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Pruritogenic mediators in atopic dermatitis: mechanisms of neurogenic crosstalk

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Pruritus is the most burdensome and persistent symptom of atopic dermatitis (AD), often impairing quality of life more profoundly than visible skin inflammation. Emerging evidence indicates that itch in AD is not merely a downstream consequence of inflammation but an active disease driver that reshapes epidermal barrier integrity and neural plasticity. At the center of AD itch lies a dynamic, bidirectional network linking keratinocytes and sensory neurons. Barrier disruption triggers the release of keratinocyte-derived pruritogens and stress signals that directly activate or sensitize cutaneous nerve fibers, amplifying itch transmission. These epithelial–neuronal interactions are further integrated by intracellular signaling pathways that coordinate environmental and neural inputs. This review synthesizes current mechanistic insights across epidermal and neural compartments and proposes a conceptual framework in which AD itch progresses from peripherally driven signaling to centrally amplified and neurally entrenched states.

KEYWORDS
atopic dermatitis, itch, keratinocytes, pruritis, sensitized

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disorder in which pruritus is the most distressing symptom. Unlike visible skin lesions that fluctuate with disease activity, itch is experienced continuously by patients and is often recognized as the most predominant disease-related burden [1, 2].

Chronic itch in AD imposes a substantial disease burden that extends far beyond the skin. Persistent pruritus disrupts sleep architecture, impairs daytime functioning, and profoundly diminishes quality of life in both pediatric and adult patients [3]. Repetitive scratching, driven by uncontrollable itch, leads to epidermal barrier disruption, secondary inflammation, and neural sensitization, thereby perpetuating the itch–scratch cycle [4]. Over time, this vicious cycle contributes to disease chronicity, treatment resistance, and psychological comorbidities, highlighting itch not merely as a symptom but as a key determinant of long-term disease trajectory.

Importantly, itch in AD is qualitatively and mechanistically distinct from pruritus associated with other inflammatory or non-inflammatory dermatoses. AD-associated itch is characteristically intense, persistent, and poorly relieved by conventional antihistamines, reflecting the predominance of non-histaminergic mechanisms [5]. Moreover, pruritus in

AD functions as a disease driver rather than a passive consequence of cutaneous inflammation, actively reshaping epidermal structure and neural plasticity. Even non-lesional skin from patients with AD exhibits heightened cowhage-induced itch compared with healthy controls, indicating that altered sensory responsiveness is an intrinsic feature of the disease rather than merely a byproduct of visible inflammation [6]. This paradigm shift challenges the traditional view of itch as a secondary manifestation and positions it as a central pathogenic process in AD.

At the core of this process lies a complex network of interactions between sensory neurons and keratinocytes. Epithelial-derived mediators and neuronal signals form bidirectional circuits that amplify itch perception while reshaping cutaneous and neural responsiveness. In this review, we summarize current evidence on the mediators and signaling pathways that coordinate epithelial and neuronal responses in AD-associated itch (Figure 1).

This review was conducted as a narrative review focusing on recent mechanistic insights into atopic dermatitis-associated pruritus. Relevant publications were primarily identified through PubMed database searches using combinations of keywords related to atopic dermatitis, itch, neuroimmune interactions, epithelial-derived mediators, cytokines, neuropeptides, neurotrophic factors, and JAK-STAT signaling pathways. Both experimental and clinical studies were considered, with emphasis placed on studies contributing to the understanding of neuro-immune-epithelial crosstalk and chronic itch mechanisms.

Epithelial injury and damage-induced pruritogenic pathways

AD is fundamentally a disease of epithelial barrier disruption. Beyond serving as a passive physical shield, epithelium is a source of potent pruritogenic signals. Damage-induced mediators released from stressed keratinocytes act on adjacent sensory nerves and immune cells, establishing a self-amplifying itch–scratch–injury cycle. Injured keratinocytes, resulting from mechanical scratching or barrier dysfunction in AD lesions, release abundant alarmins such as TSLP, IL-33, and IL-25, which play important roles in disease pathogenesis [7]. These epithelial cytokines not only serve as pivotal initiators of type 2 immune responses but can also act directly on sensory neurons. Among these alarmins, relatively limited data are available regarding the direct role of IL-25 in itch, and its contribution appears to be largely indirect [8]. Although no direct role of IL-25 in itch induction has been demonstrated in AD, it can potentiate type 2 inflammatory cytokines such as IL-13, indicating a potential indirect contribution to pruritus [9]. In the following sections, we will focus on TSLP and IL-33, which have been more extensively studied in the context of AD-associated pruritus.

