (*Mucuna pruriens*).⁸

When sensory C-fibers are directly excited by external mechanical and/or chemical stimuli, neuronal firing is transmitted to the spinal cord.^{2–4} The excitation is transmitted to spinal dorsal horn neurons via neurotransmitters, such as gastrin-releasing peptide (GRP), natriuretic peptide b (Nppb, also known as BNP) and glutamate, and then the information is conveyed through the spinal thalamic pathway and/or the spinal cord-parabrachial nucleus pathway to the brain, where itch is perceived.^{9–12} Sensory C-fibers are also excited by itch mediators released from keratinocytes and immune cells, such as mast cells, and T cells due to external stimuli or inflammation, and neuronal firing is transmitted to the brain, causing itch sensation (Fig. 1).^{3,4}

In a healthy condition, insect bites that cause acute itch are relieved by scratching.¹³ Meanwhile, chronic itch persists for more than six weeks and does not respond to existing therapies (i.e. intractable itch)¹⁴; it can significantly impair patients' quality of life (QOL), leading to disease burden.^{15,16} Against this background, treatment and prevention methods for intractable itch are being actively pursued worldwide, while the elucidation of the mechanism

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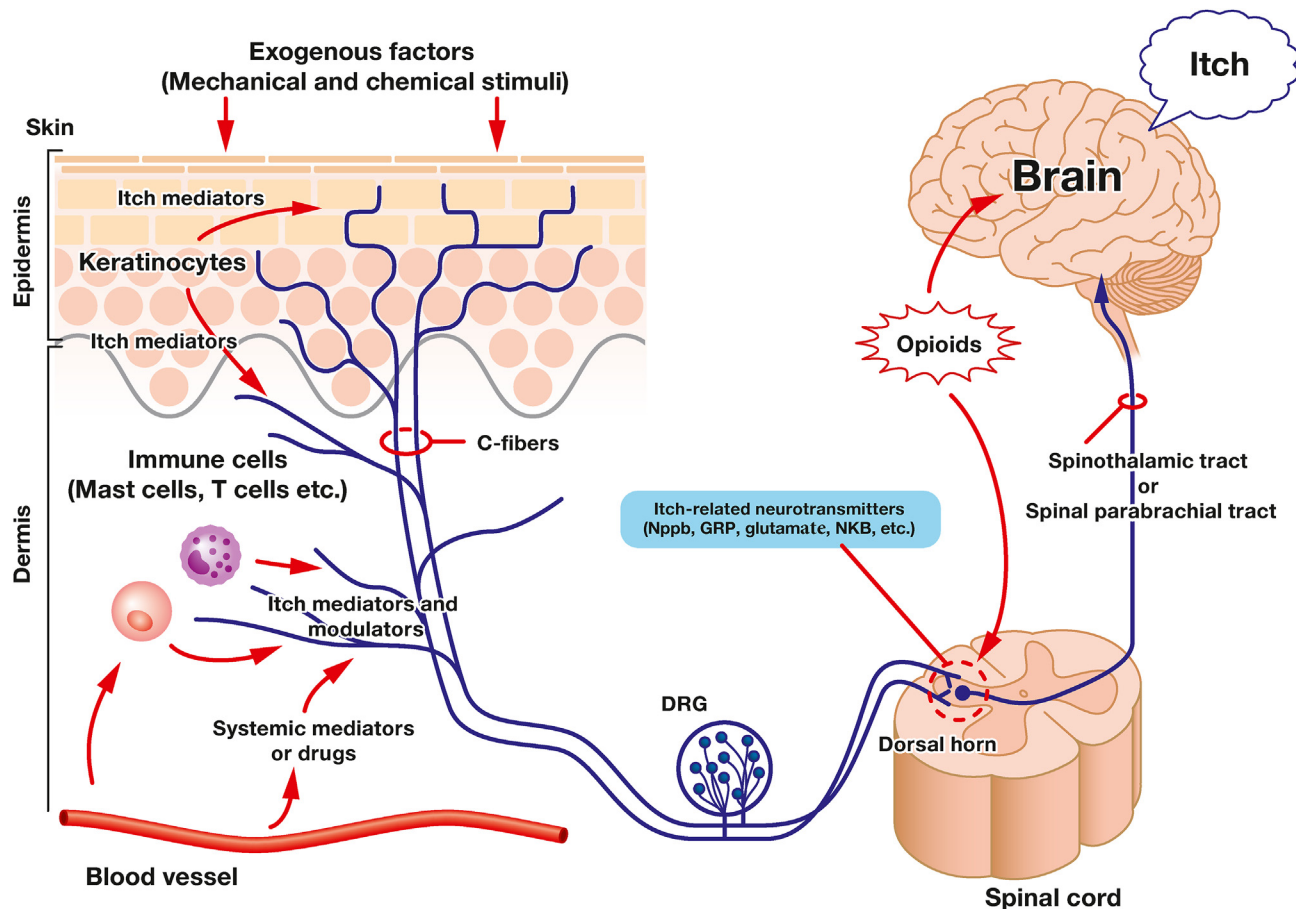


Fig. 1. Basic itch transmission pathway from skin to brain. Exogenous pruritic stimuli, both mechanical and chemical, excite sensory nerves (mainly C-fibers). Endogenous pruritogenic factors produced by epidermal keratinocytes and immune cells (mast cells, T cells, etc.) also act on and excite sensory nerve fibers via their corresponding receptors and channels. Excited sensory nerves release itch transmitters (e.g., Nppb, GRP, glutamate, NKB, etc.) to the dorsal horn of the spinal cord. The released neurotransmitters excite spinal dorsal horn neurons, which transmit itch information to the brain via the spinal cord-thalamic tract or the spinal cord-parabrachial nucleus tract. GRP, gastrin-releasing peptide; NKB, neurokinin B; Nppb, natriuretic peptide B.

of intractable itch is essential to overcome itch. More recently, therapeutic agents for atopic dermatitis targeting Th2 cytokines, their cognitive receptors and their signaling molecules have been developed, with demonstrated efficacy in clinical practice.^{17–19} However, it is difficult for these drugs to completely alleviate itching in atopic dermatitis, which has a wide range of causes.

In this review, we outline and update the mechanisms of peripheral itch sensitization in atopic dermatitis from the viewpoint of skin barrier-neuro-immune triadic connectivity.

What is itch in atopic dermatitis?

Dry skin and itch

As the outermost organ, skin serves as both a biological defense system and a moisture regulation system.^{20,21} When the skin barrier function is lowered by environmental or genetic factors, the skin becomes dry and itchy.^{3,4,22} This dry skin-induced “intractable itch” is resistant to antihistamines and existing treatments.²³

Dry skin is one of the hallmarks of atopic dermatitis. Genetic factors, such as mutations in the filaggrin gene, have been at least partly implicated in the development of dry skin in patients with atopic dermatitis, even in non-lesional areas. Environmental factors, such as surfactants and skin microflora, are also thought to be involved in the development of dry skin in atopic dermatitis.^{24–27} Dry skin can occur in patients with systemic diseases, such as renal, liver,

or skin disease; chronic and intractable itch may also manifest in these diseases.²³ Moreover, skin dryness is thought to decrease the itch threshold by increasing the density of intraepidermal nerve fibers (IENFs).^{28,29} Thus, dry skin is thought to be one of the factors that induce intractable itch and/or hypersensitivity to itch.

