Review article

The role of Janus kinase signaling in the pathology of atopic dermatitis

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Atopic dermatitis (AD) is a heterogeneous, chronic, relapsing, inflammatory skin disease associated with considerable physical, psychological, and economic burden. The pathology of AD includes complex interactions involving abnormalities in immune and skin barrier genes, skin barrier disruption, immune dysregulation, microbiome disturbance, and other environmental factors. Many of the cytokines involved in AD pathology, including IL-4, IL-13, IL-22, IL-31, thymic stromal lymphopoietin, and IFN-γ, signal through the Janus kinase (JAK)–signal transducer and activation of transcription (STAT) pathway. The JAK family includes JAK1, JAK2, JAK3, and tyrosine kinase 2; the STAT family includes STAT1, STAT2, STAT3, STAT4, STAT5A/B, and STAT6. Activation of the JAK-STAT pathway has been implicated in the pathology of several immune-mediated inflammatory diseases, including AD. However, the exact mechanisms of JAK-STAT involvement in AD have not been fully characterized. This review aims to discuss current knowledge about the role of the JAK-STAT signaling pathway and, specifically, the role of JAK1 in the pathology and symptomology of AD. (J Allergy Clin Immunol 2023;152:1394-404.)

Key words: *Atopic dermatitis, JAK-STAT, pathology, symptomology*

Abbreviations used
AD: Atopic dermatitis
FLG: Filaggrin
ILC2: Group 2 innate lymphoid cell
JAK: Janus kinase
OSMR: Oncostatin M receptor
STAT: Signal transducer and activation of transcription
TSLP: Thymic stromal lymphopoietin
TYK2: Tyrosine kinase 2

Atopic dermatitis (AD), also called atopic eczema, is a heterogeneous, chronic, relapsing, inflammatory skin disease associated with considerable physical, psychological, and economic burden.[1] Most cases arise during childhood, although adult-onset AD is increasingly recognized.[2] The lifetime prevalence of AD is up to 30% in some geographic regions.[1,3] AD is characterized by pruritic, eczematous, and painful skin lesions that manifest as erythematous patches with oozing and crusting at early stages and scaling, fissuring, and lichenification at later stages.[1] Lesions can be localized to certain areas, such as the folds of the extremities or the face, or they can be widespread in more severe disease.[4] The distribution of lesions also differs between adult-onset and childhood cases.[4,5]

Over the past few decades, human, murine, and *in vitro* studies have expanded our understanding of AD pathophysiology, and clinical trials have led to an increase in the availability of effective AD treatments with acceptable safety profiles.[1,6-8] AD is a heterogeneous disease with a complex pathology.[1,9,10] Abnormalities in immune and skin barrier genes, dysregulation of innate and adaptive immune responses (including cytokine release), microbiome disturbance (especially *Staphylococcus aureus* colonization), and environmental factors are all thought to play a role in development of the disease.[1,9] Several subtypes of AD are also recognized; for example, Asian AD cases are often characterized by higher T_H17 cell polarization, whereas European AD cases are characterized by T_H2 and T_H22 cell activation.[11] Furthermore, differences exist between pediatric-onset (more intense T_H2, T_H22, and/or T_H17 cell upregulation) and adult-onset AD (more prominent T_H1 cell activation).[12]

Many of the cytokines involved in AD pathology, including IL-4, IL-13, IL-22, IL-31, and thymic stromal lymphopoietin (TSLP), signal through the Janus kinase (JAK)–signal transducer and activation of transcription (STAT) pathway, with increased IFN-γ in chronic disease (Box 1).[13-15]

JAKs are activated following ligand binding to cytokine transmembrane receptors, and in turn, they phosphorylate and activate STATs, which then translocate to the cell nucleus to regulate transcription of target genes (Fig 1).[14-24] The JAK family includes JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2); the STAT family includes STAT1, STAT2, STAT3, STAT4, STAT5A/B, and STAT6.[14] JAK1, JAK2, and TYK2 are quite ubiquitously expressed in mammalian cells, whereas JAK3 is predominantly expressed in hematopoietic cells. Although many

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Box 1. What is known about the topic?

What is already known about this topic?	• Key type 2/T_H2 and type 22/T_H22 cytokines involved in the pathogenesis of AD, including IL-4, IL-13, IL-22, IL-25, IL-31, IL-33, and TSLP, signal via the JAK-STAT pathway • T_H2 and T_H22 cytokines have also been shown to drive features and symptoms of AD, including barrier defects, inhibition of antimicrobial peptides, dysbiosis, and pruritus
What does this article add to our knowledge?	• AD evolves over time and shows clinical and molecular differences across various disease phenotypes based on geographic regions, patient age (pediatric vs adult patients), and disease severity; thus, targeting a single cytokine pathway may not be a feasible treatment strategy for patients with AD • JAK inhibitors represent a therapeutic strategy by simultaneously disrupting many of the pathogenic cytokine signals in target tissues and alleviating symptoms such as pain, and thus, they can potentially enhance the approaches to treatment of AD
How does this study affect current management guidelines?	• This review adds key knowledge to existing data and paves the path to better understanding of the molecular mechanisms underlying AD and the role of a new class of oral medications that target various cytokines involved in the pathology of AD, allowing physicians to make mechanistic-based prescription decisions

cytokines can activate 3 of the 4 members of the JAK family (IL-4, IL-6, IL-13, and IL-23), others are more limited to JAK1 or JAK2 and TYK2 heterodimers (IL-12 and IL-22), JAK1 and JAK2 heterodimers (IL-31, TSLP, and IFN-γ), or JAK2 homodimers (IL-25 and IL-33) (Fig 1).