Thymic stromal lymphopoietin (TSLP)

TSLP is a cytokine produced by epithelial cells that signals through a heterodimeric receptor complex consisting of the TSLP receptor and the IL-7 receptor α subunit [10]. Engagement of this receptor complex potently activates myeloid dendritic cells and promotes type 2–skewed immune responses involving Th2 cells, mast cells, and natural killer T cells [11, 12]. TSLP further drives the differentiation of naïve T cells into Th2 cells, leading to the production of key type 2 cytokines, including IL-4 and IL-13 [11, 12]. Serum level of TSLP is significantly elevated in patients with AD and correlated with the disease severity [13]. Wilson *et al.* further reported that calcium-dependent ORAI1/NFAT signaling in keratinocytes regulates TSLP release which in turn directly activates transient receptor potential A1 $(TRPA1)^{+}$ sensory neurons to induce itch, thereby linking epithelial activation to neurogenic responses [14]. Interestingly, such epithelial–neuronal crosstalk via TSLP is not confined to the skin but also involves airway epithelial cells and sensory neurons, which may serve as a contributing factor to both the initiation and evolution of the atopic march [14].

IL-33

IL-33 participates in the inflammatory process of AD and mediates type 2 responses, including the induction of IL-4, IL-5, and IL-13 [15]. IL-33 also synergizes with IL-4 to mediate IL-31 production [16], a key pruritogen in AD [17]. Moreover, IL-33 enhances histamine-induced itch through mast cell activation, leading to IL-13 release, which in turn acts on sensory neurons to potentiate histamine-dependent pruritic signaling [18]. In addition to the above indirect effect, IL-33 receptor (ST2) expression has been identified in both human and mouse dorsal root ganglion (DRG) and IL-33 can sensitize DRG neurons to IL-4-, IL-13-mediated signaling [19, 20], suggesting a potential role in neuro-immune communication. Beyond peripheral neuroimmune interactions, spinal IL-33/ST2 signaling has been reported to contribute to chronic itch via activation of the astrocytic JAK2–STAT3 pathway, which subsequently enhances gastrin-releasing peptide (GRP)/GRP receptor (GRPR) axis in a murine model of inflammatory dermatitis (2,4-dinitrofluorobenzene -induced allergic contact dermatitis) mouse model, suggesting a potential mechanism relevant to chronic itch [21]. GRP, a key mediator in spinal pruritoceptive signaling [22, 23], has also been shown to implicate in AD-related pruritus. Serum GRP levels are increased in patients with AD and correlate with both disease severity and itch intensity [24, 25].

Studies in both AD patients and murine models of AD-like dermatitis (e.g., MC903-induced dermatitis) have demonstrated elevated IL-33 in circulation, which correlates with clinical severity and characteristics of skin lesions [19, 26, 27]. Functionally, one study revealed that IL-33 enhances neuronal excitability indirectly through activation of mast cells and basophils, and potentially directly via ST2-expressing sensory neuronal subsets. However, this study did not observe increased circulating IL-33 levels in patients with AD, nor a significant correlation between IL-33 expression and pruritus severity [28]. In the same study, specific single-nucleotide polymorphisms within the *IL33* gene have been associated with increased itch severity, suggesting that genetic predisposition may modulate IL-33–driven pruritic responses [28]. Another study likewise reported elevated IL-33 levels in patients with AD and in murine models of MC903-induced AD like dermatitis; however, IL-33 receptor signaling restricted to neurons was dispensable for the development of itch in AD-like disease [19]. Overall, evidence supporting IL-33 in AD-associated itch derives from both human and animal studies;

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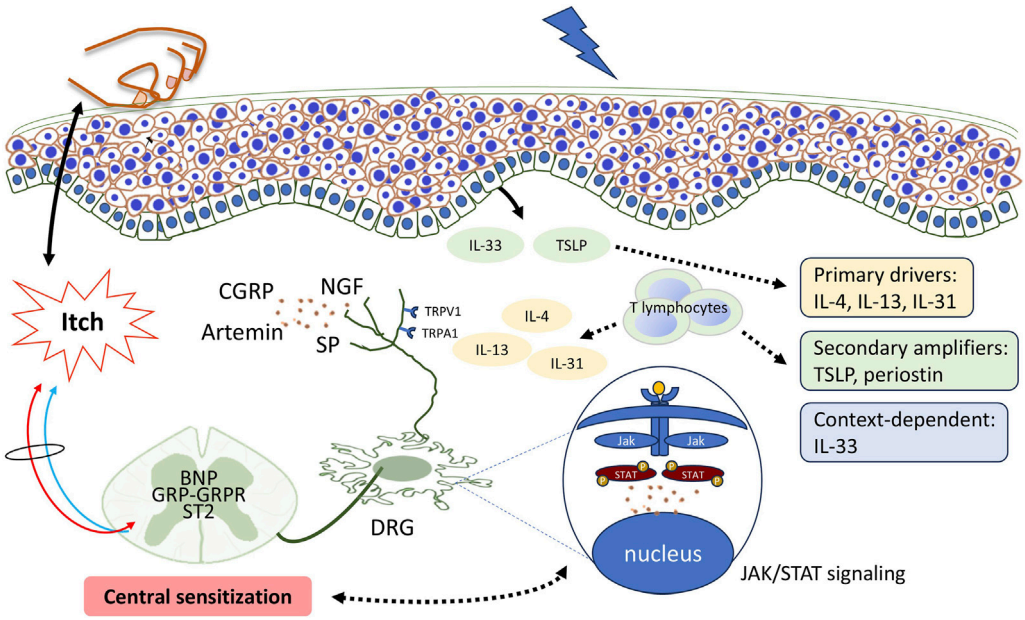