Characteristics of itch in atopic dermatitis

The skin of patients with atopic dermatitis is hypersensitive, exhibiting *alloknesis*, in which innocuous stimuli (such as rubbing by clothing) that would not normally cause itching, and *hyperknesis*, in which normal itchy stimuli cause more intense itching.^{2–4} Painful stimuli also trigger itching, which is exacerbated by scratching.^{30,31} It is also characterized by resistance to antihistamines, histamine H₁ receptor (H₁R) antagonists.^{1,32} In the past, antihistamine-resistant itch was referred to as intractable itch, but as therapeutic agents for itch have been continuously developed in recent years,^{18,32} it is currently considered as itch unresponsive to existing treatments.

Itch-scratch cycle and beyond

These itch characteristics in atopic dermatitis manifest a vicious itch-scratch cycle.^{33–36} Because the skin of patients with atopic dermatitis is hypersensitive to itch, scratching behavior occurs; however, the itch does not subside even after repeated scratching, which destroys the skin barrier. This allows allergens

and other substances to enter the body, instigating or exacerbating inflammation. In addition, itch mediators and/or modulators produced and secreted by inflammatory cells induce and enhance itch recurrence. This series of events forms the problematic itch-scratch cycle in atopic dermatitis (Fig. 2).^{34,36} To break this vicious spiral, the priority is to quell and control the intractable itch. Thus, it is important to clarify the mechanism of itch in atopic dermatitis.

Itch mediators

The itch mediators identified by previous studies are summarized in Table 1. Herein we discuss the itch mediators associated with atopic dermatitis (Fig. 3).

Histamine

Histamine is known as a classic itch mediator. In the skin, mast cells are the main histamine producers; it has been recently

reported that epidermal keratinocytes, basophils, and neutrophils also produce histamine.³⁷ Histamine secreted by these cells binds to H₁R expressed on sensory nerve fibers (mainly C-fibers) distributed in the skin and opens the transient receptor potential vanilloid 1 (TRPV1) channel. Subsequently, calcium (Ca²⁺) influx triggers neuronal excitation and induces itch.³⁷ For this reason, antihistamines designed to target the H₁R are used in clinical practice. Previous studies suggest that histamine activates the TRPV1 channel via phospholipase A2 (PLA2)/lipoyxygenase.^{38,39} Other studies have shown that histamine-induced scratching behavior is reduced in mice deficient in both PLC3 and TRPV1 genes.^{40,41} The histamine receptor, H₄R, is also involved in histamine-induced itch.³⁷ Histamine increases the production of IL-31, an itch mediator and/or modulator, by binding to H₄R expressed on Th2 cells.⁴² Notably, TRPV1 channel inhibition reduced H₁R- and H₄R-induced itch, whereas transient receptor potential ankyrin 1 (TRPA1) channel inhibition reduced H₄R- but not H₁R-induced itch.⁴³ These suggest that both channels, TRPV1 and TRPA1, are involved in the transmission of histamine-dependent itch.

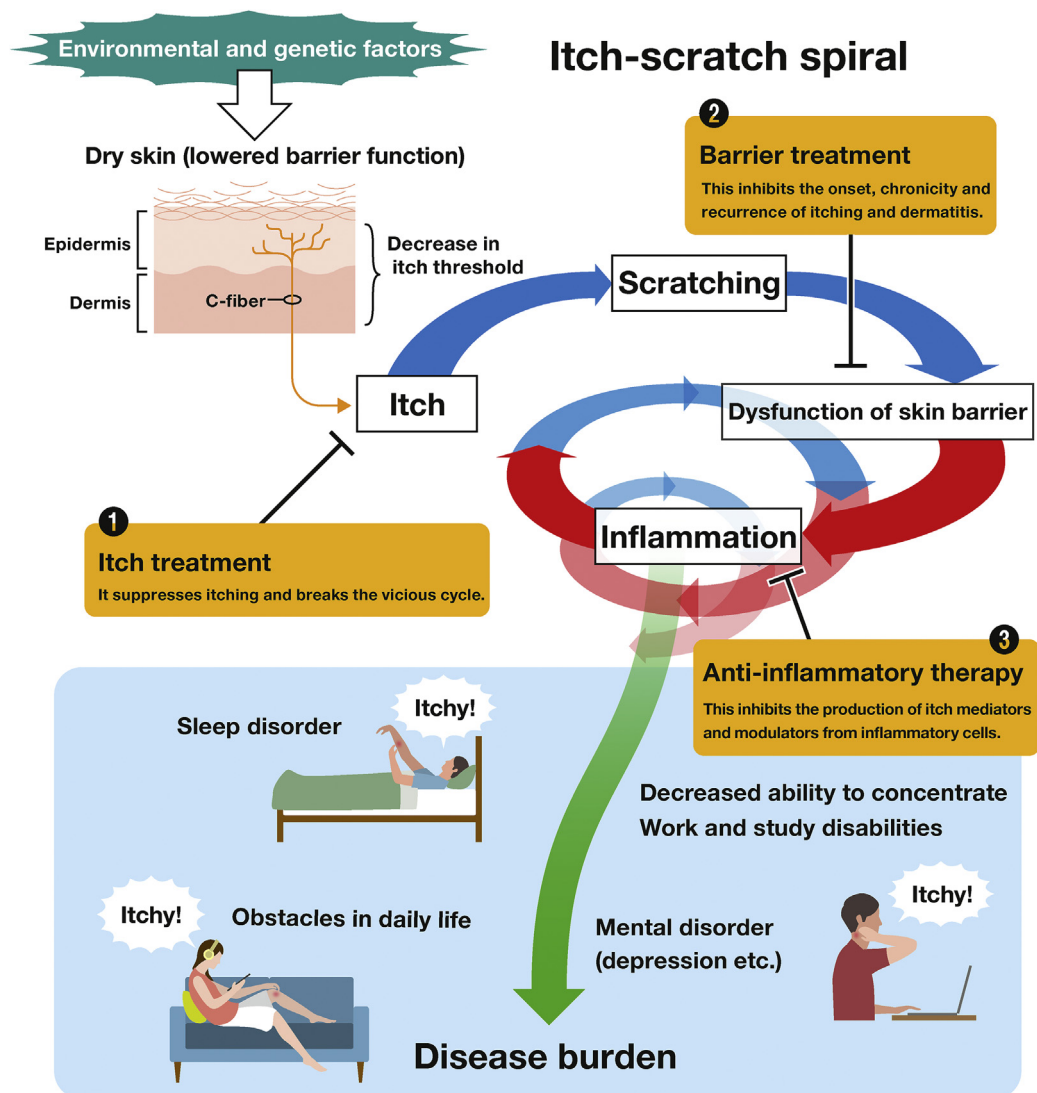


Fig. 2. Itch-scratch spiral and key points of therapeutic intervention in atopic dermatitis. Itching easily occurs when dry skin is subjected to itch stimuli. Scratching behavior breaks down the skin barrier, causing the release of various itch mediators, sensitizers, and proinflammatory substances. This leads to a vicious cycle of itchiness and repeated scratching, which exacerbates dermatitis (itch-scratch cycle). If the itch-scratch cycle cannot be broken, it becomes a negative spiral that leads to disease burden. Therefore, in the treatment of atopic dermatitis, it is most important to reduce the patient's itchiness, and at the same time, it is recommended to improve the skin barrier and provide anti-inflammatory treatment.

