Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 10, (2021)
https://www.jneonatalsurg.com

OPEN ACCESS

Atopic Dermatitis Endotypes: Molecular Pathways and Precision Treatment Strategies

Zeiad Abdulaziz Alobead*[1], Asem AlMesfer[1], Ahmad Assiri[2]

[1]Department of Dermatology, King Fahad Medical City, Riyadh, Saudi Arabia

[2]Department of Dermatology, Jazan University Hospital, Jazan, Saudi Arabia

***Corresponding author:**

Zeiad Abdulaziz Alobead,

Email ID : sts_611@hotmail.com

Cite this paper as: Zeiad Abdulaziz Alobead, Asem AlMesfer, Ahmad Assiri, (2021) Atopic Dermatitis Endotypes: Molecular Pathways and Precision Treatment Strategies. *Journal of Neonatal Surgery*, 10, 44-56.

ABSTRACT

Background: Atopic dermatitis (AD) is a complex, heterogeneous inflammatory skin disease. Traditional phenotype-based management often fails to control moderate-to-severe disease, highlighting the limitations of a "one-size-fits-all" approach. A paradigm shift toward a mechanistically-driven understanding, centered on the concept of disease endotypes, is crucial for advancing care.

Objective: This review synthesizes the current evidence on major AD endotypes, their defining molecular pathways, and the precision treatment strategies they inform.

Methods: The databases were searched for articles published in English in 3 data bases [PubMed – Google scholar- science direct] and a comprehensive analysis of the literature was conducted, focusing on studies that utilized high-throughput 'omics' technologies, genetic associations, and clinical trial data to deconstruct AD pathophysiology. The review delineates endotypes based on distinct molecular signatures and links these drivers to emerging targeted therapies.

Conclusion: The stratification of AD into molecular endotypes is foundational to precision dermatology. Moving beyond clinical phenotypes to define the underlying pathological drivers enables the selection of optimal targeted therapies, such as biologics and small molecules, leading to improved efficacy and personalized patient management. Future research must focus on validating practical biomarkers for routine endotype identification in clinical practice.

Keywords: *Atopic Dermatitis, Endotype, Precision Medicine, Biomarker, T2-High, Barrier-Defective, Th17, Th22, IL-4, IL-13, JAK-STAT, Dupilumab, JAK Inhibitors*

1. INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing, and intensely pruritic inflammatory skin disease that represents a significant and growing global health concern. With a lifetime prevalence of up to 20% in children and 10% in adults in developed nations, AD imposes a profound burden on patients, families, and healthcare systems.[1] The disease is characterized by a complex pathophysiology involving epidermal barrier dysfunction, immune dysregulation, and environmental triggers, which together manifest in the classic clinical signs of eczematous lesions, xerosis, and lichenification. For decades, the management of AD has been largely reactive and generalized, relying on a staircase approach of emollients, topical corticosteroids and calcineurin inhibitors, phototherapy, and systemic immunosuppressants such as cyclosporine. While effective for many, this broad-spectrum, phenotype-directed approach fails a substantial proportion of patients with moderate-to-severe disease, in whom treatment may yield suboptimal efficacy or be limited by significant side effects.[2]

The clinical heterogeneity of AD has long been recognized, with variations in age of onset, lesion morphology, and disease course. Historically, these observable characteristics—the *phenotypes*—were the primary basis for clinical description. However, it has become increasingly clear that distinct molecular mechanisms can underlie similar clinical presentations. This realization has catalyzed a paradigm shift from a phenotypically-driven to a mechanistically-driven understanding of the disease. The concept of the *endotype* has thus emerged as a critical framework for modern dermatology. An endotype is defined as a subtype of a condition defined by a distinct functional or pathobiological mechanism.[3]

The traditional view of AD pathogenesis has been conceptualized through the "outside-inside" and "inside-outside" paradigms, highlighting the interplay between a defective epidermal barrier and aberrant immune responses. Seminal discoveries, such as the high prevalence of loss-of-function mutations in the filaggrin gene (*FLG*), a key protein in epidermal differentiation and hydration, provided the first robust genetic evidence for the barrier-defect hypothesis.[4] Concurrently,