FIGURE 1
Neuro–immune–epithelial interactions driving pruritus in atopic dermatitis. Pruritus in atopic dermatitis (AD) arises from dynamic interactions among epidermal barrier dysfunction, immune activation, sensory neuronal sensitization (increased excitability and responsiveness of pruriceptive neurons), and environmental stimuli. Barrier disruption and external triggers induce keratinocytes to release pruritogens such as IL-33, TSLP, which activate DRG sensory neurons. Type 2 cytokines, including IL-4, IL-13, and IL-31, further enhance neuronal excitability via their receptors and downstream signaling. Activated sensory neurons transmit itch signals to the central nervous system and promote neurogenic inflammation, while scratching exacerbates barrier damage, establishing a feed-forward cycle that sustains chronic pruritus in AD. BNP: brain natriuretic peptide; CGRP: Calcitonin Gene-Related Peptide; DRG: dorsal root ganglion; GRP: gastrin-releasing peptide; GRPR: gastrin-releasing peptide receptor; IL: interleukin; JAK: Janus kinase; NGF: Nerve Growth Factor; SP: Substance P; STAT: Signal Transducer and Activator of Transcription; ST2: Suppression of Tumorigenicity 2; TRPA1: transient receptor potential ankyrin 1; TRPV1: Transient receptor potential cation channel subfamily V member 1; TSLP: thymic stromal lymphopoietin.

however, most findings remain correlative or model-dependent, and its direct causal role in human AD itch is still not fully established. Taken together, these findings suggest that IL-33 may participate in itch-related neuro-immune signaling at both peripheral and sensory neuronal (DRG) levels. However, its precise contribution to AD-associated itch remains incompletely defined, as current evidence is largely indirect and sometimes conflicting, and whether IL-33 functions as a direct driver of itch in AD requires further clarification.

Type 2–associated pruritogenic signals

IL-4, IL-13

The immune response in AD is characterized by a Th2-dominant profile, resulting in increased production of type 2 cytokines and chemokines and subsequent recruitment of inflammatory cells [29]. Among these mediators, IL-4 and IL-13 are central drivers of AD pathogenesis. IL-4 signals through both type I and type II receptor complexes, whereas IL-13 signals exclusively through the type II receptor [30]. Beyond their established immunomodulatory functions, type 2 cytokines directly interact with the sensory nervous system to promote itch. Both IL-4 and IL-13 can directly activate mouse and human sensory neurons, with IL-4 additionally sensitizing neurons to a broad range of pruritogens [31]. Mechanistically, chronic itch requires neuronal IL-4Rα–JAK1 signaling, as sensory neuron–specific deletion of IL-4Rα or JAK1 markedly reduces pruritus in mice. Importantly, a proof-of-concept clinical study shows that JAK inhibition effectively relieves recalcitrant chronic itch, even in patients unresponsive to conventional immunosuppressants. These findings highlight an evolutionarily conserved paradigm in which type 2 immune pathways function within sensory neurons, identifying neuronal IL-4Rα–JAK1 signaling as a therapeutic target in type 2–driven itch, including AD [31].

Recent study using human DRG neurons have provided direct evidence that type 2 cytokines—including IL-4, IL-13, and IL-33—can sensitize sensory neurons to both histaminergic and non-histaminergic pruritogens. Sensitization occurs rapidly, within 2 h of cytokine exposure, and a discrete subset of neurons exhibits immediate extracellular Ca^{2+}–dependent calcium influx in response to IL-4 and IL-13. With prolonged exposure, IL-4 and IL-13 induce a shared, cytokine-specific transcriptional program that is distinct from that elicited by IL-33 or other inflammatory stimuli, indicating broad and sustained neuromodulatory effects [20]. These findings demonstrate that type 2 cytokines not only shape immune responses but also directly prime human sensory neurons to amplify itch, thereby contributing to neuroinflammation and hypersensitivity in AD.