Activation of the JAK-STAT pathway has been implicated in the pathology of several immune-mediated inflammatory diseases, including inflammatory bowel disease, rheumatoid arthritis, and psoriasis.[25] In mouse models of dermatitis, excessive JAK1 activation induces spontaneous hyperproliferation of keratinocytes and phosphorylation of STAT proteins, leading to disruption of the skin barrier and development of progressive pruritic dermatitis.[26,27] Furthermore, hyperphosphorylation of epidermal JAK1 has been detected in skin samples from patients with AD, suggesting that the JAK-STAT pathway plays a role in AD.[26] However, less is known about the exact mechanisms of JAK-STAT involvement in AD. The objective of this review is to discuss current knowledge regarding the role of the JAK-STAT signaling pathway and specifically the role of JAK1 in the pathology and symptomology of AD.

SKIN BARRIER DYSFUNCTION IN AD

Skin barrier dysfunction plays a critical role in the development of AD.[1,28,29] In 20% to 40% of patients with AD, skin barrier dysfunction results from mutations in the filaggrin gene (*FLG*).[1,28] *FLG* encodes the key epidermal structural protein FLG, and loss-of-function mutations of *FLG* are associated not only with skin barrier dysfunction but also with increased risk of AD and overall more severe AD.[1,30] However, the majority of individuals with *FLG* mutations do not develop AD, suggesting that other factors are also involved.[1] Increased permeability of the skin has been associated with deficiencies of structural proteins (FLG, loricrin, and involucrin), lipids (such as ceramides), and tight junction proteins (eg, claudins) of the skin.[1,30] Furthermore, reduced Toll-like receptor function and reduced keratinocyte production of antimicrobial peptides, which are needed to control microbial replication (eg, replication of *S aureus*) on the skin, have been linked to disruption of the epidermal barrier.[28,29]

Immune-mediated mechanisms also contribute to skin barrier alterations. Cytokines that signal via the JAK-STAT pathway (eg, IL-4, IL-13, IL-22, IL-25, IL-31, IL-33), and especially JAK1-STAT3 (Fig 1), are involved in downregulating skin barrier proteins (including FLG, loricrin, and involucrin) and in the inhibition of keratinocyte terminal differentiation and lipid and antimicrobial peptide synthesis, all of which can lead to increased skin permeability.[15,29-31]

AD LESION DEVELOPMENT

Patients with AD can present with clinically normal skin or with acute or chronic lesions (Fig 2). In nonlesional/normal skin, T_H2 cytokines IL-4 and IL-13, *FLG,* and other barrier gene mutations or environmental factors contribute to the initial epidermal barrier disruption.[30,32-34] This allows allergens, microbes, and environmental pollutants to penetrate the epidermis, where they stimulate keratinocytes to produce cytokines, such as IL-1β, IL-18, IL-25, IL-33, and TSLP, to further amplify the local immune response.[1,28,35] These mediators trigger the influx and activation of dendritic cells, which in turn initiate type 2 and T_H22 cell immune responses.[7,28,32,33]

In acute lesions, T_H2 cells infiltrate the skin, followed by T_H22 cells, and to a lesser extent, T_H1 and T_H17 cells, with subsequent effector cytokine release (Fig 2).[28,32,33] Activated keratinocytes release IL-25, IL-33, and TSLP, which further promote T_H2 cell responses.[28,32] Furthermore, group 2 innate lymphoid cells (ILC2s), the levels of which are increased in AD lesions versus in healthy skin, can also produce T_H2 cytokines and promote type 2 responses.[7] Release of the T_H2 cytokines IL-4, IL-13, and IL-31 and the T_H22 cytokine IL-22 further contributes to epidermal barrier disruption and hyperplasia.[28,33] Critically, IL-4, IL-13, IL-31, and TSLP also drive symptoms including pruritus, and the resultant scratching leads to further epidermal barrier damage and inflammation.[1,28]

In chronic lesions, intensified T_H2 and T_H22 cell activation occurs and inflammation is further amplified by increased levels of T_H1 cell–derived IFN-γ, which induces keratinocyte apoptosis and the recruitment of additional inflammatory cells into the skin, leading to prolonged itch-scratch cycles and lichenification

