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REVIEW ARTICLE

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Immune mediators and therapies for pruritus in atopic dermatitis and psoriasis

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Abstract

Atopic dermatitis (AD) and psoriasis (Pso) are two common inflammatory skin diseases which are symptomatically characterized by pruritus to variable degrees. Whereas AD is nearly always associated with pruritus, only 50%-70% of patients with Pso suffer from itching. Within the last decade, the development of biologic agents targeting specific cytokines or cytokine receptors has led to tremendous progress in suppressing inflammation (and thus improving quality of life) in these two diseases. While suppressing inflammation would generally reduce pruritus in these inflammatory diseases, pruritus is still recalcitrant for treatment in some patients due to relative lack of therapeutics that specifically inhibit pruritus signaling. There is abundant evidence that certain cytokines and neuropeptides-ion channels signaling mediate pruritus that is independent of inflammation in AD and psoriasis. Of note, Janus kinase (JAK) and nerve growth factor (NGF)-tropomyosin receptor kinase A (TrkA)-transient receptor potential vanilloid 1 (TRPV1) signaling partially regulates pruritus in AD and psoriasis. JAK kinases inhibitors decrease the extent of itch in patients with AD and psoriasis. In clinical trials, topical inhibitors of TrkA and TRPV1 have been reported to reduce pruritus in patients with Pso and AD, respectively. In this article, we review recent literature knowledge regarding the mechanisms underlying pruritus in AD and Pso, providing hypotheses for why pruritus may be more common in AD than in Pso. In light of the different mechanisms underlying these two diseases, the current and developing therapeutics, either in human clinical trials or animal studies, for targeting pruritus are also discussed.

KEYWORDS
IL-31, neuropeptide, PAR2, SP, thymic stromal lymphopoietin, TRPA1, TRPV1

Sebastian Yu and Yanxi Li contributed equally to the manuscript.

1 | INTRODUCTION

Pruritus is defined as an unpleasant perception that provokes the desire to scratch to itch. Often resulting from the activation of free nerve endings by pruritogenic, or itch inducing, stimuli in the skin and regarded as an ancient self-defense mechanism among nearly all mammals to remove the pruritogenic stimuli, pruritus is a common feature of many inflammatory skin diseases, including atopic dermatitis (AD) and psoriasis (Pso). In skin, the propagation of itch can result from both inflammatory (eg, AD, Pso) and noninflammatory diseases (eg, uremic pruritus, cholestatic pruritus).[1] Both AD and Pso are prototypic inflammatory skin diseases that are accompanied by pruritus. AD and Pso are complex diseases with genetic,[2] immunological,[3] and environmental[4] contributions. Less understood perhaps are the roles of neuronal sensitization and skin barrier disruptions which likely contribute to pruritus as well. In this review article, we will focus predominantly on the similarities and, importantly, differences in pruritus between AD and Pso. This comparison will not only help define the mechanisms underlying pruritus but also contribute to specific therapeutic targets of pruritus in these two common skin diseases.

2 | ITCHING IN ATOPIC DERMATITIS

2.1 | Itch characteristics in AD

Atopic dermatitis is a chronic relapsing disease with intense itch that is felt by early all affected individuals. In early characterizations of AD, itching was an essential symptom for the diagnosis of AD.[5] Others have defined AD by the presence of elevated immunoglobulin E (IgE) and pruritus that is often accompanied by other allergic diseases.[6,7] Different from Pso, AD generally develops in early childhood with 90% of patients demonstrating onset within the first 5 years of life.[8] Itch is a nearly universal feature of AD and is an essential clinical component in most diagnostic criteria.[9–11]

The itch in AD is often characterized by patients as burning and stinging, suggesting a neurogenic origin.[12] The pruritus can be intense even when there are no visible skin lesions. In fact, AD is commonly referred as "the itch that rashes," which reflects itch often precedes skin lesions in AD.[13,14] Sleep disturbance due to itch is common in patients with AD, and this itch is often exacerbated at night in a circadian manner.[15] Furthermore, transepidermal water loss (TEWL) is associated with itch intensity in AD,[16] and TEWL increases at night in patients with AD, which may explain why AD patients have nocturnal bouts of itch.[17] Moreover, patients with AD often develop lesions on flexor surfaces, which has led others to suggest that sweating may play a role in the pathogenesis of AD.[18]