IL-31

IL-31 is a crucial cytokine implicated in the pathophysiology of AD. Acting through its receptor complex composed of IL-31

receptor A (IL-31RA) and oncostatin M receptor (OSMR), IL-31 plays a dual role in promoting itch and modulating cutaneous inflammation. Although OSMR is shared with the oncostatin M signaling pathway, current evidence primarily supports a role for IL-31—rather than OSM itself—in directly mediating pruritus. IL-31 is produced predominantly by Th2 cells but is also expressed by other immune cells, including basophils and macrophages [32]. In addition to Th2 cells, recent evidence has identified M2-polarized macrophages as an additional and clinically relevant source of IL-31 in AD. In lesional skin, IL-31$^+$CD68$^+$CD163$^+$ macrophages closely correlate with epidermal TSLP expression, dermal periostin levels, and basophil infiltration, suggesting a coordinated immune network sustaining chronic itch [33]. In the MC903-induced AD-like mouse model, upregulation of TSLP and periostin has been associated with basophil recruitment and the presence of IL-31–producing macrophages, resulting in augmented scratching behavior. These findings delineate a TSLP–periostin–basophil–macrophage axis that reinforces neuroinflammatory signaling, defined as bidirectional communication between immune mediators and sensory neurons, and IL-31 driven pruritus in AD [33].

In line with its pruritogenic role, IL-31RA is expressed both in human and mice DRG. Cutaneous or intrathecal administration of IL-31 induces robust scratching behavior [34]. At the neuronal level, IL-31RA signaling triggers intracellular Ca^{2+} release and ERK activation in a restricted population of IL-31RA$^+$/TRPV1$^+$/TRPA1$^+$ sensory neurons, thereby mediating T cell–dependent itch [34]. Additionally, a recent study has revealed that upon IL-31 stimulation, STAT3 undergoes rapid activation and nuclear translocation in IL-31R$^+$ neurons, followed by propagation of signaling to other pruriceptive neuronal subsets, enhancing itch responses to diverse pruritogens. Notably, STAT3 not only functions downstream of the IL-31R but also transcriptionally regulates IL-31R expression, establishing a feed forward loop that amplifies neuronal sensitivity to IL-31. Moreover, dermatitis-associated pruritus is highly dependent on sensory neuronal STAT3 [35], indicating that STAT3 contributes to both IL-31–dependent and IL-31–independent neuroinflammatory itch circuits in AD.

IL-31 also exhibits neuropoietic activity. Both IL-31 transgenic mice and mice receiving exogenous IL-31 display increased cutaneous nerve fiber density. Accordingly, IL-31 promotes axonal elongation and branching selectively in small-diameter sensory neurons through STAT3 phosphorylation [17]. This provides a mechanistic explanation for neuronal hyperplasia and heightened itch sensitivity in chronic AD.

Beyond peripheral neuronal activation, IL-31 also engages central itch pathways. Pitake *et al.* demonstrated that IL-31 induces the expression of B-type natriuretic peptide (BNP), encoded by the *NPPB* gene in sensory neurons, which transmits itch signals through natriuretic peptide receptor A in the spinal cord [36], an essential pathway for central itch processing [37]. Furthermore, IL-31 has been shown to promote neuroinflammation by inducing SNARE-dependent release of brain natriuretic peptide (BNP), encoded by the *NPPB* gene, from sensory nerves. BNP subsequently enhances cytokine production associated with AD in keratinocytes and dendritic cells through GSK3- and c-Jun–dependent signaling [38]. Collectively, these findings establish IL-31 as a critical mediator linking peripheral sensory neuron activation, central itch processing, and cutaneous immune amplification through IL-31 induced neuropeptide signaling. IL-31 therefore represents one of the most well-validated cytokines directly linking immune activation to neuronal itch signaling in both experimental and clinical settings.

Among type 2 cytokines, IL-4/IL-13 and IL-31 have the strongest clinical and therapeutic evidence for direct involvement in itch, particularly supported by successful targeting in human studies, whereas other upstream mediators show more indirect neuroimmune effects.

Periostin

Periostin is a downstream mediator of type 2 inflammation, primarily secreted by dermal fibroblasts and has emerged as a conserved pruritogen capable of directly inducing itch across multiple species, including mice, dogs, and non-human primates [39, 40]. Serum periostin levels are significantly elevated in patients with AD and positively correlate with disease severity [41]. Periostin is required for the expression of NF-κB–related cytokines (e.g., IL-1B, IL-24, and IL-33) as well as chemokines involved in neutrophil recruitment. In addition, periostin reciprocally induces keratinocyte-derived TSLP, further amplifying type 2 inflammation [42, 43].