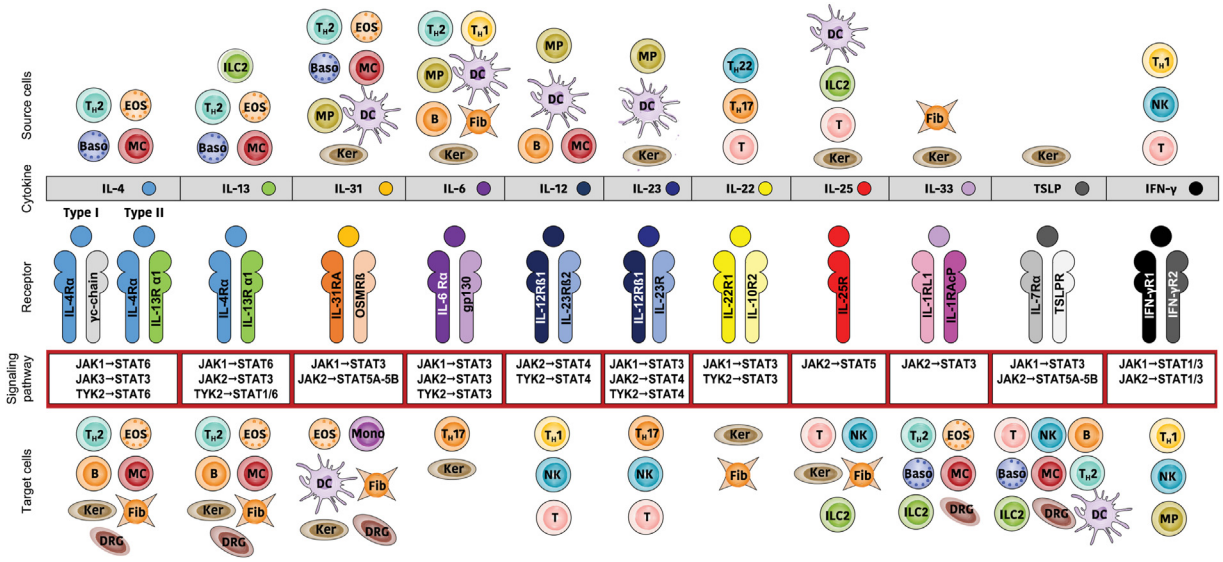

FIG 1. AD cytokines, JAK-STAT signaling pathways, and target cells. After being produced by their source cells, cytokines bind their receptors and activate the JAK-STAT signaling pathway. JAKs are activated following ligand binding to cytokine transmembrane receptors, and in turn, they phosphorylate and activate STATs, which then translocate to the cell nucleus to regulate transcription of target genes in target cells. *B*, B cell; *Baso*, basophil; *DC*, dendritic cell; *DRG*, dorsal root ganglia neuron; *EOS*, eosinophil; *Fib*, fibroblast; *Ker*, keratinocyte; *MC*, mast cell; *Mono*, monocyte; *MP*, macrophage; *NK*, natural killer cell; *R*, receptor; *T*, T cell.

(Fig 2).[32,33,36] Overall, the immune pathology of AD is complex and involves various differentiated T_H cell subtypes, activated keratinocytes, and multiple inflammatory cytokines. We will next look at these cytokines in more detail.

THE JAK-STAT PATHWAY IN THE PATHOLOGY OF AD

Type 2 cytokine: IL-4

Local production of IL-4, which is produced by cells such as T_H2 cells, mast cells, and eosinophils in the skin, is associated with acute AD.[1,15,37] In addition to being involved in B-cell proliferation and IgE isotype switching, IL-4 regulates T_H2 target genes by signaling through JAK1, JAK3, and STAT6 (Fig 1).[1,15,24] The role of IL-4 in T_H2 cell differentiation and AD has been demonstrated in animal studies.[38,39] Transgenic mice that overexpress IL-4 develop AD-like skin lesions,[39] and mice constitutively expressing active STAT6 develop an atopic phenotype and skin inflammation in an IL-4–dependent manner.[40] However, STAT6-deficient mice can also develop AD-like skin lesions via a T_H2 cell–independent mechanism.[41] IL-4 (or IL-13 [see later]) also attenuates expression of key structural proteins, including FLG, loricrin, and involucrin, as well as tight-junction–related proteins, such as claudin, leading to disruption of the normal integrity of the keratinocyte architecture,[42] and it upregulates additional T_H2 cytokines, including IL-5, IL-10, and IL-13,[38,39] and chemokines known to have a role in AD as well as other proinflammatory cytokines (eg, IL-1α, IL-19, IL-20, IL-25).[43] The efficacy of IL-4 inhibition in AD has also been demonstrated in clinical trials and in real-world clinical practice using dupilumab, which inhibits IL-4 and IL-13 activity.[44,45]

Type 2 cytokine: IL-13

IL-13 is secreted primarily by T_H2 cells but is also by stimulated ILC2s, mast cells, and eosinophils, among others.[1,15,17,37] IL-13 shares some characteristics and functions with IL-4, including promotion of B-cell proliferation and IgE switching, but it also plays a role in pulmonary fibrosis and airway hyperreactivity.[15,17,46] IL-13 signals through JAK1, JAK2, TYK2, and STAT6 to activate IL-13–responsive genes (Fig 1).[1,15,17] Similar to IL-4, IL-13 plays a role in AD pathology by attenuating expression of several structural proteins (including FLG, loricrin, involucrin, and claudin), disrupting keratinocyte integrity, and stimulating keratinocytes to produce chemokines, leading to recruitment of T cells and eosinophils.[15,42,47] IL-13 is also a major inducer of the T_H2 cell response independently of IL-4, indicating an important role in AD pathology.[47] A recent study demonstrated that homeostatic production of IL-13 by dermal ILCs directs dendritic cell differentiation to promote a T_H2 cell response and inhibits T_H17 cell polarization in healthy skin.[48] Similar to the efficacy of IL-4, the efficacy of IL-13 inhibition in AD was demonstrated with dupilumab in clinical trials and real-world practice and with the IL-13 inhibitors tralokinumab (which is approved for moderate-to-severe AD[44,45]) and lebrikizumab (which has recently completed phase 3 trials).[49]