Itch mediators other than histamine

Previous studies have identified at least 40 itch mediators other than histamine (Table 1). Serotonin (5-hydroxytryptamine [5-HT]) binds to serotonin receptors (5-HT_{2A}R, 5-HT₇R) expressed on sensory nerve fibers and induces itch by Ca²⁺ influx from the TRPV4 or TRPA1 channel.^{44–46} Proteases (e.g., tryptase, kallikreins), peptides (e.g., substance P [SP], endothelin-1), lipid mediators (e.g., lysophosphatidic acid [LPA]), and cytokines (e.g., IL-31, TSLP) also act on receptors expressed on sensory nerves to induce itch (Table 1, Fig. 3).^{3,23,34,47}

Some Mas-related G-protein-coupled receptors (Mrgpr) agonists have also been identified as itch mediators.⁴⁷ Chloroquine (CQ), an antimalarial drug, and bovine adrenal medulla (BAM) 8–22, a cleavage product of proenkephalin, induce itch via MrgprX1, which is expressed in human C-fibers. In mice, CQ and BAM8-22 bind to MrgprA3 and MrgprC11, respectively. Previous studies using genetically modified animals have shown that CQ binds to MrgprA3, opens the TRPA1 channel via G $\beta\gamma$ activation, and

excites DRG neurons.⁴⁸ In addition, BAM8-22 binds to MrgprC11, activates G α_q , and then excites DRG neurons by opening the TRPA1 channel via PLC β activation.⁴⁸ Meanwhile, a recent electrophysiological study demonstrated that the TRPA1 channel is not required for the CQ-induced neuronal response, rather, anoctamin-1 (ANO1), a calcium-activated chloride channel, is partially involved.⁴⁹ Thus, the MrgprA3 signaling mechanism remains under debate. β -alanine, a known muscle-building supplement, also induces itch by binding to MrgprD.⁴⁷ SP also activates MrgprA1 on sensory neurons, rather than neurokinin-1 receptor (NK-1R), to induce itch in mice.⁵⁰

Recent studies on atopic dermatitis identified IL-31 and TSLP as highly selective itch mediators.^{36,51,52} IL-31 is mainly produced by Th2 cells and is increased in the lesions and serum of atopic dermatitis patients.^{51,53,54} IL-31 binds to IL-31 receptors (heterodimers formed from IL-31RA and OSMR) expressed on sensory nerve fibers and causes neuronal excitation via TRPV1 and/or TRPA1 channels to induce itch.³⁶ IL-31RA is also expressed on epidermal keratinocytes; when IL-31 acts on epidermal keratinocytes, they produce and secrete LTB₄, which binds to BLT1 receptors on sensory nerve fibers to induce itch.⁵⁵

A more recent study reported that basophils release LTC₄ upon stimulation with antigen-specific IgE, which binds to CysLTR₂ (LTC₄ receptor) expressed on sensory nerve fibers (mainly the NP3 neuron) to induce acute itch in atopic dermatitis.⁵⁶ In the MC903-treated dermatitis model, CysLTR₂ is also involved in chronic itch.⁵⁷ Therefore, LTC₄-CysLTR₂ has attracted attention as a molecular signaler that promotes itch in atopic dermatitis.

Sphingosine 1-phosphate (S1P) is a bioactive sphingolipid associated with a variety of skin diseases, such as atopic dermatitis and psoriasis.⁵⁸ A recent study has shown that S1P causes both itch and pain sensations, and that S1P receptor 3 (S1PR3)-TRPA1 signaling expressed in sensory nerves contributes to the onset of itch.⁵⁹

Glucosylsphingosine, an endogenous sphingolipid, is highly accumulated in the epidermis of patients with atopic dermatitis due to abnormal ceramide metabolism. More recent studies revealed that glucosylsphingosine induces itch through activation of 5-HT_{2A}R and the TRPV4 channel in sensory neurons.^{60,61} Thus, glucosylsphingosine-5-HT_{2A}R-TRPV4 signaling is at least partly involved in the induction of itch in atopic dermatitis.

TSLP produced by epidermal keratinocytes binds to TSLP receptors formed by heterodimers of TSLPR and IL7R expressed on C-fibers, and then activates the TRPA1 channel to induce itch.⁵² Recent studies have shown that TSLP and the TRPV4 channel play a central role in dry skin-induced itch.⁶²

The alarmin molecule IL-33 is secreted by epidermal keratinocytes during the breakdown of the skin barrier and acts on ILC2 to induce the production of cytokines involved in type 2 inflammation.²⁷ Concomitantly, IL-33/ST2 signaling is functionally present in primary sensory neurons and contributes to itching in poison ivy-induced allergic contact dermatitis.⁶³ However, IL-33 is currently thought to function more as an itch sensitizer than an itch mediator.⁶⁴

Periostin is an extracellular matrix involved in the exacerbation of allergic inflammation, such as atopic dermatitis.⁶⁵ A more recent study reported that intradermal administration of periostin to mice, beagle dogs, and monkeys induced itch, and further investigation revealed that periostin binds to integrin $\alpha v \beta 3$ expressed on sensory nerve fibers and that itch is mediated by both TRPV1 and/or TRPA1 channels.⁶⁶

Endothelin (ET)-1 is a 21-amino acid peptide with potent vasoconstrictor activity.⁶⁷ The receptors for this peptide are endothelin-A (ET_A) and endothelin-B (ET_B), which are expressed on epithelial cells, immune cells, and sensory neurons.⁶⁷ Although ET-

Table 1
Itch mediators and their cognate receptors and channels in the periphery.

Category	Itch mediators	Receptors and channels in sensory neurons
Amines	Histamine 5-HT	H ₁ R/TRPV1, H ₄ R/TRPA1 5-HT _{2A} , 5-HT ₇ , TRPA1, TRPV4
Proteases (includes tethered ligands)	SLIGRL AYPGKF Tryptase Mucinain Kallikrein 5, 7, 14 Cathepsin S	PAR-2, MrgprC11 PAR-4 PAR-2 PAR-2, PAR-4 PAR-2 PAR-2, PAR-4, MrgprC11
Peptides	Substance P Endothelin-1 α -MSH	NK-1R, MrgprA1 (mouse) ETA receptor MC1R, MC5R
Lipids	PAF LPA LTB ₄ LTC ₄ TXA ₂ 12-HETE S1P Glucosylsphingosine	PAF receptor LPA5, TRPA1 BLT1 receptor, TRPV1, TRPA1 CysLT ₂ R TP receptor BLT2 receptor S1PR3, TRPA1 5-HT _{2A} , TRPV4
Cytokines	IL-31 IL-33 TSLP CXCL10 (IP-10)	IL-31RA, OSMR, TRPV1, TRPA1 IL-1RACp/ST2 TSLPR (in complex with IL-7Ra), TRPA1, TRPV4 CXCR3
Mrgpr agonists	Chloroquine BAM8-22 β -alanine DEFB103 Defb3 Defb14 IP defensins 1&2	MrgprX1 (human), MrgprA3 (mouse), TRPA1 MrgprX1 (human), MrgprC11 (mouse), TRPA1 MrgprD MrgprX1 (human) MrgprA1 > A3 > B2 MrgprA1 > A3 > B2 > A2b > C11 MrgprX1 (human), MrgprC11 (mouse), TRPV1
Uncategorized	Bile acids Bilirubin Periostin Poly(I:C) Imiquimod Oxidative stress miR-711	TGR5 (mouse), MrgprX4 (human), TRPA1 MrgprA1 (mouse), MrgprX4 (human) Integrin receptor $\alpha v \beta 3$, TRPV1, TRPA1 TLR3 TLR7 TRPA1 TRPA1