Beyond its indirect pro-pruritic effects via type 2 cytokine induction, periostin directly promotes itch by triggering spontaneous firing of itch-related DRG sensory neurons. In a mouse model of facial AD with scratching (FADS), periostin was shown to activate DRG neurons and induce scratching behavior through engagement of integrin αvβ3 [42]. Consistently, Mishra *et al.* demonstrated that periostin binding to integrin αvβ3 directly activates sensory neurons by inducing extracellular calcium influx and disruption of neuronal β3 integrin significantly attenuates scratching behavior. They also showed that periostin-induced itch is mediated by TRPV1 and TRPA1 channels, with BNP serving as a key neuropeptide effector [40]. Importantly, periostin production in keratinocytes is itself induced by TSLP through the JAK2–STAT3 pathway [40]. Thereby establishing a feed-forward epithelial–neuronal signaling loop.

Neuro-immune signaling mediators

Bidirectional communication between the nervous and immune systems plays a critical role in the pathogenesis of AD associated pruritus. A growing body of evidence highlights neuro-immune signaling mediators that link sensory nerve activity to cutaneous inflammation, epidermal remodeling, and chronic itch.

NGF

Patients with AD exhibit systemic upregulation of neurogenic mediators, including plasma NGF and other neuropeptides such as vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), and neuropeptide Y (NPY), with NGF showing the strongest correlation with disease activity [44]. NGF, a neurotrophin critical for the development, survival, and plasticity of sensory neurons [45], is significantly elevated in the stratum corneum of lesional skin from patients with AD compared

with healthy controls. Elevated epidermal NGF levels correlate with itch severity, erythema, xerosis, and systemic markers of disease activity, including eosinophil counts and serum lactate dehydrogenase [46]. In addition, immunohistochemical analyses of early AD lesions demonstrate marked upregulation of NGF and its receptors within both the epidermis and papillary dermis. P75 NGF receptor–positive nerve fibers are significantly increased in number, size, and branching within the dermal papillae [47]. Ultrastructural analysis reveals increased schwann cell–axon complexes in AD skin, which are associated with plasma NGF levels [44]. Effective treatment with antihistamines and/or topical corticosteroids leads to a rapid reduction in epidermal NGF, paralleling clinical improvement in pruritus and inflammatory skin changes [46]. These findings support a central role for NGF in driving neuroimmune interactions and nerve remodeling in AD, potentially contributing to heightened skin nerve sensitivity. Consistent with this concept, blockade of NGF signaling using high-affinity p75 NGF receptor antagonists or anti-NGF antibodies markedly ameliorates dermatitis severity and scratching behavior in the NC/Nga mouse model of AD [48, 49].

Substance P (SP)

SP is a neuropeptide that exerts its biological effects primarily through activation of the neurokinin-1 (NK1) receptor, which is widely expressed in the central nervous system as well as on various immune cells. Activation of sensory nerve endings by SP induces neurogenic inflammation and is implicated in chronic itch and neural sensitization [50]. Early studies showed that SP stimulation enhances the production of both IL-4 and interferon-γ in peripheral blood mononuclear cells from patients with AD, indicating its capacity to influence T cell–associated immune responses. [51]. Subsequent work demonstrated that SP increases the release of IL-10 and TNF-α from peripheral blood mononuclear cells, an effect associated with upregulated NK1 receptor expression [52]. Clinically, immunological profiling has revealed elevated plasma SP levels together with increased expression of SP and NK1 receptors on $CD8^+$ T cells in patients with AD [53]. In addition, circulating SP levels are elevated in patients with AD and correlate with disease severity, accompanied by a marked increase in SP-positive nerve fibers in lesional skin [54, 55]. In parallel, SP signaling has been implicated in neuropsychological comorbidities, as depression scores correlate with the number of NK1 receptor–positive dermal cells in both lesional and non-lesional skin, linking tachykinin signaling cutaneous inflammation, chronic itch, and emotional dysregulation [54]. At the molecular level, transcriptomic analyses of itchy AD skin further demonstrate that SP expression positively correlates with patient-reported itch intensity, providing direct evidence for its role in pruritus [29]. Although a histamine-dependent pathway has been proposed, which was supported by observations of reduced SP levels following antihistamine therapy [56], accumulating evidence indicates that SP can also evoke itch through histamine-independent mechanisms. In a picrylchloride-induced NC/Nga mouse model of AD, NK1 antagonists were able to inhibit scratching behavior [57]; however, mas-related G protein-coupled receptors (MRGPRs) have emerged as key mediators in this context [58]. Specifically, SP has been shown to activate MRGPRX2 on mast cells and MRGPRA1 on sensory neurons, rather than NK1 receptors, to induce non histaminergic itch [59, 60].