Type 2 cell–associated cytokine: IL-31

IL-31 is a T_H2 cytokine produced by numerous cells, including non-T_H2 cells, such as cutaneous lymphocyte antigen–positive (CLA^+) T cells, dendritic cells, macrophages, and mast cells.[22,50] The IL-31 receptor consists of IL-31RA and the oncostatin M receptor (OSMR), the latter increasing the affinity of IL-31 binding to IL-31RA.[51,52] After binding to its receptor on eosinophils, dendritic cells, or keratinocytes, IL-31 signals through JAK1, JAK2,

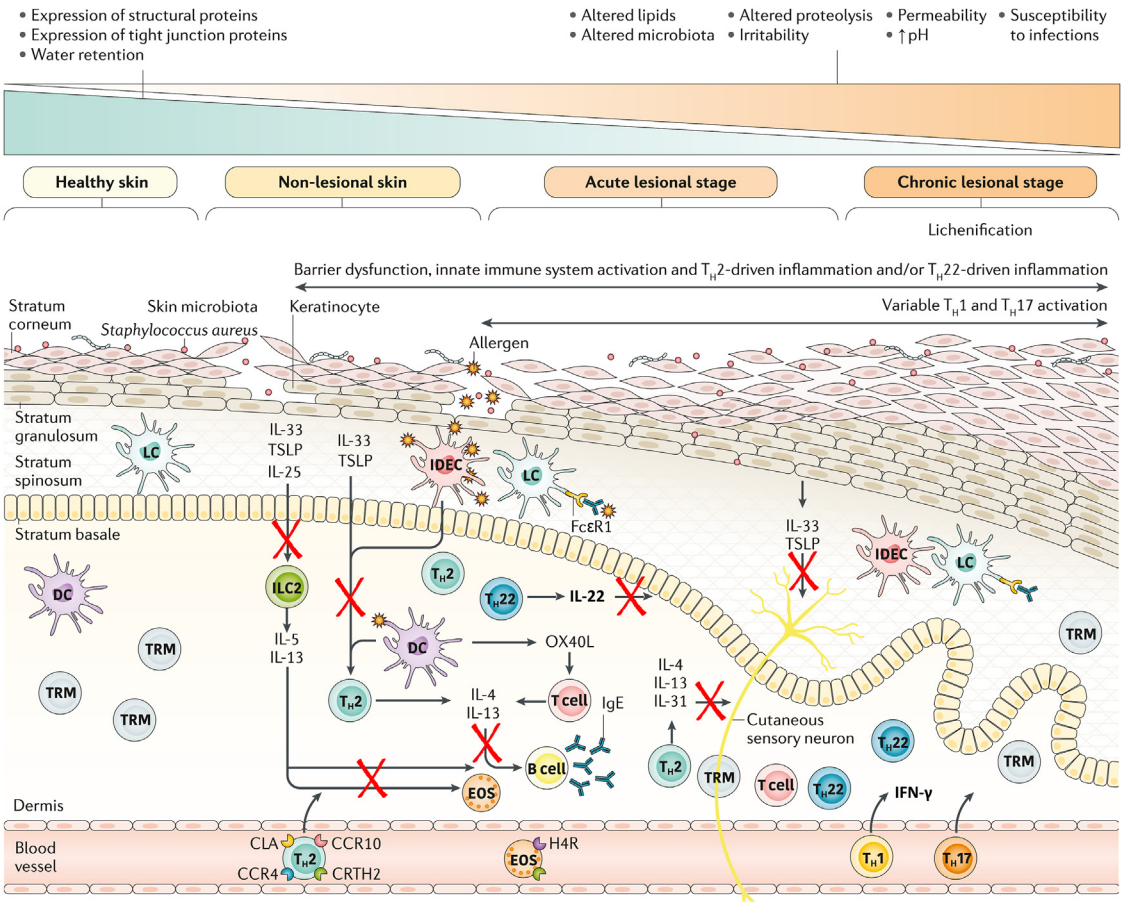

FIG 2. Pathogenesis and stages of AD. Healthy skin versus development of AD lesions, which are divided into nonlesional skin, acute lesions, and chronic lesions. In nonlesional skin, T_H2 cytokines (IL-4 and IL-13), *FLG,* and other barrier gene mutations or environmental factors contribute to the initial epidermal barrier disruption. In acute lesions, T_H2 cells infiltrate the skin, followed by T_H22 cells and, to a lesser extent, T_H1 and T_H17 cells, with subsequent effector cytokine release. In chronic lesions, intensified T_H2 and T_H22 cell activation occurs and inflammation is further amplified by increased T_H1 cell–derived IFN-γ. Red crosses indicate signaling pathways affected by JAK inhibitors (see Fig 1 for more detailed pathways). *CCL17,* CC-chemokine ligand 17; *CCR,* C-C chemokine receptor; *CLA,* cutaneous lymphocyte antigen; *DC,* dendritic cell; *EOS,* eosinophil; *H4R,* histamine H4 receptor; *IDEC,* inflammatory dendritic epidermal cell; *LC,* Langerhans cell; *MDC,* macrophage-derived chemokine; *OX40L,* OX40 ligand; *TRM,* T resident memory cell. Adapted from Weidinger et al.[1]