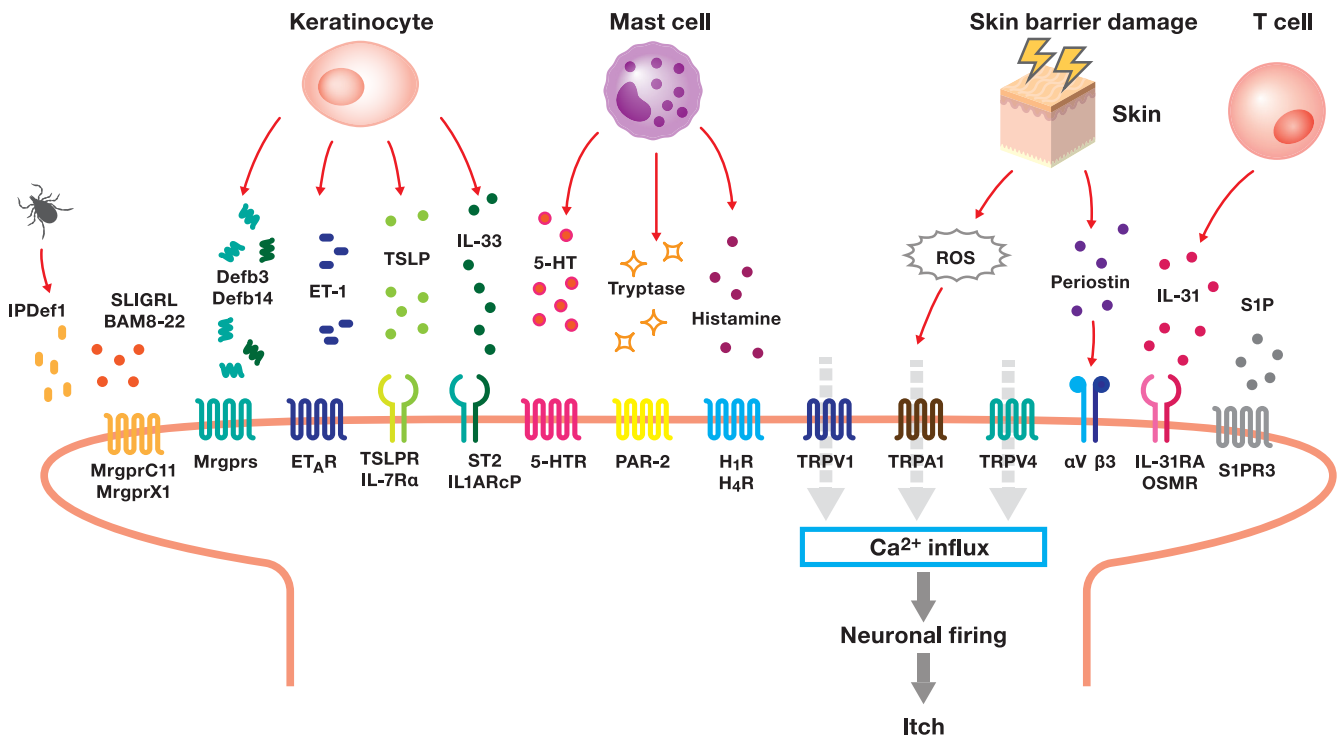


Fig. 3. Itch mediators and their cognate receptors and channels in atopic dermatitis. The itch mediators that are related (or likely to be related) to the development of itch in atopic dermatitis are summarized.

1 is important in mediating acute pain and hyperalgesia,^{68–70} recent studies have shown that it is also a mediator of itch.^{71–75} ET-1-evoked scratching was decreased by an antagonist of the TRPA1 channel and was significantly attenuated in TRPA1-knockout mice, but not in TRPV1-knockout mice.^{74,76} Thus, ET_A receptor-TRPA1 signaling may be involved in ET-1-induced itch in mice. Several human studies have shown that intradermal injection of ET-1 induces burning itch.^{74,77,78} Moreover, it evoked short-lived pain and prolonged itch, and the level of ET-1 was upregulated in patients with chronic itch due to prurigo nodularis or atopic dermatitis.^{74,79}

β-defensins are antimicrobial peptides produced by epithelial cells, such as keratinocytes, and are highly expressed in the epidermis of patients with psoriasis and atopic dermatitis.⁸⁰ More recently, it has been shown that mouse and human β-defensins, as well as tick-derived defensins, bind to Mrgprs expressed in sensory nerves and induce itch.^{81–83} A mouse study revealed that intradermal administration of Defb14, a homologous molecule of human β-defensin 3 (DEFB103), and Defb3, which is homologous to part of human β-defensin 2 (DEFB4), caused scratching behavior in mice, with a higher scratching frequency with Defb14 than with Defb3.^{81,83} The study using cell lines expressing Mrgprs revealed that Defb14 binds with affinity in the order MrgprA1 > A3 > B2 > A2b > C11, while Defb3 binds with affinity in the order MrgprA1 > B2 > A3.⁸³ Similar studies have shown that human DEFB103 binds with an affinity in the order MrgprX1 > X2 > X3, and DEFB4 binds with an affinity in the order MrgprX2 > X1.⁸³ Therefore, although there is no direct evidence that these β-defensins act on sensory nerves to cause itch in humans, the affinity results for Mrgprs and the expression of MrgprX1 in human sensory nerves suggest that β-defensins, especially DEFB103, are likely to function as itch mediators in humans. In addition, intradermal administration of tick salivary peptides, IP defensin 1 (IPDef1) and IR defensin 2 (IRDef2), induced itch in mice.⁸² In this case, IPDef1 induced more intense itching than IRDef2.⁸² Moreover, IPDef1 binds

to mouse MrgprC11 and human MrgprX1, which are expressed in sensory nerves, suggesting that IPDef1 induces itch via the TRPV1 channel.⁸²

TLRs are pattern recognition receptors important for innate immunity. Since TLR3 is also involved in the expression of itch and its agonist is double-stranded RNA, viral-derived or *in vivo*-produced double-stranded RNA may induce itch via TLR3.⁸⁴ One study reported that miR-711 induced itch via TLR3.⁸⁵ MicroRNA binds to the TRPA1 channel and induces itch. Moreover, in a chronic-itch mouse model of cutaneous T-cell lymphoma (CTCL), miR-711 levels were increased in serum and foci, suggesting that miR-711 is one of the mediators of itching associated with CTCL.⁸⁵ The TRPA1 channel is also sensitive to oxidative stress and is involved in the development of oxidative stress-induced itch.⁸⁶ Thus, many itch mediators other than histamine have been identified, against which antihistamines are ineffective.

Subtype of NP neurons for itch

Primary sensory nerves in the skin are responsible for the transmission of itch.⁸⁷ In 2015, sensory neurons in murine DRG were classified into four clusters and further divided into 11 subsets through large-scale single-cell RNA sequencing analysis.⁸⁸ Notably, NP1, NP2, and NP3 neurons express receptor genes for itch mediators (Table 2).⁸⁸

The NP1 neuron specifically and strongly expresses *Mrgprd*, a receptor for β-alanine, and expresses, *Lpar3* and *Lpar5*, receptors for lysophosphatidic acid (LPA). The NP2 neuron expresses *Mrgpra3*, a receptor for chloroquine; *Mrgprc11*, a receptor for BAM8-22; and *Hrh1*, a receptor for histamine. The NP3 neuron expresses the IL-31 receptor (*Il31ra*, *Osmr*), serotonin receptors (*Htr1f*, *Htr2a*), *Hrh1*, leukotriene C₄ receptors (*Cysltr2*), and *Nppb*. Neurotensin (*Nts*), somatostatin (*Sst*), and low levels of *P2rx3* have also been detected in NP3. The common denominator of these neurons is the

expression of IL-4/IL-13 receptors. Thus, there are at least three subtypes of primary sensory nerves for itch, each with a unique response profile.

More recently, single-nucleus transcriptomic analysis classified human lumbar 4 (L4) and L5 DRG neurons into H1 to H15 classes.⁸⁹ Among these classes, it has been suggested that the H10 and H11 classes correspond to NP1, NP2, NP3, and C-LTMRs in mice (Table 2). These findings shed light on the differences in neuronal cell types and the expression of key genes between humans and mice.