Notably, despite substantial evidence supporting pro-pruritic and pro-inflammatory roles of SP, SP has also been reported to exert protective actions in certain experimental settings. Topical administration of SP was able to enhance skin barrier function while reducing the presence of itch-evoking nerve fibers in the epidermis, and alleviated scratching behavior in a 2,4,6-trinitrochlorobenzene (TNCB)–induced AD-like dermatitis model in NC/Nga mice [61]. Additionally, another study demonstrated that SP attenuated inflammation by suppressing systemic immune responses, including reductions in TSLP and TNF-α levels [62]. These findings suggest that SP exerts context-dependent and bidirectional effects in AD pathophysiology, with predominantly pro-pruritic and pro-inflammatory roles supported by clinical and translational evidence, but with potential protective or modulatory effects observed in specific experimental settings.

CGRP

CGRP is a sensory neuropeptide implicated in pruritus. In patients with AD, lesional skin exhibits a marked increase in CGRP-positive nerve-like fibers, accompanied by greater epidermal infiltration of inflammatory cells [63]. In lesional skin, CGRP-positive nerve fiber density correlates with depression and anxiety scores, and CGRP-positive epidermal inflammatory cells show a similar association with depressive symptoms, supporting potential neuroimmune–neuropsychological interactions. Notably, keratinocytes in lesional skin also express CGRP, suggesting that its role extends beyond sensory neurons [63]. Functional studies using innervated skin models reveal that sensory neurons drive keratinocyte proliferation and epidermal thickening in a CGRP-dependent manner, independent of SP [64]. Atopic keratinocytes display increased neurite outgrowth, higher CGRP release, and upregulated CGRP receptor components, making them more responsive to CGRP and resulting in exaggerated epidermal hyperplasia [64]. Collectively, these findings highlight CGRP as a key mediator linking sensory nerve activity to abnormal epidermal remodeling in AD.

Artemin

Artemin, a member of the glial cell line–derived neurotrophic factor family, binds to the GFRα3 receptor [65]. Increased artemin expression has been observed in lesional AD skin, and artemin-expressing fibroblasts accumulate in patients with AD. In addition, SP has been shown to induce artemin expression in fibroblasts [66, 67]. In animal models, intradermal injection of artemin induces peripheral nerve sprouting, thermal hyperalgesia, and scratching behavior in response to warm stimuli, highlighting its role in altering nerve structure and sensitivity [66]. Moreover, emerging evidence links environmental and microbial signals to artemin regulation in AD. The aryl hydrocarbon receptor (AhR), a key environmental sensor in keratinocytes [68, 69], induces *ARTN* (artemin) expression upon activation by organic components of air pollutants, which are common aggravating factors in AD [70, 71]. Epidermal AhR

TABLE 1 Pruritogenic mediators in atopic dermatitis across epithelial and neuro-immune compartments: sources, receptors, and downstream mechanisms.

Mediator	Cellular source	Receptor	Downstream pathway/ Mechanism	Type of evidence	Therapeutic relevance
TSLP	Keratinocytes	TSLPR/IL-7Rα	Activates DC→ Th2 polarization; directly activates TRPA1$^+$ sensory neurons via ORAI1/NFAT signaling	Human (↑ serum), mouse models, neuronal studies	Targeted by anti-TSLP (e.g., tezepelumab, investigational in AD)
IL-33	Keratinocytes, epithelial cells	ST2 (IL1RL1)	Induces IL-4, IL-5, IL-13; enhances IL-31 production; sensitizes DRG neurons; activates spinal astrocytic JAK2–STAT3 → GRP/GRPR axis	Human + mouse (conflicting itch correlation in AD), genetic studies	Potential upstream target; indirect pruritogenic role
IL-4	Th2 cells	Type I/II IL-4R (IL-4Rα)	Direct neuronal activation; sensitizes neurons to pruritogens via JAK1 signaling	Human + mouse + neuronal studies	Targeted by dupilumab
IL-13	Th2 cells	Type II IL-4R	Direct neuronal sensitization; overlaps with IL-4 signaling	Human + mouse + neuronal studies	Targeted (tralokinumab, lebrikizumab)
IL-31	Th2 cells, basophils, M2 macrophages	IL-31RA/OSMR	Activates TRPV1$^+$/TRPA1$^+$ neurons; STAT3 activation; induces BNP → central itch signaling; promotes nerve growth	Strong human + mouse + mechanistic studies	Targeted by nemolizumab
Periostin	Dermal fibroblasts	Integrin αvβ3	Direct neuronal activation (Ca^{2+} influx); TRPV1/TRPA1-dependent; induces TSLP (feed-forward loop)	Animal models + translational studies	Emerging target
NGF	Keratinocytes, immune cells	TrkA, p75NTR	Promotes nerve growth, branching, sensitization	Human + mouse	Anti-NGF strategies (experimental)
SP	Sensory neurons	NK1R; MRGPRX2 (mast cells), MRGPRA1 (neurons)	Neurogenic inflammation; histamine-dependent and independent itch	Human + mouse	NK1R antagonists (limited efficacy); MRGPR pathway emerging
CGRP	Sensory neurons, keratinocytes	CGRP receptor	Promotes keratinocyte proliferation and epidermal hyperplasia	Human + *in vitro* models	Indirect target
Artemin	Fibroblasts, keratinocytes	GFRα3	Induces nerve sprouting, hyperinnervation; downstream of AhR and TLR signaling	Animal + translational	Emerging environmental link target
JAK1 (pathway)	Keratinocytes, neurons	Cytokine receptors (e.g., IL-4R, IL-31R)	Central signaling hub for itch cytokines; neuronal sensitization; TRPV1 modulation	Strong human + mouse + clinical	JAK inhibitors (upadacitinib, abrocitinib)