AD has been predominantly classified as a T-helper 2 (Th2) cell-mediated disease, with cytokines such as interleukin (IL)-4, IL-13, and IL-31 playing central roles in driving inflammation, IgE production, and the debilitating symptom of pruritus.[5] The cytokine-receptor interactions in this pathway largely signal through the Janus kinase–signal transducer and activator of transcription (JAK-STAT) pathway, presenting a nodal point for therapeutic intervention.[6]

"T2-high" endotype is the most prevalent and well-characterized. It is defined by a robust signature of Th2 cytokines, including IL-4, IL-13, and IL-31. IL-4 and IL-13 are pivotal in promoting B-cell class switching to IgE, downregulating filaggrin expression, and driving skin inflammation.[5] IL-31 is directly implicated in the neuroimmune axis of pruritus, a core symptom of AD.[6] This endotype is often associated with elevated serum IgE levels and high eosinophil counts. The molecular pathways involved, particularly the JAK-STAT signaling cascade, are highly targetable, as demonstrated by the efficacy of biologic agents that block IL-4/IL-13 receptor signaling and small-molecule JAK inhibitors.[6]

The "barrier-defective" endotype is primarily driven by intrinsic impairments in the skin barrier, often of genetic origin. The most established genetic risk factor for AD is the presence of *FLG* loss-of-function mutations, which lead to a compromised stratum corneum, increased transepidermal water loss, and enhanced penetration of allergens and microbes.[4] This defective barrier facilitates the release of alarmins, such as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, which in turn initiate and potentiate Th2-polarized immune responses, creating a vicious cycle of inflammation. Patients with this endotype may present with early-onset, more persistent disease and a high risk of associated atopic march conditions like asthma. [7]

Emerging evidence points to other distinct endotypes, including a "T22" and a "T17" polarity. These are often identified in specific demographic subgroups or unique clinical phenotypes, such as the Asian population or patients with psoriasiform AD lesions. This endotype is characterized by elevated levels of IL-22 and IL-23, leading to epidermal hyperplasia and a different pattern of inflammation, and in some cases, a combined Th17/Th22 signature.[8]

The delineation of these endotypes is not merely an academic exercise; it has direct and profound implications for therapeutic development and clinical practice. The advent of targeted biologic therapies and Janus kinase (JAK) inhibitors has provided the first tools for testing the precision medicine hypothesis in AD. The success of dupilumab, a monoclonal antibody blocking the shared receptor for IL-4 and IL-13, has validated the T2-high endotype as a clinically relevant entity. Similarly, the development of agents targeting TSLP, IL-31, and JAK enzymes represents a concerted effort to match specific drugs to specific pathogenic pathways. This review article aims to synthesize the current understanding of atopic dermatitis endotypes, with a focused exploration of their defining molecular pathways and the emerging precision treatment strategies they inform. [9]

Patient Subgroups Through Distinct Molecular Signatures

The traditional classification of atopic dermatitis (AD) has relied almost exclusively on clinical phenotypes—observable characteristics such as age of onset (infantile, childhood, adult), lesion morphology (acute, subacute, chronic lichenified), and disease severity (mild, moderate, severe). While this phenotypic description is useful for diagnosis and general prognostication, it has proven inadequate for predicting disease course, comorbidity risk, and, most critically, response to therapy. The fundamental limitation of a phenotype-centric view is that it groups together patients who may share superficial clinical features but harbor profoundly different underlying biological mechanisms. This "one-size-fits-all" approach to diagnosis inevitably leads to a "one-size-fits-all" approach to treatment, leaving a significant portion of patients with uncontrolled disease despite broad-spectrum immunosuppressive therapies.[8]