STAT1, STAT3, and STAT5, stimulating the secretion of proinflammatory cytokines (Fig 1).[22,50] Elevation of plasma IL-31 level and upregulation of IL-31RA in epidermal keratinocytes have been reported in patients with AD, and IL-31 serum levels are correlated with AD severity.[22,50,53] At the initiation of the AD inflammatory cascade, disruption of the skin barrier triggers IL-31 production by T_H2 cells.[22] Subsequently, IL-31 activates the secretion (by eosinophils) of several cytokines and chemokines that then activate T_H2 cells, leading to the secretion of IL-4 and IL-13.[22] The role of IL-31 in the pathology of AD was demonstrated in studies of nemolizumab, an antibody that blocks the IL-31 receptor, resulting in rapid improvement in itch when compared with placebo.[15,54]

T_H22 cytokine: IL-22

IL-22 is part of the IL-10 cytokine family, and its levels in AD skin and blood are elevated. IL-22 is produced by T_H17, T_H22, and γδ T cells; it signals through JAK1 and TYK2, and it induces phosphorylation of STAT1, STAT3, and STAT5 (Fig 1).[16,36,55] After binding to its receptor, which is expressed by epithelial cells, IL-22 upregulates the expression of proinflammatory genes in keratinocytes, resulting in keratinocyte proliferation and epidermal acanthosis (Fig 1).[36,55] In mouse models, IL-22 stimulates T_H2 cell responses in both acute and chronic AD lesions; it leads to increased skin permeability and decreased expression of *FLG2* and claudin, and it increases susceptibility to *S aureus* colonization.[56] IL-22 targeting in AD significantly ameliorated clinical disease severity, particularly in patients with more severe disease and in those with higher IL-22 expression, indicating a pathogenic role for IL-22 in AD, at least in a subset of patients.[57,58]

T_H1 cytokine: IFN-γ

The T_H1 cytokine IFN-γ signals via JAK1, JAK2, STAT1, and STAT3 and plays a key role in inflammation, macrophage

activation, and T_H1 cell responses (Fig 1).[59-61] IFN-γ is secreted during the chronic stages of AD and contributes to lymphocyte extravasation, amplification and chronicity of the inflammatory response, and skin thickening.[16,59,60]

T_H1 and T_H17 cytokines: IL-12 and IL-23

Although the role of IL-12 and IL-23 cytokines in psoriasis is more firmly established,[62] these cytokines may also play a role in AD.[63-65] IL-12 drives the development of T_H1 responses, and IL-23 is important for the development of T_H17 responses (Fig 1).[66] Both cytokines signal via JAK2, TYK2, STAT3 (IL-23), and STAT4 (IL-23 and IL-12).[13,16,67] Patients with AD show elevated serum IL-12 levels, which are directly correlated with disease severity.[63,64] Some AD subtypes, such as AD in patients from Asia and AD in children, show greater IL-23 and/or IL-17 levels than do other subtypes, such as AD in European or US patients or AD in adults, respectively.[7,68,69] However, there are conflicting reports on the benefit of targeting IL-12/IL-23 in AD,[70,71] and more studies are needed to clarify the role of IL-23/IL-17 across the different AD phenotypes based on ethnicity and age.

Keratinocyte-derived alarmins: TSLP, IL-25, and IL-33 cytokines

Alarmins, such as TSLP, IL-25, and IL-33, are released in response to tissue damage and subsequently induce inflammation.[1] Levels of TSLP, IL-25, and IL-33 are also elevated in infants with early-onset AD.[72] TSLP is expressed by keratinocytes, and when upregulated, they can lead to the development of chronic skin inflammation.[73] TSLP receptors are found on various cell types, including dendritic cells, basophils, T cells, and mast cells (Fig 1).[73] After binding to its receptor, TSLP signals via JAK1 and JAK2 to activate STAT5.[73,74] TSLP-activated dendritic cells play a role in T_H2 cell priming, which is characterized by release of high levels of IL-4, IL-5, and IL-13.[73] TSLP also has a critical effect on type 2 inflammation and basophils, which produce IL-4.[73]

Keratinocytes also produce IL-25, the levels of which are elevated in skin affected by AD.[35] IL-25 has been shown to reduce FLG synthesis in keratinocyte cultures, which could directly result in skin barrier disruption.[35] IL-25 has been shown to signal via JAK2 and STAT5 and may thus play a role in AD in a JAK-STAT–dependent way (Fig 1).[75] Similar to IL-25, IL-33 is produced by keratinocytes, signals via JAK2, and has been shown to be elevated in skin affected by AD.[15,37,76] IL-33 stimulates ILC2s to produce T_H2 cytokines, especially IL-5 and IL-13, and it also induces IL-31 production, promoting pruritus.[15,37,76]

IL-10 family of cytokines: IL-19

IL-19 is a proinflammatory cytokine that belongs to the IL-10 family of cytokines and has been reported to be induced by IL-4 and IL-17A.[77,78] It signals via JAK1 and TYK2 to activate STAT 3 and STAT 5.[79] IL-19 levels are elevated in the sera and lesional skin of patients with AD and have been shown to be positively correlated with disease severity and disease-associated markers such as IL-4, thymus- and activation-regulated chemokine, and absolute eosinophil count.[78,80] In addition, IL-19 stimulates the production of T_H2 cells and may also play a role in bridging T_H17 to T_H2 in AD.[77]

Taken together, the data indicate that the multiple inflammatory cytokines that signal via the JAK-STAT pathway, and especially JAK1, are involved in the pathology of AD (Fig 1). Inhibiting JAK1 represents a logical therapeutic strategy by simultaneously disrupting many of the pathogenic cytokine signals in target tissues.