AhR, aryl hydrocarbon receptor; BNP, B-type natriuretic peptide (encoded by NPPB); CGRP, calcitonin gene-related peptide; DCs, dendritic cells; DRG, dorsal root ganglion.
GFRα3, glial cell line–derived neurotrophic factor family receptor alpha 3; GRP, gastrin-releasing peptide; GRPR, gastrin-releasing peptide receptor; IL, interleukin; IL-4Rα, interleukin-4, receptor alpha; IL-7Rα, interleukin-7, receptor alpha; JAK, janus kinase; MRGPRA1, Mas-related G protein-coupled receptor member A1; MRGPRX2, Mas-related G protein-coupled receptor member X2; NF-κB, nuclear factor kappa B; NGF, nerve growth factor; NK1R, neurokinin-1, receptor; NPPB, natriuretic peptide B gene; OSMR, oncostatin M receptor; p75NTR, p75 neurotrophin receptor; SP, substance P; STAT3, signal transducer and activator of transcription 3.
ST2, suppression of tumorigenicity 2 (IL-33, receptor, IL1RL1); Th2, type 2 helper T cells; TLR, Toll-like receptor; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor; TrkA, tropomyosin receptor kinase A.

activation in patient skin correlates with artemin expression, and experimental models demonstrate that AhR-driven artemin upregulation leads to sensory hyperinnervation and AD-like phenotypes [70, 71]. In parallel, dermatophagoides farinae, one of the major species of HDMs, stimulation via toll like receptor (TLR) 1/2 in keratinocytes induce upregulation of artemin, which promotes neurite outgrowth, neuronal migration, and epidermal hyperinnervation [67]. Collectively, artemin emerges as a key downstream effector linking diverse upstream signals to sensory nerve remodeling and itch in AD.

Neurotrophic mediators such as NGF, CGRP, and artemin primarily derive their evidence from correlative human studies and animal models, with strong support for neuronal remodeling but less direct evidence for causal itch induction in human AD.

JAK–signal transducer and activator of transcription (STAT)

The JAK–STAT pathway is a central signaling cascade that mediates cytokine- and growth factor–driven regulation of intracellular gene expression. In this pathway, JAKs function as receptor-associated kinases that transduce extracellular cytokine signals to activate downstream STAT transcription factors [72], To date, four JAK family members (JAK1, JAK2, JAK3, and TYK2) and seven STAT family members (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) have been identified [72]. Increasing evidence indicates that cytokines signaling through the JAK pathway are critically in the pathogenesis of a variety of inflammatory disorders, including AD [73]. One study demonstrated that

lesional skin from patients with AD exhibits broad activation of the JAK–STAT pathway across both epidermal and dermal compartments [74]. Increased expression of phosphorylated JAK3 was observed in the epidermis, whereas dermal inflammatory infiltrates showed enhanced activation of phosphorylated JAK1-3. Consistent with this upstream kinase activation, downstream STAT signaling was also upregulated, with increased phosphorylation of STAT2 and STAT3 in AD lesions [74]. Notably, hyperphosphorylation of epidermal JAK1 has been reported in patients with AD [75]. These findings indicate aberrant activation of the JAK–STAT pathway in lesional AD skin.