The pruritus in AD is very difficult to treat and does not respond well to traditional antipruritic treatments such as oral antihistamines.[1] There is an "itch-scratch cycle" that exacerbates skin lesions and pruritus.[19] Mechanical scratching due to itch eventuates in secondary rash and occasional infection or colonization with microorganisms, particularly *Staphylococcus aureus* (*S. aureus*),[20] which further aggravates the disease course. It is often observed that patients with AD present with initial edema, erythema, and papules, progressing to secondary skin lesions such as lichenification, exudation, and crusting. As mentioned before, itching often precedes visible dermatitis. The sequential change of the skin lesions reflects the effect of pruritus and scratching in the course of disease development. Scratching-induced lesions are more frequently observed in AD than Pso. Among these scratch-induced lesions, lichenification is more common in AD (80%) compared with Pso (33%).[21] Dryness and sweating are important triggers for AD flares, and there is a positive relationship between SCORing Atopic Dermatitis (SCORAD) and itch intensity.[22]

2.2 | Immune mechanisms of pruritus in AD

The precise allergens in most patients with AD are not known, but AD in some patients is associated with house dust mite and fungal allergens.[23] After allergens penetrate the impaired skin barrier, they bind to Langerhans cells and activate Th2 cells to release inflammatory cytokines mainly IL-4 and IL-13. These cytokines stimulate IgE production and reduce production of antimicrobial peptides, which may facilitate microbial infections such as *S. aureus*.[24,25] Research has indicated microbial infections such as *S. aureus* emerge during the onset of atopic dermatitis, and antibiotic treatments for these microbial infections eliminated skin inflammation.[26] More specifically, *S. aureus* digests the epidermal barrier via serine proteases to penetrate epidermis and induces expression of AD-associated cytokines, including IL-4, IL-13, IL-22, and thymic stromal lymphopoietin (TSLP).[27,28] Conversely, human skin commensal coagulase-negative *Staphylococcus* (CoNS) such as *Staphylococcus epidermidis* and *Staphylococcus hominis* secrete antimicrobials to kill *S. aureus*, and reintroduction of antimicrobial CoNS strains to human subjects with AD decreased colonization by *S.aureus*.[20]

Th2 cells also release IL-31, a recently identified member of the IL-6 family, that can be a critical driver of pruritus in AD,[29–31] but is generally not thought to be expressed at high levels in the skin of Pso patients.[32] In mice, IL-31 induces pruritus through IL-31 receptors that are expressed by the primary afferent neurons, mediating action through the TRPV1 and TRPA1 ion channels.[32] In humans, IL-31 injection evoked delayed onset itch, implicating an indirect pruritogenic mechanism.[33] It has been proposed that IL-31 induces pruritus indirectly via keratinocytes and subsequently released secondary mediators such as vascular endothelial growth factor (VEGF).[34,35] IL-31 also promotes β-endorphin production by keratinocytes to transmit itch sensation.[31] IL-31 also remodels and thickens the epidermis which leads to impaired skin barrier function resulting in an increased TEWL.[36]

IL-22 is thought to play a distinct role in AD pathogenesis. In contrast to Th17 cells in Pso skin that produce both IL-17 and IL-22, Th22 cells in AD skin independently express IL-22 with lower expression of IL-17 and are responsible for epidermal hyperplasia and lichenification that are typical of chronic AD skin.[37]