JAK-STAT IN AD IN PRURITUS AND PAIN

In addition to being involved in development of AD lesions, the JAK-STAT pathway plays a critical role in development of the AD symptoms, pruritus and pain. Pruritus is a key symptom of AD, resulting from a complicated cascade that involves skin barrier damage and influx of allergens and pathogens, and on a cellular level, interaction between keratinocytes, immune cells, and nerve fibers, often leading to an itch-scratch cycle that further exacerbates lesions and contributes significantly to the burden of the disease for the patient.[81]

IL-31 has been suggested as the key cytokine involved in the development of pruritus, and severe pruritic skin lesions similar to AD were observed in IL-31–overexpressing transgenic mice.[22,82] Skin dendritic cells are critical cellular sources of IL-31 during wound repair, and they are sufficient to induce itch in mice.[83] IL-31–mediated activation of IL-31RA via JAK1 and JAK2 induces STAT3-mediated β-endorphin production by keratinocytes, which may contribute to the peripheral itching in AD.[22,53,84] IL-31 is believed to induce itching sensation by binding to and stimulating IL-31RA–positive dorsal root ganglia fibers and by promoting the release of pruritic factors from keratinocytes,[22] including TSLP. Inhibition of IL-31 or IL-31RA results in attenuation of scratching behavior in mice with AD-like skin inflammation.[51] Further, IL-31 activity seems to be dependent on IL-31RA and OSMR receptors and blocking either of these 2 receptors decreases IL-31–induced IL-4 and IL-13 release by basophils.[85]

In addition to IL-31, IL-4 and IL-13 can activate human and mouse dorsal root ganglia, which express the IL-4 and IL-13 receptors (IL-4RA and IL-13RA1), and activate neurons of the itch-sensory pathway in a JAK1-dependent manner.[86] Current evidence suggests that IL-4 and IL-13 sensitize sensory neurons to pruritogens, such as IL-31.[86] Furthermore, IL-4 and neuronal JAK1 are mediators of chronic itch in both inflammatory and noninflammatory settings, and JAK inhibition has been shown to improve pruritus symptoms in patients with chronic idiopathic pruritus.[86] This neuronal JAK1-mediated itch may be independent of STAT.[86]

TSLP and IL-22 have also been shown to play a role in itch. Keratinocytes release TSLP, which induces the secretion of periostin via the JAK/STAT pathway and subsequently activates sensory neurons to trigger histamine-independent itch.[87,88] TSLP may also trigger pruritus indirectly by stimulating the release of IL-4 and IL-13, which in turn induce pruritus.[73] Furthermore, TSLP may play a role in maintaining the itch-scratch cycle in AD based on increased TSLP expression after mechanical injury, which in turn drives T_H2 responses in skin.[89]

Overexpression of IL-22 caused chronic pruritic dermatitis in mice with signs resembling those of human AD, such as pruritus, skin barrier impairment, and enhanced antigen sensitization.[56] In mice, IL-22 administration enhances the pain response and decreases the nociceptive threshold.[90] IL-22 also induces production of IL-1β, a proinflammatory cytokine that is associated with

TABLE I. Overview of topical and systemic therapies currently approved or in development for the treatment of AD