Spinal itch transmission

Itch information generated in the skin is transmitted from primary afferent C-fibers to spinal dorsal horn neurons (secondary neurons) via neurotransmitters.^{2,47,90} Glutamate/ α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-type glutamate receptor (AMPA), GRP/GRP receptor (GRPR), and Nppb/natriuretic peptide receptor A (NPRA) have been identified as neurotransmitters for spinal itch transmission (Fig. 1). Recently, it was suggested that neurokinin B (NMB)'s involvement in spinal itch transmission differs from that of GRP.⁹¹ GRP conveys itch induced by CQ, SLIGRL-NH₂, and BAM8-22, whereas NMB conveys itch induced by histamine and 5-HT. It is presumed that NMB excites NMB receptor-expressing neurons (NMBR⁺ neurons) in the dorsal horn of the spinal cord, and that the excited NMBR⁺ neurons release glutamate to GRPR⁺ neurons to transmit itch information.⁹¹

Neurokinin B (NKB) is involved in the neurotransmission of itch induced by IL-31.⁹² NKB conveys IL-31-induced itch to GRPR⁺ neurons via NK-3 receptor-expressing neurons in the dorsal horn of the spinal cord.⁹²

Skin barrier-neuro-immune triadic connectivity for itch sensitization in atopic dermatitis

Densification of IENFs

Decreased barrier function leads to skin dryness, which prompts sensory nerve fibers to elongate and branch in the epidermis.^{29,93,94} Since the barrier function is weakened, mechanical and chemical itch stimuli may directly excite intraepidermal nerve fibers (IENFs) and cause hypersensitivity to itch.^{95–98} This densification is thought to be partly responsible for the formation of the itch-scratch cycle (Fig. 4A, B).²⁹ In addition, since histamine-H₁R and H₄R are not involved in this itch pathway, antihistamines do not alleviate itch caused by firing of IENFs.

The densification of IENFs is regulated by nerve elongation factors (NEFs), which act as attractants, and nerve repulsion factors (NRFs), which act as retractors (Fig. 4C).²⁹ Nerve growth

factor (NGF), amphiregulin (AR), and artemin produced by epidermal keratinocytes have been reported as NEFs involved in the growth of IENFs.^{93,99,100} Meanwhile, semaphorin 3A (Sema3A) and anosmin-1 are known as NRFs.^{101,102} In comparison with normal skin, the expression of NGF is increased in the epidermis of individuals with dry skin and atopic dermatitis, and conversely, the expression of Sema3A is decreased.²⁹ This epidermal environment is thought to promote sensory nerve elongation into the epidermis. When Sema3A was topically applied to mice with atopic dermatitis, the density of nerve fibers in the epidermis decreased, scratching behavior was suppressed, skin barrier function was restored, and skin inflammation was improved.⁹⁸ This suggests that Sema3A may be a therapeutic target molecule that regulates IENFs.

One study demonstrated that NGF induces matrix metalloproteinase-2 (MMP-2) gene expression in DRG neurons, and that the MMP-2 protein and its activity are localized on the plasma membrane of growth cones.¹⁰³ MMP-2 degrades the extracellular matrix, including basement membrane components, such as gelatin, type IV collagen, fibronectin, laminin, and elastin.¹⁰⁴ The activation of MMP-2 involves the complex formation of MT5-MMP-TIMP-2-proMMP-2 on the cell membrane of DRG neurons.¹⁰³ In addition, NGF-induced MMP-2 expression in DRG neurons was suppressed by Sema3A and enhanced by the extracellular matrix substrate component of MMP-2 itself.¹⁰³ Under such complex regulation, it was suggested that NGF-induced membrane-bound MMP-2 could locally disrupt the basement membrane and allow nerve fibers to penetrate the basement membrane in patients with dry skin and atopic dermatitis (Fig. 4D).

For sensory nerve fibers to elongate and branch in the dermis, the extracellular matrix of the dermis, consisting mainly of type I and type III collagen, must be degraded. It was found that NGF action on DRG neurons induced MMP-8 gene expression and increased the amount of MMP-8 in the culture supernatant.¹⁰⁵ MMP-8 is an enzyme that uses type I and type III collagen, the stromal components, as its substrate.¹⁰⁴ It is therefore suggested that MMP-8 synthesized in sensory neurons by NGF stimulation is secreted from growth cones and is involved in dermal nerve elongation and growth in atopic dermatitis. In addition, Sema3A was shown to regulate MMP-8-mediated nerve fiber elongation and growth in the dermis by suppressing NGF-induced MMP-8 expression.¹⁰⁵ Notably, one study reported that dermal fibroblasts also express Sema3A.¹⁰⁶ Type I and III collagen enhance the expression of MMP-8 in DRG neurons.¹⁰⁵ These results suggest that under the control of Sema3A and extracellular matrix components, NGF-induced MMP-8 secreted by nerve fibers degrades dermal collagens and is involved in the elongation and growth of nerve fibers in the dermis (Fig. 4D).

Table 2
Transcriptomic analyses of itch-related sensory neuronal types.

Mouse L4-L6 DRG	Markers	Responsivity	Putative function	Human L4-L5 DRG	Markers	Putative function
NP1	<i>MrgprD</i> , <i>Lpar3</i> , <i>Lpar5</i>	β -alanine, IL-4/IL-13	Itch, Mechanical	H10	<i>OSMR</i> , <i>IL-31RA</i> , <i>HRH1</i> , <i>NPPB</i> , <i>PIEZO2</i> , <i>GFRA2</i> , <i>PRDM8</i> , <i>RERG</i>	
NP2	<i>Mrgpra3</i> , <i>Mrgprc11</i> , <i>Hrh1</i>	CQ, BAM8-22, Histamine, IL-4/IL-13	Itch			Itch and mechanical (Corresponding to murine NP1, NP2, NP3 and C-LTMRs)
NP3	<i>NPPB</i> , <i>Nts</i> , <i>Sst</i> , <i>Il31ra</i> , <i>Osmr</i> , <i>Htr1f</i> , <i>Htr2a</i> , <i>Hrh1</i> , <i>Cyslr2</i> , <i>P2rx3low</i>	IL-31, Serotonin, Histamine, LTC4, IL-4/IL-13	Itch	H11	<i>OSMR</i> , <i>IL-31RA</i> , <i>HRH1</i> , <i>NPPB</i> , <i>SST</i> , <i>CCK</i> , <i>JAK1</i> , <i>CALCA</i> , <i>GFRA2</i> , <i>TRPC3</i> , <i>HTR3A</i>	