TABLE 1 Neuropeptides involved in atopic dermatitis

Neuropeptide	Secrete from	Act on	Effects	References
Substance P	Sensory neurons	Mas-related G protein-coupled receptor A1 (MrgprA1) on sensory neurons; Neurokinin 1 receptor (NK1R) on immune cells, keratinocytes, and cutaneous nerve endings	Production of cytokines to mediate neurogenic inflammation; Release of additional itch mediators	55,56,57
Calcitonin gene-related peptide	Sensory neurons	Cutaneous lymphocyte-associated antigen (CLA)+ T cells	Production of IL-13 to induce an immune shift from Th1 to Th2; Production of IL-13 to stimulate expression of TRPA1 on mast cells to evoke itch via afferent nerves	54,58
Nerve growth factor	Sensory neurons and keratinocytes	Tropomyosin receptor kinase A (TrkA) on sensory neurons	Sensitization and sprouting of sensory neurons; Increase of expression and sensitivity of TRPA1 on sensory neurons	55,60
β-endorphin	Sensory neurons and keratinocytes	μ-opioid receptor isoform MOR1D on sensory neurons	Internalization of MOR1D and subsequent itch transmission	16,31,91,93
Gastrin-releasing peptide	Sensory neurons	Gastrin-releasing peptide receptor (GRPR) on spinal interneurons	Transmission of itch to higher level neurons	55,61,62

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling comprises a cell membrane receptor, receptor-associated JAKs, and recruited STATs. More specifically, when the cytokine receptor is activated by a cytokine, JAKs phosphorylate tyrosine residues on the receptor, which in turn recruits STATs to bind to the phosphorylated tyrosine residues with SH2 domains. Once STATs are recruited, JAKs phosphorylate tyrosine residues on STATs, and then, two STATs bind together to form a dimer. The dimer can translocate to the nucleus and transcript target genes. The intracellular signaling pathway JAK-STAT plays a crucial role in up-regulation of IL-4, IL-13, IL-31, and IL-22-induced pro-inflammatory cytokines.[30,38]

While Th2 and Th22 immune response are predominant in many patients with AD, Th17 pathways are also activated in certain subtypes such as intrinsic, pediatric, and Asian-origin AD.[38–43] Th17-associated cytokines such as IL-17 are increased in AD but not as prominently as Pso. IL-17 is a pro-inflammatory cytokine, and it can downregulate the expression of filaggrin and involucrin, both of which are important skin barrier proteins, through the P38 and ERK pathways.[44] The elevation of IL-17 and subsequent downregulation of filaggrin in certain subtypes of AD may lead to skin barrier dysfunction in patients who don't carry filaggrin mutations.[45] Disruption of the skin barrier function can have several consequences in skin by potentially increasing allergen penetration and by provoking a barrier repair response that includes specific inflammatory responses.

2.3 | Ion channels and neuropeptides in AD

The transient receptor potential (TRP) channels are a family of ion channels with a myriad of roles, many of which act as biological sensors for heat, cold, pressure, osmolarity, and chemicals.[46] While TRP channels have a clear role in the transmission of pain, they are also important for the transmission of itch. The receptors for pruritogenic signaling molecules will bind to their cognate receptors expressed on primary afferent neurons and will activate TRP channels through second messenger G-proteins to ultimately open TRP channels, thus inducing electrical activity of the neurons. TRPV1 is a thermally sensitive channel that mediates response to noxious heat and has a critical role in mediating the histamine-induced itch pathway.[47] The expression of TRPV1 is up-regulated in a murine AD model and in pruritic skin of patients with AD.[2,48] TRPV1 has been shown to be closely linked with skin barrier disruption.[49,50] TRPV1 on keratinocytes regulates calcium gradient along different layers of epidermis and helps maintain normal barrier function.[50]

TRPA1 is sensitive to a number of environmental allergens and noxious agents. It responds to allyl isothiocyanate, cinnamaldegyde as well as extreme cold. Similar to TRPV1, TRPA1 has a role in mediating itch response to nonhistaminergic pruritogens.[51] TRPA1 is required for histamine-independent, Mas-related G protein-coupled receptor-mediated itch.[51] Eighty percent of TRPA1-positive cells express protease-activated receptor 2 (PAR2), which has been reported to be increased in the skin of AD patients with chronic pruritus.[52,53] PAR2 is co-expressed with

TRPV1 in small-to-medium diameter dorsal root ganglion (DRG) neurons.[53] TRPA1 expression is highly enhanced in the dermal afferent nerves, their dorsal root ganglia, mast cells, and the epidermis in the lesional skin biopsies from patients with AD, compared with skin from healthy subjects.[54,55]