The rationale for moving beyond phenotype to endotype is therefore rooted in the principle of precision medicine: to deliver the right treatment to the right patient at the right time. An endotype is defined as a subtype of a condition defined by a distinct functional or pathobiological mechanism.[9] This mechanistic definition implies that endotypes are driven by specific molecular pathways, can be identified by reliable biomarkers, and, ideally, predict response to a therapy that targets that specific pathway. The primary goal of endotyping in AD is to deconstruct the heterogeneous clinical entity we call "eczema" into discrete, molecularly defined subgroups. This stratification allows for a more profound understanding of disease etiology and a more rational, effective, and potentially preventative therapeutic strategy.[2]

The transition from a phenotypic to an endotypic framework is predicated on the discovery and validation of distinct molecular signatures through high-throughput "omics" technologies. Transcriptomic analysis of lesional and non-lesional AD skin, in particular, has been instrumental in revealing this hidden biological diversity. Seminal studies using genomic-wide association studies (GWAS) and RNA sequencing have consistently demonstrated that while a Th2-signature is a common feature in many AD patients, its magnitude and the presence of accompanying immune polarizations vary significantly.[10] These tools allow for the objective quantification of disease-associated pathways, moving the field from hypothesis-driven to data-driven subgrouping.

Major Molecularly Defined Endotypes in Atopic Dermatitis

Based on converging evidence from genetic, molecular, and cellular studies, several key AD endotypes have been delineated. It is important to note that these endotypes are not always mutually exclusive and may coexist or vary over time within a single individual, adding a layer of dynamic complexity.

1. The T2-High Endotype:

This is the most prevalent and well-characterized endotype, representing the classic AD pathophysiology. Its molecular signature is dominated by cytokines interleukin (IL)-4, IL-13, and IL-31.

Molecular Signature: High expression of genes such as *CCL17* (TARC), *CCL18* (PARC), *CCL26*(eotaxin-3), and *POSTN* (periostin) in skin and serum. This signature reflects the activation of Th2 lymphocytes and type 2 innate lymphoid cells (ILC2s). The alarmins TSLP, IL-25, and IL-33 are often upstream initiators of this cascade.[11]

Pathophysiological Consequences: IL-4 and IL-13 directly inhibit the expression of key epidermal differentiation proteins, including filaggrin, thereby impairing the skin barrier. They also promote B-cell class switching to IgE and recruit eosinophils. IL-31 is a primary mediator of pruritus, driving the itch-scratch cycle that exacerbates skin damage.[12]

Identifying Biomarkers: Elevated serum IgE, peripheral blood eosinophilia, and high levels of serum TARC (CCL17) or periostin are correlative biomarkers for this endotype. The strength of the Th2 signature on skin transcriptomics is the most direct measure.

2. THE BARRIER-DEFECTIVE ENDOTYPE:

This endotype is primarily driven by intrinsic, often genetic, defects in epidermal structure and function, which precede and potentiate immune activation.

Molecular Signature: The most definitive genetic marker is the presence of loss-of-function mutations in the filaggrin gene (*FLG*), present in up to 50% of patients with moderate-to-severe AD in European and Asian populations.[13] Beyond *FLG*, mutations or downregulation of other epidermal complex genes (e.g., *LOR*, *CLDN1*, *SPINK5*) contribute to a shared molecular signature of impaired cornification and tight junction function.

Pathophysiological Consequences: A compromised stratum corneum allows for increased transepidermal water loss (xerosis) and enhanced penetration of allergens, microbes, and irritants. This breach of the barrier triggers the release of epidermal alarmins (e.g., TSLP), which then activate dendritic cells to polarize naïve T cells toward a Th2 phenotype, creating a self-perpetuating "outside-inside" loop of inflammation.[14]

Identifying Biomarkers: *FLG* mutation status is a direct, albeit static, biomarker. Other biomarkers include elevated transepidermal water loss (TEWL), even in non-lesional skin, and a reduced natural moisturizing factor (NMF) level measured by Raman spectroscopy.

3. The Non-T2 Endotypes (T22/T17): Emerging data, particularly from Asian cohorts, has identified AD patients with immune polarizations that deviate from the classic Th2-high model. These are often associated with unique clinical phenotypes.