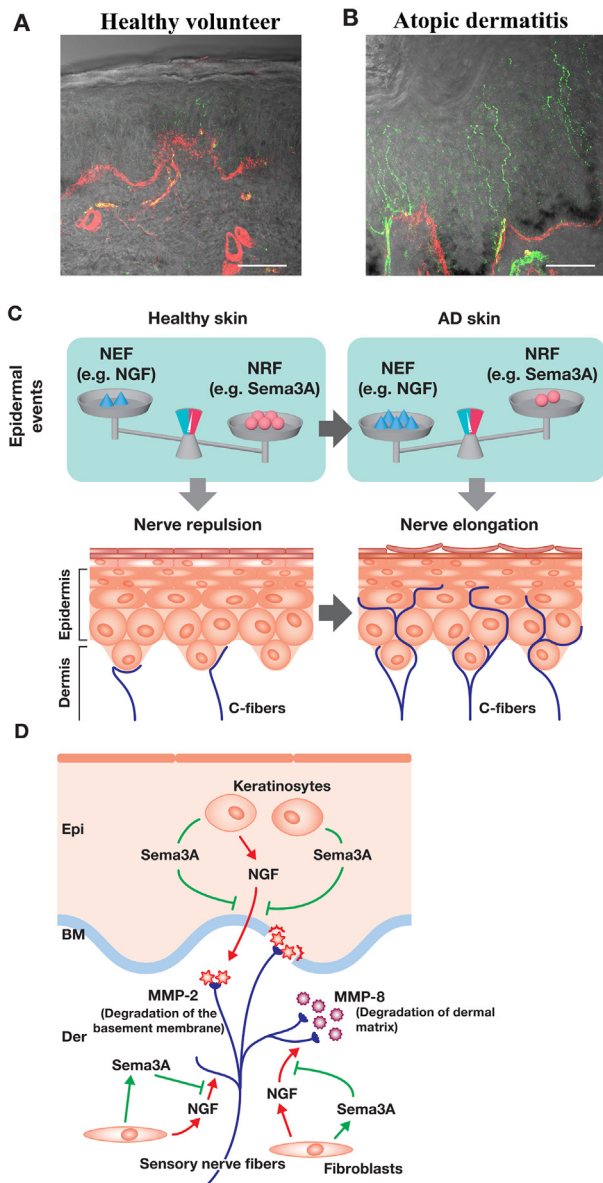


Fig. 4. A control model of intraepidermal nerve fiber density in skin. **A, B:** intraepidermal PGP9.5 positive fibers are increased in patients with atopic dermatitis (**B**) compared to normal skin (**A**). Green visualizes anti-PGP9.5 antibody-positive nerve fibers, and red visualizes basement membrane with anti-type IV collagen. Scale bars = 50 μ m. **C:** The epidermis of healthy controls has low expression of NEFs and high expression of NRFs. As a result, sensory nerve fibers converging at the epidermal-dermal border cannot penetrate the epidermis because the epidermis is a highly neurorepulsive environment (left panel). In the epidermis of dry skin and atopic dermatitis, the expression of NEFs is increased, while the expression of NRFs is decreased. This changes the quantitative balance between NEFs and NRFs to a nerve elongation-dominant intraepidermal environment, allowing sensory nerve fibers distributed in the subepidermis and dermis to invade the epidermis (right panel). **D:** It is presumed that MMP-2 distributed in the growth cones degrades the basement membrane, allowing nerve fibers to penetrate the epidermis. MMP-8 is also involved in growth of dermal nerve fibers. Both MMP-2 and MMP-8 are upregulated by NGF, while Sema3A cancels the NGF-induced increase in their expression. BM, basement membrane; Der, dermis; Epi, epidermis; MMP, matrix metalloproteinase; NEFs, nerve elongation factors; NGF, nerve growth factor; NRFs, nerve repulsion factors; PGP9.5, protein gene product 9.5.

With the recent development of imaging technology, the distribution of sensory nerve fibers has been investigated by visualizing the entire skin of chronic atopic dermatitis using immunofluorescent staining or genetic modification.^{107–109} The

results revealed that the density of IENFs was lower in the skin of patients with lichenified atopic dermatitis than in those with normal skin, despite their complaints of intense itching.^{107,108} This implies that the distribution of IENFs changes depending on pathological conditions, such as skin dryness and inflammation. In fact, sensory nerve fibers invaded the epidermis of acetone-treated mice within 24 h, peaked at 48 h, and returned to normal within a week.²⁸ One study found that reactive oxygen species (ROS) cause nerve retraction in guinea pig parasympathetic nerves.¹¹⁰ These findings raise the possibility that IENF density increases in the early stages of atopic dermatitis onset, and with chronicity, physical damage from scratching and ROS associated with inflammation may damage IENFs, resulting in a decrease in IENF density.

Neurogenic inflammation

Scratching stimulates nerve fibers in the epidermis and induces axonal reflexes, which promote the release of neuropeptides, such as SP.¹¹¹ It is possible that psychological stress also causes the release of SP from sensory nerve endings.¹¹² A more recent study showed that HDMs with cysteine protease activity could directly activate TRPV1⁺ neurons to release SP.¹¹³ The released SP binds to MrgprA1 and surrounding sensory nerves to induce itch.⁵⁰ Concomitantly, the released SP binds to NK-1R or MrgprB2/X2 on mast cells, and stimulates the release of histamine, tryptase, TNF, NGF, and IL-31 from mast cells.^{112–114} These mediators induce neurogenic inflammation via cognate receptors on sensory nerve fibers, leading to further itch-scratch events (Fig. 5). In addition, the released tryptase and NGF act on PAR-2 and TrkA expressed on the mast cells themselves in an autocrine or paracrine fashion, respectively, resulting in the release of additional inflammatory mediators.¹¹² Thus, neurogenic inflammation through sensory nerve-mast cell communication is partly involved in the formation of itch sensitization in atopic dermatitis.

Cytokine-induced itch sensitization

Recently, it has been shown that cytokines involved in the pathogenesis of atopic dermatitis, such as IL-33, IL-4, and IL-13, cause sensitization to itch.

IL-33

IL-33 is a member of the IL-1 cytokine family and is constitutively expressed in structural and lining cells, including fibroblasts, endothelial cells, and keratinocytes, of the gastrointestinal tract and lungs. IL-33 is one of the key drivers in type-2 innate immunity via activation of allergic inflammation-related eosinophils, basophils, mast cells, macrophages, and ILC2 through its receptor ST2-IL-1RacP complex.¹¹⁵

A more recent study using IL-33R^{fllox} mice with loxP sites inserted at the *Il1rl1* gene locus reported that loss of IL-33R in sensory neurons significantly suppressed dry skin-induced scratching behavior in acetone-ether-water (AEW)-treated mice, but not the MC903-induced atopic dermatitis model.⁶⁴ The expression of IL-33 mRNA in the skin of AEW-treated mice was significantly increased compared to control mice.⁶⁴ Notably, intra-dermal administration of IL-33 to naïve mice did not induce scratching behavior. In contrast, stimulation of cultured DRG neurons with recombinant IL-33 significantly increased the number of chloroquine (CQ)-responsive neurons.⁶⁴ Although CQ is not an intrinsic itch mediator, these results suggest that IL-33 increases the responsiveness of at least CQ-responsive neurons (possibly NP2) to itch mediators produced under dry skin conditions (Fig. 6A).