In AD, neuropeptides such as substance P (SP), calcitonin gene-related peptide (CGRP), and nerve growth factor (NGF) play an important role in cross-talk between the immune and nervous systems. Neuropeptides can directly act on immune cells to secrete cytokines to induce inflammatory response. On the other hand, immune cells release histamine and cytokines that bind directly to receptors on primary afferent neurons to mediate itch. SP mediates pruritus by activating Mas-related G protein-coupled receptor A1 (MrgprA1) on sensory neurons.[56] SP also acts via neurokinin 1 receptor (NK1R) on immune cells, keratinocytes, and cutaneous nerve endings, which in turn upregulate cytokines such as IL-1, IL-8, and IL-10 to mediate neurogenic inflammatory response and release additional itch mediators.[55,57] CGRP can increase the production of IL-13 from cutaneous lymphocyte-associated antigen (CLA)+ T cells and induce an immune shift from a Th1 to a Th2 cytokine profile.[58] The IL-13 cytokine stimulates expression of TRPA1 on tryptase-positive mast cells, which can act on afferent nerves to transmit itch.[54]

NGF plays an important role in inflammatory disease and is increased in the plasma and lesion site of AD.[59] The increased nerve density in AD lesions is partly mediated by the release of NGF by keratinocytes.[55] NGF binds to its high-affinity receptor tropomyosin receptor kinase A (TrkA), which sensitizes and sprouts the small diameter sensory neurons, and upregulates the expression and sensitivity of TRPV1 via TrkA on sensory neurons.[60] The NGF-TrkA-TRPV1 signaling loop is regarded as a key mechanism of itch in many of the inflammatory diseases, including Pso and AD. Gastrin-releasing peptide (GRP) and gastrin-releasing peptide receptor (GRPR) are involved in sensation of itch, but their role in AD remains unclear.[55] GRP, which is released by neurons in dorsal root ganglion, activates GRPR on spinal interneurons and transmits itch.[61] Severity of pruritus in AD correlates with serum GRP levels.[62] Table 1 shows neuropeptides that are involved in pruritogenic signaling in AD.

2.4 | The relationship among keratinocytes, nervous system, and the immune system in AD

The mechanism of chronic itch in AD is a complex cross-talk between keratinocytes, neurons, and immune system. Keratinocytes and immune cells can release inflammatory mediators such as cytokines, histamine, and serotonin. Many of these inflammatory mediators can activate sensory nerves to mediate itch in the skin.[63] Sensory neurons released neuropeptides such as SP and CGRP that stimulate keratinocytes to secrete NGF, which in turn promotes proliferation of keratinocytes and hyperinnervation of sensory neurons. SP and CGRP also act on Th2 cells to skew inflammation and act on mast cell to induce degranulation.[63]

The communication between skin and the nervous system is not restricted to the peripheral nervous system. Neurodegenerative diseases such as Parkinson's disease and dementia are more prevalent in elderly patients who met diagnostic criteria of AD.[64] The exact mechanism underlying this phenomenon is unclear, but it has been reported that BP180- and BP230-specific IgG autoantibodies are associated with pruritus in elderly patients.[65] Immunosenescence of T cells may result in a loss of immune tolerance and the development of BP180- and BP230-specific IgG autoantibodies. This, in turn, may lead to a chronic generalized eczema mimicking atopic dermatitis that may be regarded as a preclinical variant of bullous pemphigoid.[64–66]

Another connection between skin and the nervous system which contributes to pathophysiology of AD lies in circadian rhythms. Circadian rhythm is a biological clock that controls physiological functions throughout the body.[67] Skin physiology parameters such as TEWL and cutaneous blood flow fluctuate with circadian rhythm.[67] AD often exacerbates at night, and this phenomenon is related to increased TEWL at nighttime.[17] Melatonin is a hormone mainly secreted by pineal gland that regulates the circadian rhythm and sleep.[68] The circadian melatonin rhythm was abolished or diminished in patients with AD,[69] and melatonin supplementation has been demonstrated as an effective way to improve AD severity in children.[70]

Keratinocyte-derived TSLP plays a crucial role in the pathophysiology of AD. TSLP binds to neuronal TSLP receptor (TSLPR), which in turn activates TRPA1 to mediate TSLP-induced itch.[71] The release of TSLP from keratinocytes is regulated by ORAI1/NFAT calcium signaling pathway. An association between single nucleotide polymorphism of ORAI1 and the susceptibility of AD has been reported in Japanese and Taiwanese populations.[72]