Therapy	Target	Type	Approval status for AD
Approved therapies			
Dupilumab	IL-4, IL-13	Biologic (mAb)	US, EU, Canada, UK, Japan
Tralokinumab	IL-13	Biologic (mAb)	US, EU, UK, Canada
Abrocitinib	JAK1	SMA	US, EU, UK, Canada, Japan
Baricitinib	JAK1, JAK2	SMA	EU, Japan
Delgocitinib (topical)	JAK1, JAK2, JAK3, TYK2	SMA	Japan
Ruxolitinib (topical)	JAK1/JAK2	SMA	US
Upadacitinib	JAK1	SMA	US, EU, UK, Canada, Japan
Difamilast (topical)	PDE4	SMA	Japan
Cytokine inhibitors			
Bermekimab	IL-1α	Biologic (mAb)	Phase 2 (NCT03496974, NCT04021862)
CBP-201	IL-4Rα	Biologic (mAb)	Phase 3 (NCT05614817)
Benralizumab	IL-5Rα	Biologic (mAb)	Phase 2 (NCT04605094, NCT03563066)
Ustekinumab	IL-12, IL-23	Biologic (mAb)	Phase 2 (NCT01945086, NCT01806662)
Lebrikizumab	IL-13	Biologic (mAb)	Phase 3 (NCT04250350, NCT04178967, NCT04392154)
Secukinumab	IL-17A	Biologic (mAb)	Phase 2 (NCT03568136, NCT02594098)
Fezakinumab	IL-22	Biologic (mAb)	Phase 2a (NCT01941537)
Risankizumab	IL-23	Biologic (mAb)	Phase 2 (NCT03706040)
Nemolizumab	IL-31	Biologic (mAb)	Phase 3 (NCT03989349)
Astegolimab	IL-33	Biologic (mAb)	Phase 2 (NCT03747575)
Etokimab	IL-33	Biologic (mAb)	Phase 2 (NCT03533751)
MEDI3506	IL-33	Biologic (mAb)	Phase 2 (NCT04212169)
REGN3500	IL-33	Biologic (mAb)	Phase 2 (NCT03738423)
Spesolimab	IL-36R	Biologic (mAb)	Phase 2 (NCT03822832, NCT04086121)
JAK-STAT inhibitors			
SHR0302	JAK1	SMA	Phase 3 (NCT04875169)
Jaktinib	Pan-JAK	SMA	Phase 3 (NCT05526222)
Other systemic inhibitors/therapies			
ZPL-3893787	H_4R	SMA	Phase 2 (NCT02424253)
FB825	mIgE	Biologic (mAb)	Phase 2 (NCT04413942, NCT05059509)
Omalizumab	IgE	Biologic (mAb)	Phase 4 (NCT02300701)
Serlopitant	NK1R	SMA	Phase 2 (NCT02975206)
Tradipitant	NK1R	SMA	Phase 3 (NCT03568331, NCT04140695)
GBR830	OX40	Biologic (mAb)	Phase 2 (NCT02683928, NCT03568162)
KHK4083	OX40	Biologic (mAb)	Phase 3 (NCT05398445, NCT05651711)
KY1005	OX40L	Biologic (mAb)	Phase 2 (NCT03754309, NCT05131477 NCT05492578)
BLU-5937	P2X3	SMA	Phase 2 (NCT04693195)
Apremilast	PDE4	SMA	Phase 2 (NCT01393158, NCT02087943)
BMS-986166	S1PR1	SMA	Phase 2 (NCT05014438)
Etrasimod	S1PR1, S1PR4, S1PR5	SMA	Phase 2 (NCT04162769)
SCD-044	S1PR1	SMA	Phase 2 (NCT04684485)
Topical therapies			
Tapinarof	AhR	SMA	Phase 3 (NCT05142774, NCT05014568, NCT05032859)
ATI-1777	JAK1/JAK3	SMA	Phase 2 (NCT04598269, NCT05432596)
Brepocitinib	JAK1/TYK2	SMA	Phase 2 (NCT03903822)
SHR0302	JAK1	SMA	Phase 3 (NCT04717310)
HY209 (taureoxycholic acid)	GPCR19	SMA	Phase 2 (NCT04530643)
ALX 101	LXR-β	SMA	Phase 2 (NCT03175354, NCT03859986)
Jaktinib	Pan-JAK	SMA	Phase 2 (NCT04539639)
DRM02	PDE4	SMA	Phase 2 (NCT01993420)
Hemay-808	PDE4	SMA	Phase 2 (NCT04352595)
LEO 29102	PDE4	SMA	Phase 2 (NCT01037881)
Lotamilast	PDE4	SMA	Phase 2 (NCT03394677, NCT02950922)
PF-07038124	PDE4	SMA	Phase 2 (NCT04664153, NCT05375955)
Roflumilast	PDE4	SMA	Phase 3 (NCT04773587, NCT04773600, NCT04804605, NCT04845620)
FB-401	TLR5, TNFR	Bacterial strain	Phase 2 (NCT04936113, NCT04504279)

(Continued)

TABLE I. *(Continued)*

Therapy	Target	Type	Approval status for AD
ATx201 (niclosamide)	Skin microbiome	Small molecule antibacterial	Phase 2 (NCT03304470, NCT04339985)
B244	Skin microbiome	Bacterial strain	Phase 2 (NCT04490109, NCT03235024)
Omiganan	Gram-positive/gram-negative bacteria and fungi	Cationic peptide antimicrobial	Phase 2 (NCT03091426, NCT02456480)

AhR, Aryl-hydrocarbon receptor; *EU*, European Union; *GPCR*, G protein–coupled receptor; *H_4R*, type 4 histamine receptor; *LXR*, liver X receptor; *mIgE*, membrane form of IgE; *NK1R*, neurokinin 1 receptor; *P2X*; purinoreceptor; *PDE*, phosphodiesterase; *S1PR*, sphingosine 1–phosphate receptor; *SMA*, small molecule antagonist; *TLR*, Toll-like receptor; *TNFR*, TNF receptor; *UK*, United Kingdom; *US*, United States.

neuropathic pain in rheumatoid arthritis (RA).[90] IL-22 signals via JAK1, TYK2, STAT1, STAT3, and STAT5[55] and induces epidermal hyperplasia, production of S100A7 (psoriasin), and differentiation abnormalities.[91]

Of note, histamine-induced itch, although present in AD, is not the primary mechanism underlying AD-related pruritus, as demonstrated by lack of effect of antihistamines for chronic pruritus.[92,93] Histamine-independent itch, triggered by pruritogens such as IL-31, IL-4, IL-13, and TSLP, seems to play a more important role in chronic AD itch, as discussed earlier in this review.[92]

Skin pain can be associated with itch-scratch but may also be an independent symptom of AD.[94] Although the role of the JAK-STAT pathway in pain is less well understood, multiple cytokines that signal via the JAK-STAT pathway, such as IL-6, IL-22, and IFN-γ, have also been implicated in pain modulation.[95,96]

IL-6 is a proinflammatory cytokine that activates JAK1 and JAK2 phosphorylation of STAT1 and STAT3 and plays a role in regulating joint pain in rheumatoid arthritis.[95,96] Neurons of the spinal cord and dorsal root ganglia are susceptible to IL-6 signaling, and IL-6 alone or in complex with soluble IL-6 receptor has been shown to trigger pain.[97]

IFN-γ is a T_H1 cytokine secreted during the chronic stages of AD and signals via JAK1, JAK2, STAT1, and STAT3.[59-61] IFN-γ levels are increased in patients with chronic pain conditions, and it is implicated in neuropathic pain.[98-100] Spinal administration of IFN-γ induced tactile allodynia in a dose-dependent manner in wild-type rats but not in IFN-γ receptor knockout rats.[101]

Taken together, the data indicating that many cytokines implicated in pruritus and pain transduce their signals via the JAK-STAT pathway suggest that this pathway may play a key role in these burdensome symptoms in AD.