Using SPADE, a spontaneous mouse model of pruritic dermatitis caused by an epidermal JAK1 gain-of-function mutation, study has further demonstrated that intrinsic activation of JAK1 signaling in keratinocytes is sufficient to drive skin barrier dysfunction, chronic inflammation, and pruritus [75]. In addition, hyperactivation of JAK1 induces pruritic dermatitis through disruption of epidermal barrier integrity and overexpression of serine proteases [75]. Beyond the skin, JAK1 is enriched in pruriceptive neurons and plays a crucial role in the sensation of chronic itch through its function in sensory neurons. Importantly, multiple pruritogenic cytokines—including IL-4, IL-13, and IL-31—signal through JAK-dependent pathways in sensory neurons, highlighting JAK1 as a key convergence point for cytokine-mediated itch signaling. As discussed above, JAK1 is responsible for neuronal IL-4Rα signaling for chronic itch transduction [31]. Mice with sensory neuron–specific deletion of JAK1 exhibited a marked reduction in scratching behavior during experimentally induced chronic itch, despite persistent skin inflammation. Furthermore, these mice showed abolished neuronal IL-4 responses, providing direct evidence for a neuronal JAK1–dependent mechanism linking type 2 cytokine signaling to itch [31]. In addition, epithelial-derived cytokines such as TSLP signal through the TSLPR/IL-7Rα receptor complex and activate JAK-STAT pathways, which can directly stimulate pruriceptive neurons and contribute to non-histaminergic itch signaling [76–78]. Beyond type 2 cytokine–mediated itch, JAK inhibitors also exert broad antipruritic effects. Another study demonstrated that oclacitinib (a selective JAK1 inhibitor) and tofacitinib (a pan-JAK inhibitor) suppress scratching induced by diverse pruritogens—including IL-31, TNF-α, histamine, chloroquine, PAR2-activating peptide, and capsaicin—at least in part through direct inhibition of TRPV1 channels, rather than via JAK signaling [79].

In addition to their peripheral actions, JAK1-selective inhibition can directly modulate central neuronal activity. In cultured frontal cortex neurons, electrophysiological studies revealed that neuronal inhibition increases with greater JAK1 selectivity. The selective JAK1 inhibitor upadacitinib produced pronounced effects on neuronal activity, including reduced burst and spike rates, altered burst structure, enhanced firing regularity, and increased network synchronization. In contrast, the pan-JAK inhibitor tofacitinib had minimal effects, whereas JAK1/2 inhibition with baricitinib caused moderate suppression of bursting and firing irregularities [80]. These findings suggest that JAK1-preferential inhibition may directly influence cortical neuronal excitability and network dynamics, supporting a potential neuromodulatory role of JAK signaling beyond immune regulation.

Importantly, JAK–STAT signaling represents the most clinically validated pathway linking immune cytokine signaling to pruritus, as evidenced by robust responses to JAK inhibition in both experimental models and clinical practice.

Discussion

Chronic itch in AD represents a qualitatively distinct state shaped by repeated stimulation, maladaptive neural plasticity, and sustained peripheral signaling. Although itch is initially triggered by epithelial stress, barrier disruption, and persistent activation progressively sensitizes sensory neurons and broadens their responsiveness to both inflammatory and non-inflammatory cues. Over time, itch becomes less tightly coupled to peripheral epithelial cues and more reflective of structural and functional remodeling within itch-processing neurons, leading to altered baseline excitability across peripheral and central circuits.

Recurrent peripheral signaling can further drive central sensitization, blurring the boundary between peripheral- and neuronally-driven mechanisms. This is reflected by the persistence of severe itch even in non-lesional skin, highlighting that altered sensory responsiveness is an intrinsic feature of AD rather than a mere consequence of visible inflammation. Conceptually, AD itch can be understood as a dynamic continuum, progressing from peripherally driven, epithelial-mediated signaling to centrally amplified, neurally entrenched states.

Taken together, this framework emphasizes the importance of integrating epithelial and neuronal compartments to fully capture the evolving biology of chronic itch. To integrate these diverse epithelial, immune, and neuro-immune pathways, Table 1 summarizes the major pruritogenic mediators in AD (Table 1). Future studies should further define how epithelial stress responses, and peripheral neuronal pathways interact to shape central sensitization, and how early intervention that limits repetitive itch–scratch cycles might prevent long-term neuronal remodeling and restore normal itch perception.

Author contributions

L-SW: conceptualisation (lead), formal analysis (lead), writing – original draft (lead), writing – review and editing (equal). J-HY: conceptualisation (supporting), writing – original draft (supporting), writing – review and editing (equal). Y-TY: investigation (equal), writing – original draft (supporting), writing – review and editing (equal). J-LY: conceptualisation (supporting), formal analysis (supporting), investigation (equal), supervision (equal), writing – original draft (supporting), writing – review and editing (equal). All authors contributed to the article and approved the submitted version.

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Conflict of interest

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