3 | ITCHING IN PSO

3.1 | Itch characteristics in Pso

Pso is an immune-mediated chronic inflammatory disease that commonly affects the skin and, in a minority of patients, affects the joints. Pso affects approximately 2%-11% of Caucasian populations while its prevalence is around 0.24%-5.5% in Asian populations.[73] Patients with an early onset tend to have a more severe course and a positive family history, whereas patients with late onset have a more mild disease and often have a negative family history.[74] In the last decade, it has become clear that Pso is a systemic disease with multiple comorbidities, including enhanced cardiovascular risk, obesity, and psychiatric disorders.[75–77] Itch exacerbates patients' quality of life and may account for increased psychological burden and psychiatric comorbidities of Pso.[78,79]

Despite its name (psoriasis is derived from "psor", Greek, to itch), pruritus is not regarded as a universal symptom of Pso since pruritus affects ~60-90% of patients,[80] especially females.[81] The itching sensations are not limited to lesional areas and often include areas on the scalp, groin, and buttocks.[82] Itch also induces scratching and leads to damage to the skin and development of Koebner phenomenon. Therefore, relief of itch is very important for treatment of Pso.

Compared with patients with AD, however, patients with Pso experience fewer problems with insomnia and sleep quality.[83] A systemic review reported that the prevalence of insomnia in patients with Pso is similar to that in the general population.[84]

3.2 | Immune mediators and neuropeptides in the pathogenesis of pruritus in psoriasis

An explosion of clinical and experiment data has emerged in recent years regarding the immune mechanisms that give rise to psoriasis in the skin.[85,86] Pso represents an example of a disease predominantly driven by a single polar immune pathway. While early studies suggested that Th1 cells were found in Pso skin and, indeed, IL-12 and interferon-g are found in psoriatic skin, careful clinical studies suggest that Th1 cytokines do not correlate with disease activity in the same way that Th17 cytokines clearly do.[87] Thus, the Th17 axis is now considered paramount psoriatic disease. TNF-α activated dendritic cells (DCs) are thought to be critical drivers in the Th17 response. Activated Th17 cells secrete cytokines such as IL-17, which activate STAT3 in keratinocytes and induce subsequent epidermal hyperplasia and neutrophil recruitment, creating a "feed forward" inflammatory response.[88] Downstream events include the eventual activation and recruitment of the Th22 T-cell subsets into psoriatic lesions, which may further contribute to epidermal hyperplasia.[89,90]

Much of the pathogenesis of pruritus in Pso remains to be elucidated, but neurogenic inflammation seems to be crucial.[80] In contrast to AD patients, Pso patients rarely complain of itching in the absence of obvious skin redness and scaling. The number of epidermal nerve fibers is increased in skin lesions of psoriatic patients with pruritus.[91] The sensory nerve fibers in the skin not only mediate pruriception but also release bioactive substances such as SP, which can mediate the inflammation and is responsible for the itching sensation in Pso. The active form SP cleaved by dipeptidyl peptidase IV (DPPIV) is increased in sera of patients of Pso. DPPIV-knockout mice and mice treated with DPPIV inhibitors show decreased SP-induced scratching behavior.[92] There is also enhanced growth of nerve C-fibers found in Pso.[93] Another neuropeptide important for Pso is NGF, which can trigger the outgrowth of C-fibers, leading to pruritus. NGF and platelet-derived growth factor (PDGF) with some cytokines such as IL-17 and IL-22 activate phosphatidylinositol 3-kinase (PI3K)-AKT-mTOR kinase system, elucidating the inflammatory and proliferative cascades.[94]

Prokineticin 2 (PK2) is a neuroendocrine peptide, which can upregulate cytokines such as TNF-α, IL-23, IL-17 and induce keratinocyte and macrophage production of IL-1. IL-1 feeds back on macrophages to induce PK2 production, forming a positive feedback loop.[95] VEGF may also mediate pruritus in Pso. In an imiquimod-induced murine model of Pso, VEGF partially induces pruritus via epidermal hyperinnervation.[96]