TARGETED THERAPIES IN AD

As already discussed, AD is a complex, heterogeneous disease involving numerous immune pathways that may differ depending on geographic region, age at onset, disease severity, and other factors and can evolve and change over time in the same individual.[5,9,68] Thus, a treatment strategy targeting a single inflammatory pathway may work for one patient but not for another, or it may work at one stage of a patient's disease course but not at another. Tralokinumab and dupilumab are the only biologic therapies currently approved for AD. Dupilumab inhibits IL-4 and IL-13 by targeting IL-4Ra, which signals through the JAK-STAT pathway.[44] Although dupilumab has been shown to be effective in AD, it inhibits a single inflammatory pathway involved in AD pathology, and some patients do not respond to treatment or respond only partially.[45] Several other therapies targeting specific cytokines or molecules involved in the AD cascade, such as IL-13, IL-22, IL-33, IL-31, IL-36, and TSLP inhibitors, are currently in development (Table I). Although these therapies have the potential to ameliorate the disease to some degree, targeting a single pathology axis may limit efficacy in a disease as highly complex and heterogeneous as AD. For example, although the IL-22 inhibitor fezakinumab significantly improved clinical outcomes (eg, SCOring Atopic Dermatitis score, Investigator Global Assessment finding, and body surface area involvement) compared with placebo in a specific subset of patients with AD (ie, those with severe AD or high baseline levels of IL-22 mRNA skin expression), patients outside that subset received little benefit from treatment.[57,58] These data indicate that although the IL-22 axis plays a role in AD pathology, treatment targeting this axis alone offers only modest benefit in a subset of patients. Similarly, the IL-12/IL-23 inhibitor ustekinumab and IL-33 inhibitor astegolimab failed to reach clinical effects versus placebo in patients with moderate to severe AD.[71,102] These findings highlight the complexity of the disease, the need for more personalized/stratified treatment strategies, and the potential benefits of targeting multiple inflammatory pathways with 1 molecule.[103]

JAK inhibitors, such as upadacitinib, baricitinib, and abrocitinib, all of which are now approved for the treatment of moderate to severe AD in several countries and territories, inhibit the JAK-STAT pathway and can thus simultaneously reduce the signaling of multiple cytokines (including IL-4, IL-13, IL-22, IL-31, TSLP, and IFN-γ)[13] that contribute to the pathology and symptomology of AD.[104] Upadacitinib and abrocitinib are second-generation selective JAK inhibitors with greater selectivity toward JAK1 than the other JAKs, whereas baricitinib is a first-generation selective JAK1 and JAK2 inhibitor.[105] These 3 JAK inhibitors differ in their chemical structure,[105] and they have all demonstrated efficacy in placebo-controlled clinical trials, as well as over the long term, with acceptable safety profiles (Table I).[106-116] No head-to-head trials between upadacitinib, abrocitinib, and baricitinib have been conducted; therefore, comparisons between efficacy and safety outcomes cannot be made.

TYK2 inhibitors have also been investigated for the treatment of immune-mediated dermatologic conditions. Similar to other JAK family members, TYK2 may play a role in signaling of cytokines (such as IL-23, IL-12, and IL-13) that are associated with the pathology of AD (Fig 1). An oral TYK2 inhibitor, deucravacitinib, has been approved for psoriasis and is under investigation for multiple immune-mediated inflammatory diseases, but it has not been investigated in AD to date. The topical TYK2/JAK1 inhibitor brepocitinib also demonstrated efficacy versus vehicle at higher doses in a phase 2 study in patients with moderate to severe AD[117]; however, the future development

status of brepocitinib for AD remains unknown (Table I). The efficacy of TYK2 inhibitors for the management of AD remains speculative.

Overall, JAK inhibitors, specifically JAK1 inhibitors, are highly efficacious treatments for moderate to severe AD, likely owing to multiple polar cytokine targeting, which may be required to optimize outcomes for patients with a disorder as complex and heterogeneous as AD. A recent review with expert commentary on different AD therapies discusses rationale for therapy choices in more detail.[103] Furthermore, IL-13, TSLP, IL-17, and IL-22 have been implicated in the "atopic march,"[118,119] suggesting that the JAK-STAT pathway may also be involved in progression of atopic diseases from AD to allergic rhinitis and asthma.[120] The role of JAK inhibitors in prevention of the atopic march remains to be investigated.

CONCLUSIONS

Unlike the primarily T_H17/IL-23–centered inflammation in psoriasis, AD involves multiple inflammatory pathways (T_H2, T_H22, T_H1, and T_H17 cells), with varying contributions driving the heterogeneity of AD across multiple disease subtypes and over time. The JAK-STAT pathway plays a central role in the pathology and symptomology of AD. Indeed, many key cytokines involved in the pathology of AD signal via the JAK-STAT pathway, with JAK1 involved in IL-4, IL-13, IL-22, IL-31, TSLP, and IFN-γ signaling. Therefore, targeting the JAK-STAT pathway offers a new therapeutic modality for the treatment of AD.

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