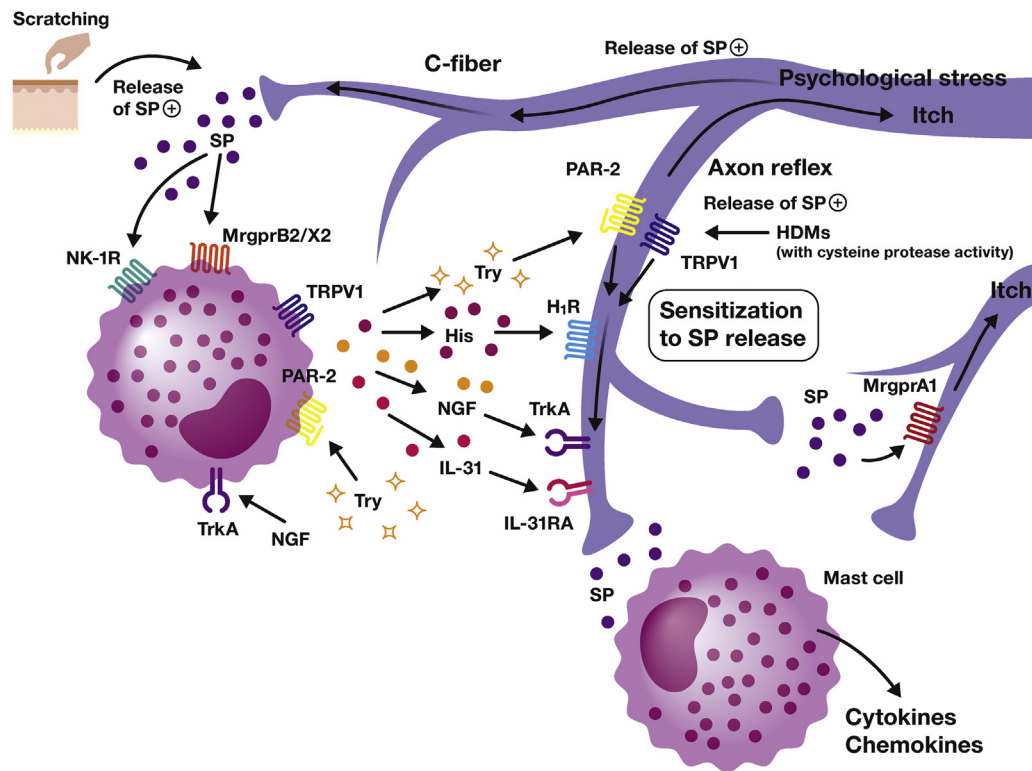


Fig. 5. Neurogenic inflammation by neuro-mast cells interaction. Psychological stress, scratching, and HDMs (with cysteine protease activity) promote SP release from nerve fiber endings. The released SP binds to MrgprB2/X2 and/or NK-1R on mast cells, causing mast cells to degranulate and release itch mediators (Try, His, IL-31) and NGF. These cause the onset and potentiation of itch and further SP release by axonal reflexes. The released SP also binds to MrgprA1 expressed in sensory nerve fibers, thereby inducing itch. His, histamine; Mrgpr, Mas-related G protein-coupled receptor; NGF, nerve growth factor; SP, substance P; Try, tryptase.

Type 2 cytokines: IL-4 and IL-13

In 2017, Dr. Kim's group showed that sensory nerves express IL-4 and IL-13 receptors and that IL-4 enhances histamine, CQ, IL-31, and TSLP-induced itch via IL-4R in sensory nerves.¹¹⁶ Although the potentiating effect of IL-13 remains unclear, it is thought that Janus kinase 1 (JAK1), which is responsible for intracellular signaling of IL-4R, is involved in the sensitization of itch by Th2 cytokines.¹¹⁶ A more recent study reported that IL-13 enhanced responsiveness of human DRG neurons to histamine, serotonin, and BAM8-22, and that this enhancement was suppressed by lebrikizumab, an anti-IL-13 monoclonal antibody.¹¹⁷ These findings suggest that IL-4 or IL-13 signaling is involved in itch sensitization in atopic dermatitis (Fig. 6B).

Oncostatin M (OSM)

OSM is a cytokine belonging to the IL-6 family, and its receptors have been identified as OSMR/gp130 and LIFR/gp130.¹¹⁸ In normal skin, very few cells express OSM, and these OSM-expressing cells express CD45, a pan-leukocyte marker. Meanwhile, CD4⁺ and CD3⁺ T cells, CD14⁺ monocytes, and CD45⁺ cells within the dermis express OSM in the lesions of psoriasis patients.¹¹⁹ A more recent study using whole cell electrophysiological recording and calcium imaging showed that short-term OSM treatment (1–2 min) does not directly act on sensory nerves to cause itch but rather enhance histamine-evoked currents. Long-term OSM stimulation (2–3 days) also altered the baseline excitability of Nppb⁺ neurons to tonic firing. Such changes were also observed in Nppb⁺ neurons treated with IL-31.¹¹⁹ OSM also induced more intense itch when administered intradermally to mice with histamine or LTC4 than itch induced by histamine or LTC4 alone. Moreover, a comparative study of OSM mRNA expression in the skin of patients with psoriasis,

atopic dermatitis or CTCL showed that OSM expression was higher in these diseases than in healthy individuals, especially in psoriasis patients, where only OSM expression was increased. When psoriasis-like symptoms were induced by imiquimod (IMQ) in OSMR-deficient mice, scratching behavior was significantly suppressed by OSMR deficiency. These findings suggest that OSM selectively sensitizes Nppb⁺ sensory neurons, and that OSM contributes significantly to itch sensitization in patients with psoriasis (Fig. 6C).¹¹⁹

Itch-related opioids

In clinical practice, morphine is used as an analgesic, but its side effect is itching. Recent studies have shown this itch is induced when μ -opioid system (β -endorphin/ μ -opioid receptor [MOR]) activation is predominant over the κ -opioid system (dynorphin A/ κ -opioid receptor [KOR]), whereas when activation of KOR exceeds that of MOR, itch is inhibited (Fig. 7).^{3,4,120–122} One study reported that GRPR forms heteromers with μ -opioid receptor 1D (MOR1D) in dorsal horn neurons co-expressing MOR1D and GRPR, and that morphine binding to MOR1D activates intracellular GRPR signaling and induces itch.¹²³ More recent studies demonstrated that dynorphin acts as a neuromodulator to inhibit itch in the dorsal horn of the spinal cord, and that morphine acts on spinal dynorphin neurons to cause itch through disinhibition.^{124,125} Thus, it is suggested that neuraxial opioids function as modulators of itch rather than mediators.¹²² This idea is also supported by recent findings that intrathecal morphine induces hyperknesis and allodynia.¹²⁵

However, itch-related opioid receptors and their endogenous ligands are also distributed in skin, including epidermal keratinocytes, fibroblasts, and sensory nerves.^{126–128} In the epidermis of

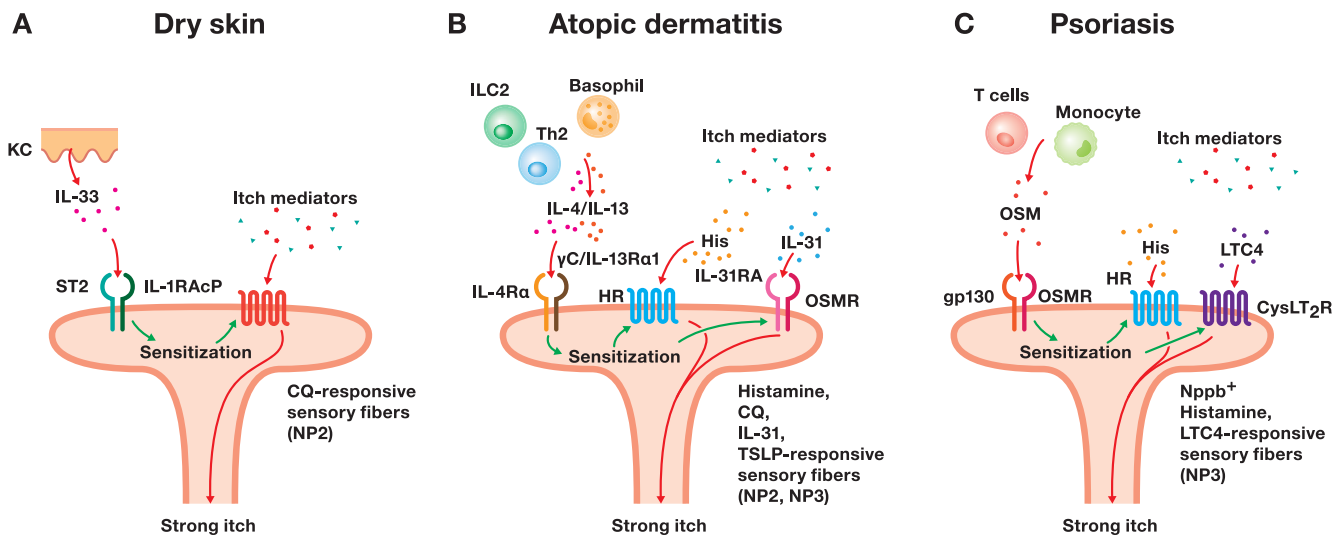


Fig. 6. Peripheral itch sensitization by cytokines. A: In dry skin, IL-33 is involved in itch sensitization. B: In atopic dermatitis, the type 2 cytokine IL-4/IL-13 acts on nerves and is involved in sensitization to itch. C: It is presumed that in psoriasis, OSM acts on sensory nerves, causing sensitization to itch. It is thought that itch sensitization by these cytokines may overlap in the three diseases. CQ, chloroquine; His, histamine; Nppb, natriuretic peptide b; OSM, oncostatin M.