β-endorphin is an endogenous opioid neuropeptide that preferentially binds to the μ-opioid receptor rather than the κ-opioid receptor. A common side effect of μ-opioid receptor agonists is pruritus, while κ-opioid receptor agonists reduce itch. Itch induced from μ-opioid receptor agonists, like morphine, is mediated through the μ-opioid receptor (MOR) isoform MOR1D. When bound, MOR1D heterodimerizes with the GRPR and is internalized to evoke itch.[97] In AD, IL-31 induces production of β-endorphins and the blood level of β-endorphins correlate with itch intensity.[16,31] Recently, it has been reported that the κ-opioid receptor pathway is downregulated in lesional skin of Pso patients and positively correlate with itch sensation. In contrast, the μ-opioid receptor pathway is uniformly expressed by epidermal keratinocytes of psoriatic skin.[98] Taken together, these findings suggest that homeostasis of epidermal opioid receptors may be involved in the generation of itch in both AD and Pso.[99]

3.3 | Ion channels in the pathogenesis of pruritus in Pso

The ion channels are known to participate in the itch of cutaneous neurogenic inflammation, which is related to itch. TRPV1 and TRPA1 are not only expressed in neuronal cells, which exist in cutaneous C- and Aδ-type sensory nerve endings, but are also expressed in non-neuronal cells such as keratinocytes.[46] The activation of the TRPV1 channel can upregulate of the expression of SP and CGRP in DRG neurons in a Ca2+ dependent manner. TRPV1+Na_v1.8+ nociceptors, by interacting with dermal DCs, drive the response of IL-23/IL-17 pathway.[100] As in AD, the NGF-TrkA-TRPV1 interaction partially mediates pruritus in Pso. A topical TrkA inhibitor, CT327, has been reported to reduce pruritus in patients with Pso.[101] Our recent studies showed that TRPV1 knockout mice have significantly reduced epidermal and dermal inflammation and TEWL compared to wild-type mice in the IMQ-mediated model of psoriasiform dermatitis.[102] We did not see marked changes in behavior signs of pruritus in the TRPV1 knockout mice under the same conditions, suggesting that dermal inflammation and pruritus can be independently mediated in some cases (manuscript submitted).

The role of TRPA1 in mediating pruritus of Pso is not as well defined. TRPA1 is generally regarded as a contributor of chronic pruritus.[103] Activation of TRPA1 triggers the expression of Pso-related genes, including IL-33, CCL20, CXCL2, CXCR2, lipocalin, and Slc9a3r1.[103] In a topical imiquimod-induced murine model of psoriasiform dermatitis, spontaneous scratching to the imiquimod-treated sites and alloknesis are observed.[104] In that study, no significant change in the mRNA expression of TRPV1 or TRPA1 in DRG cells was observed. The mRNA expression levels of histidine decarboxylase and tryptophan hydroxylase 1, as well as the intensity of histamine and serotonin immunoreactivity, transiently increased in the skin but returned to baseline by the end of imiquimod 7-day treatment course. In parallel with that finding, histamine H1-receptor antagonists significantly inhibited spontaneous scratching on day 2, but not day 7. These results may explain the limited antipruritic effects of histamine H1-receptor antagonists in human Pso.[104] In a recent article, TRPA1 is reported to act in a protective manner in an imiquimod murine model of psoriasiform dermatitis.[105] Intriguingly, another study using the same imiquimod murine model found that

blockade, either genetic or pharmacological approaches, of common sensory neurogenic mechanisms for TRPV1, TRPA1, SP, and CGRP inhibits spontaneous biting/licking behaviors, which are indicative of cutaneous discomfort.[106] This indicates neuropeptides-ion channels signaling can induce cutaneous discomfort, but its role in psoriatic inflammation, either pro-inflammation or anti-inflammation, remains to be clarified.

4 | TREATMENT OF PRURITUS FOR AD AND PSO

For mild disease in both AD and Pso, topical corticosteroids remain the gold standard for treatment based on their known efficacy and safety profiles. When larger surface areas are involved, graduated treatment to other topicals such as tacrolimus (for AD) or calcipotriol (for Pso) or to light therapy may be added. Patients with moderate-to-severe AD or Pso who have larger degrees of body surface involvement or resistance to topicals historically were treated with systemic agents such as methotrexate and cyclosporine, but due to their enhanced risk profiles, these broadly immunosuppressive agents are gradually being replaced by biologic agents and a new generation of targeted small molecules as discussed below.