Molecular Signature:

T22 Polarity: Characterized by high levels of IL-22 and IL-23, with increased expression of genes like *S100A's* and *DEFB4*.

T17 Polarity: Displays elevated IL-17A and IL-17C, with a transcriptomic profile overlapping with psoriasis, including upregulation of *PI3*, *ELOVL4*, and *IL-36G*.[15]

Pathophysiological Consequences: IL-22 induces epidermal hyperplasia and acanthosis, leading to a more psoriasiform morphology. IL-17 promotes neutrophil recruitment and further amplifies inflammation through a different axis than Th2. This endotype may explain the clinical observation of a "psoriasiform eczema" phenotype and the co-occurrence of AD and psoriasis in some patients [11].

Identifying Biomarkers: A low or negative serum IgE, a history of later-onset disease, and specific morphological cues (e.g., more scaly, less exudative plaques) can be clinical hints. Confirmation requires skin transcriptomic profiling to quantify the relative contributions of Th22- and Th17-associated genes.

Synthesizing Endotypes for Clinical Application

The true power of endotyping lies in synthesizing these molecular signatures into a coherent framework for patient stratification. A single patient might be best described by a combination of endotypes—for example, a "T2-high/Barrier-defective" patient with early-onset, severe, IgE-associated disease and confirmed *FLG* mutations, versus a "T22-dominant" patient with adult-onset, psoriasiform lesions and normal IgE levels [9]. This refined classification system moves the field toward a multidimensional definition of AD, as illustrated in Table 1.

Table 1: Proposed Major Endotypes of Atopic Dermatitis and Their Defining Features

Endotype	Key Molecular Drivers	Genetic Associations	Characteristic Biomarkers	Typical Clinical Correlates

T2-High	IL-4, IL-13, IL-31, TSLP	Polygenic; not *FLG*-specific	↑ Serum IgE, ↑ Eosinophils, ↑ TARC (CCL17)	Early-onset, classic flexural eczema, high IgE
Barrier-Defective	Filaggrin deficiency, ↓ epidermal differentiation proteins	*FLG* LOF mutations, other EDC genes	↑ TEWL, ↓ NMF, *FLG* mutation status	Early-onset, persistent disease, ichthyosis vulgaris, keratosis pilaris
Non-T2 (T22/T17)	IL-22, IL-23, IL-17A/C	Largely undefined; may overlap with psoriasis loci	↓/Normal IgE, ↑ IL-22/IL-17 in skin, psoriasiform transcriptome	Adult-onset, psoriasiform morphology, ethnic associations (e.g., Asian)

LOF: Loss-of-Function; EDC: Epidermal Differentiation Complex; TEWL: Transepidermal Water Loss; NMF: Natural Moisturizing Factor.

Pathophysiological Heterogeneity

The clinical presentation of atopic dermatitis (AD)—from the oozing vesicles of an infant's cheeks to the lichenified plaques on an adult's flexures—represents the final common pathway of a complex and heterogeneous interplay of pathological mechanisms. For decades, the pathophysiology of AD was oversimplified into linear models, most notably the "outside-inside" (primary barrier defect initiating inflammation) and "inside-outside" (primary immune dysregulation disrupting the barrier) hypotheses. While instructive, these dualisms fail to capture the spectrum of biological pathways that can be differentially activated across patient subgroups.[15] The concept of pathophysiological heterogeneity moves beyond this binary view, positing that the diverse clinical phenotypes of AD are the direct consequence of variations in the dominant underlying molecular drivers. Understanding this heterogeneity is paramount, as it explains why a therapy targeting a single pathway, such as the Th2 axis, may be transformative for one patient yet offer limited benefit to another.

The Epidermal Barrier: A Foundation of Heterogeneity

The stratum corneum is the first line of defense, and its integrity is a major source of pathophysiological variation in AD. The barrier is not a monolithic structure but a complex matrix of corneocytes, lipid lamellae, and tight junctions.