atopic dermatitis patients, the expression levels of MOR and β -endorphin were similar to those in individuals with normal skin, but the expression levels of KOR and dynorphin were markedly reduced.¹²⁷ Moreover, when 1% naltrexone cream (a MOR antagonist) was topically applied to 11 patients with atopic dermatitis, more than 70% of them reported that itching was suppressed.¹²⁹ Application of an ointment containing nalfurafine, a KOR agonist, to mice with atopic dermatitis attenuated scratching behavior.¹³⁰ Given that KOR expression was undetectable in murine epidermal keratinocytes,¹³¹ it may act not only on keratinocytes but also on sensory nerves to suppress itch. In fact, recent studies using genetically engineered mice demonstrated that KORs are expressed in peptidergic primary afferents and circumferential and lanceolate low-threshold mechanoreceptors around hair follicles, and that the activation of KORs suppresses itch behavior, neurogenic inflammation, and nociceptor sensitization.¹²⁸ Conversely, intradermal administration of the KOR antagonist 5'-guanidinonaltrindole (GNTI) to mice induced scratching behavior.¹³² A more recent mouse study found that intradermal administration of the endogenous MOR agonist endomorphin at low concentrations induced mechanical allodynia, but it induced itch-related scratching behavior along with mechanical allodynia at high concentrations.¹³³ Thus, even at the peripheral level, opioids are implicated in modulating itch.

Other factors

SLIGRL-NH₂, an itch mediator, also enhances itch caused by CQ and BAM8-22.¹³⁴ A previous study reported that intradermal administration of histamine, serotonin, BAM8-22, and PAR-4 agonist (AYPGKF) induces mechanical allodynia in mice.¹³⁵ Several studies also suggest that artemin is involved in the induction of mechanical and thermal allodynia.^{99,100} The aryl hydrocarbon receptor (AhR) and 11 β -hydroxysteroid dehydrogenase-1 (HSD11 β) in keratinocytes are thought to be involved in the regulation of artemin expression.^{100,136} In addition, a more recent study raised the possibility that IL-4 and IL-13 derived from eosinophils and basophils induce mechanical allodynia in dry skin conditions.¹³⁷

Transition of itch sensitization during the pathogenesis of atopic dermatitis

Molecular and cellular transitions are also involved in itch sensitization during the pathogenesis of atopic dermatitis (Fig. 8).

Normal skin

In normal skin, the skin barrier, immune response, and itching are normal. Epidermal keratinocytes produce NRFs, such as Sema3A and anosmin-1, and thereby the density of IENFs is thought to be normal.^{4,101,102}

Dry skin (or non-lesional skin of atopic dermatitis)

As discussed, environmental and genetic factors lead to dry skin, which initiates the pathogenesis of atopic dermatitis.^{20,21,24–27} Dry skin tilts the expression levels of nerve elongation factors (NEFs) and nerve repulsion factors (NRFs) in epidermal keratinocytes toward the nerve elongation side, allowing sensory nerve fibers to penetrate the epidermis and increase receptivity to itch stimuli.^{4,29}

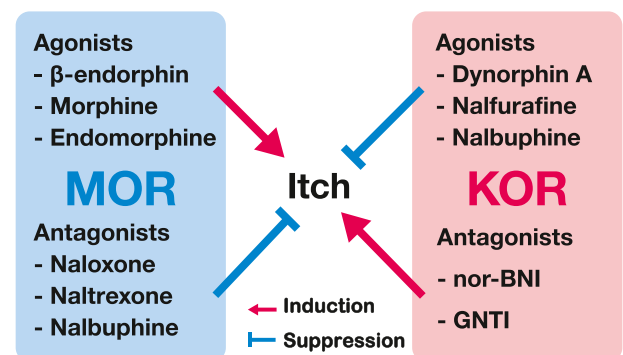
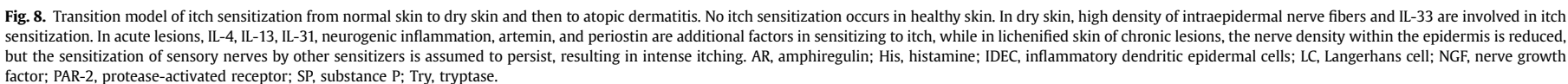


Fig. 7. Itch modulation by opioids. μ -opioid receptor activation induces itch, while κ -opioid receptor activation suppresses itch. GNTI, 5'-guanidinonaltrindole; KOR, κ -opioid receptor; MOR, μ -opioid receptor; nor-BNI, nor-binaltorphimine.



Concomitantly, IL-33 is released from epidermal keratinocytes as alarmin, which sensitizes nerves via ST2 receptors expressed on sensory nerve fibers (probably NP2 neurons).⁶⁴ In addition, keratinocytes produce and secrete TSLP, which act on sensory nerve fibers to induce itch.⁵² IL-33 and TSLP activate ILC2, which in turn secretes IL-13 and IL-5 to induce type 2 inflammation. In addition, Langerhans cells near the stratum corneum catch external allergen antigens and trigger a type 2 inflammatory response mediated by acquired immunity.^{24,26,27,138}

Acute lesion of atopic dermatitis

IL-4 and IL-13 are secreted by Th2 cells in acute lesions of atopic dermatitis, and their action on sensory nerves causes further itch sensitization (probably NP2 and NP3 neurons).¹¹⁶ Th2 cells also produce and secrete IL-31 as an itch mediator and/or sensitizer, which acts on sensitized sensory nerves and induces intense itch.^{36,119} HDMs (with cysteine protease activity) and scratching directly stimulate sensory nerves and lead to the release of SP from nerve endings.^{111,113} The released SP binds to MrgprB2/X2 on mast cells and releases NGF, tryptase, IL-31, and histamine to induce neurogenic inflammation, promoting further itch and inflammation.^{112–114} Moreover, IL-4 and IL-13 act on fibroblasts within the dermis to promote artemin-induced nerve elongation and itch hypersensitivity (i.e., allodynia) and periostin-induced itch.^{65,66,99,100} Concomitantly, Th2 cells produce and secrete IL-22, causing acanthosis.²⁷

Chronic lesion of atopic dermatitis

In chronic lesions, the stratum corneum barrier is further disrupted by itch-scratching, which leads to the entry of external foreign substances into the epidermis and a continuing inflammatory response. In this context, the IENF density is reduced to a level comparable to that of healthy individuals,^{107,108} but the sensory nerves are already sensitized by cytokines, which presumably maintains or enhances itch hypersensitivity.

The combination of itch mediators (Fig. 3), opioid modulation (Fig. 7), and spatial contrast between itch-selective sensory and pain-selective sensory nerves¹³⁹ are thought to diversify the quality of itch in atopic dermatitis.

Conclusion

As described in this review, cytokines are central to peripheral itch sensitization, and the addition of opioids as modulators might tune itch intensity. In addition, the diversity of itch mediators and the types of sensory nerves that receive them are presumed to alter the quality of itch sensation in atopic dermatitis. In the future, these issues could be uncovered, and evidence-based medicine could be provided to overcome the itchiness of atopic dermatitis.

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Conflict of interest

The authors have no conflict of interest to declare.

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