4.1 | Biologic agents

Traditional antihistamine drugs have limited effects for the treatment of pruritus in AD and Pso, so the histamine-independent itch pathways are suggested to dominate in these two diseases. Th17 signaling is the main pathway of Pso, and cytokines including IL-17, IL-23, TNF-α contribute to the immunopathogenesis of Pso. So biologic drugs targeting TNF-α, IL-12/-23, and IL-17 are highly efficacious for the treatment of Pso. As skin disease diminishes with effective treatment, the itch nearly always subsides. In AD, dupilumab, a fully human monoclonal antibody against shared IL-4/13 receptor α component, inhibits both IL-4 and IL-13 signaling and demonstrates significant efficacy, reducing the itch of moderate-to-severe AD.[107,108] It not only has a dramatic antipruritic effect but also decreases the anxiety or depression associated with AD.[107] Inhibitors of IL-31 (nemolizumab) [109,110] and IL-13 (lebrikizumab, tralokinumab) [111,112] have had promising results from phase 2 clinical trials for patients with moderate-to-severe AD. Fezakinumab, an IL-22 monoclonal antibody, showed efficacy only for severe AD (SCORAD ≥50) in a phase 2 clinical trial.[113] Another report suggested that fezakinumab may be more effected for patients with high baseline IL-22 expression.[114] Interestingly, selective targeting of some propruritogenic factors such as TSLP has shown mixed results in clinical testing. For example, the anti-TSLP monoclonal antibody, tezepelumab, showed efficacy for uncontrolled asthma in a phase 2 clinical trial,[115] but its efficacy for atopic dermatitis has not been validated.[116] Omalizumab, which targets IgE, is currently undergoing a clinical trial to determine its efficacy for severe recalcitrant pediatric AD.[117] Other anti-IgE agents such as MEDI4212 and ligelizumab have undergone phase 1 clinical trials but their efficacy for AD has yet to be evaluated.[118,119]

4.2 | Small molecule drugs

Phosphodiesterase 4 (PDE4) is an enzyme which degrades cyclic adenosine monophosphate (cAMP). Apremilast is an oral PDE4 inhibitor that is used for treatment for immune-mediated diseases, including Pso, although its clinical efficacy is not as great as those of biological agents.[120] Crisaborole ointment is a FDA-approved topical PDE4 inhibitor for the treatment of mild-to-moderate AD.[121] Interestingly, apremilast is not considered to be effective for AD.[122]

Janus kinase (JAK) is a family of tyrosine kinases. Many of the cytokines of Pso utilize the JAK-STAT pathway.[123] Because of JAK inhibitors are small molecules, they can penetrate the epidermal barrier and therefore can be used in topical formulations. In Pso, oral and topical JAK inhibitors are used for treatment. STAT3 has been proved to play a role in keratinocyte differentiation and proliferation, upregulation of keratin 17, which is a hallmark of Pso, activation of T cells, and release of the inflammatory cytokine IFN-γ, which in turn can increase the expression of K17 through the STAT2 pathway.[124] The anti-JAK1/3 inhibitor tofacitinib is a therapeutic agent for treatment of Pso both orally and topically and shows effective and fast treatment with safe effects.[125,126] Topical JAK1/2 inhibitor INCB018424 has also been shown efficacy for the treatment of Pso.[127,128] Tyrosine kinase 2 (TYK2) belongs to the JAK family and is involved in a large number of cytokine signaling cascades.[129] A TYK2 inhibitor BMS-986165 showed greater clearing of Pso than placebo over a period of 12 weeks in a phase 2 clinical trial.[130]

In AD, all three JAKs and STATs are overexpressed. The JAK/STAT pathway is a potential therapeutic target to AD. JTE-052 is a novel JAK inhibitor, which can inhibit JAK1/JAK2/JAK3 pathways as well as the Th1-, Th2-, Th17-mediated inflammation and relieve itching induced by IL-31. Experiments on AD mice confirmed it has excellent curative effects in a dose-dependent manner by oral use in AD.[131] JTE-052 has obvious effects and works fast in the treatment for moderate-to-severe AD by topical use in a clinical phase 2 clinical trial.[132] In AD, the JAK1/3 and STAT6 pathways can mediate the IL-4 signaling. Topical JAK1/3 inhibitor tofacitinib has been shown effective for AD in phase 2 clinical trial.[133] Oral tofacitinib is also effective for deceasing severity and itching in AD in some case series, but further clinical trials with larger sample sizes are warranted to validate the efficacy.[134,135] In a murine model of AD, a PAR2 antagonist PZ-235 significantly inhibits PAR2-mediated inflammation and epidermal thickening and reduces pruritus, suggesting PAR2 as a therapeutic target for AD.[136]

4.3 | Ion channel inhibitors and potential targeted therapies

NGF-TrkA-TRPV1 partially mediates pruritus in AD and Pso. The amount of NGF is 10 times higher in keratinocyte cultures of Pso compared to the healthy individuals.[137] Topical TrkA inhibitor CT327

showed significant clinical effect in reducing chronic pruritus in Pso patients.[101] In AD, TrkA is expressed in all layers of keratinocytes. Th2 cytokines such as IL-4 and IL-13 enhance TrkA expression. The development of inhibitors of NGF and TrkA can decrease IL-4-induced keratinocyte proliferation.[138]

TRPV1 is mainly expressed in keratinocytes, nerve fibers, as well as mast cells.[53] PAC-14028, a TRPV1 antagonist, was shown to be effective by topical administration for the treatment of atopic dermatitis.[49] It not only blocks Ca2+ influx into keratinocytes and accelerates skin barrier repair but also suppresses the degranulation of mast cells and decreases the serum IgE, which in turn blocks the downstream inflammatory response and relieves the itching and controls the scratching behavior. Suppression of TRPV1 activation in nerve fibers can decrease neuropeptide release, contributing to the alleviation the cutaneous neurogenic inflammation.[139] While PAC-14028 shows promise, another TRPV1 inhibitor SB705498 shows no effect on itch relief.[140] JAK inhibitors oclacitinib and tofacitinib can decrease itch in AD and Pso, which are linked with the inhibition of TRPV1 receptor channels.[141]

While TRPV1 is necessary for histaminergic itch, TRPA1 is necessary for many types of itch that are independent from histamine (nonhistaminergic itch) including TSLP-induced itch.[71] The PAR2/TRPA1 pathway maybe a potential target for treating AD itch.[142] Although a TRPA1 inhibitor has not been used to treat itch clinically, recent work has shown that IL-13 induces chronic pruritus in AD via a novel TRPA1-dependent pathway, and a TRPA1 antagonist alleviated pruritus in AD mice.[54]

5 | CONCLUSIONS

AD and Pso are prototypic inflammatory skin diseases that are characterized by intense pruritus. It is tempting to speculate that neurogenic itching may precede obvious cutaneous inflammation (and skin changes) in AD, which is radically different from the itching that generally follows obvious dermatitis in Pso. Although AD is traditionally regarded as Th2 predominant and Pso is Th17 predominant, recent research shows these two diseases have some common immune pathways, at least in certain subtypes of AD.[38] Understanding of the similarities and discrepancy between AD and Pso would lead to development of treatments that are efficacious for both diseases or specific to either one. While inhibiting inflammation would generally reduce pruritus in AD and Pso, there is evidence that certain cytokine and neuropeptides-ion channels signaling can induce pruritus that is independent of inflammation in AD and Pso.[71,106,143] Curiously, there are AD patients who have generalized pruritus with no or minimal dermatitis. Current therapies are truly lacking to adequately manage these patients in which topical corticosteroids are not particularly effective. Agents therefore that target itch pathways may be more appropriate. More specifically, TRPV1- and TRPA1-associated signaling pathways are potential therapeutic targets to inhibit pruritus.[54,101,141] Current treatments for AD and Pso focus on inhibiting immune-mediated inflammation. Further understanding of admittedly complex pruritogenic signaling pathways would help develop tailored treatment to reduce pruritus to improve patient quality of life.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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