Filaggrin-Centric Barrier Failure: In a significant subset of patients, the barrier defect is fundamentally genetic. Loss-of-function mutations in the filaggrin gene (*FLG*) represent the strongest known genetic risk factor for AD.[13] Filaggrin is proteolytically broken down into natural moisturizing factors (NMFs), such as urocanic acid and pyrrolidone carboxylic acid, which are critical for skin hydration and acidity (pH). A deficiency in NMF leads to a dry, alkaline skin surface that is permissive for the activation of protease activity, including kallikrein-related peptidases (KLKs). These elevated proteases not only further impair barrier function by prematurely degrading corneodesmosomes but also initiate inflammation by activating protease-activated receptor-2 (PAR-2), which in turn stimulates the release of the alarmin thymic stromal lymphopoietin (TSLP).[16] This pathway defines a clear endotype where an intrinsic structural defect is the primary instigator of inflammation.

Non-Filaggrin Barrier Defects: Not all barrier dysfunction in AD is driven by *FLG* mutations. Many patients with a severe barrier defect, as measured by high transepidermal water loss (TEWL), have normal *FLG* alleles. This points to alternative mechanisms, including:

Lipid Abnormalities: A reduction in ceramides, particularly long-chain ceramides, and an alteration in the cholesterol:free fatty acid:ceramide ratio compromise the lamellar lipid bilayers that form the mortar of the stratum corneum.[17] This lipid defect can be driven by inflammatory cytokines (e.g., IL-4/IL-13 downregulate enzymes involved in ceramide synthesis) or by polymorphisms in genes encoding lipid-metabolizing enzymes.

Tight Junction Dysfunction: Tight junctions, located in the stratum granulosum, form a second functional barrier. Impairment of tight junction proteins like claudin-1, due to genetic variation or cytokine-mediated downregulation, allows for increased antigen penetration and contributes to the "leaky epidermis" seen in AD, independent of filaggrin status.[18]

This heterogeneity in barrier pathogenesis means that a "one-size-fits-all" approach to barrier repair (e.g., with emollients) may be insufficient; strategies tailored to specific defects, such as ceramide-dominant formulations for lipid-deficient patients, may yield better outcomes.

Immune Dysregulation: Beyond the Th2 Paradigm

The immune landscape of AD is a tapestry of intersecting and variably expressed pathways. While type 2 immunity is a central player, its dominance is not universal.

The Expanding Type 2 Cytokine Network: The classic Th2 cytokines IL-4 and IL-13 are master regulators of AD pathology. They directly inhibit the expression of filaggrin and other epidermal differentiation proteins, promote IgE class switching, and recruit eosinophils. However, the type 2 network is broader. IL-31, primarily produced by Th2 cells, is a potent pruritogen that directly activates sensory neurons, forging a critical link between immune activation and the neuroimmune system.[12] IL-5 is crucial for eosinophil maturation and survival, contributing to tissue eosinophilia. The cellular sources of these cytokines are also diverse, involving not only CD4+ Th2 cells but also type 2 innate lymphoid cells (ILC2s), which can be rapidly activated by epithelial-derived alarmins like TSLP, IL-25, and IL-33.[11] The relative contribution of adaptive versus innate type 2 immunity can vary between patients and over time.

The Non-Type 2 Immune Axes: A key advance in understanding pathophysiological heterogeneity has been the identification of immune polarizations that deviate from the Th2-high model.

Th17/Th22 Polarization: A subset of AD patients, particularly those of Asian ethnicity and/or with a more psoriasiform clinical phenotype, exhibit a strong Th17 and Th22 signature. This is characterized by elevated levels of IL-17A, IL-17C, IL-22, and IL-23 in the skin.[15] IL-22 induces keratinocyte proliferation and epidermal acanthosis, while IL-17 promotes neutrophil recruitment. This endotype demonstrates significant molecular overlap with psoriasis and may explain the lack of efficacy of pure Th2-targeted therapies in some individuals.[19]

Th1 Polarization: In chronic AD lesions, there is often a noted increase in interferon-gamma (IFN-γ), a Th1 cytokine. This is thought to represent a secondary immune response to chronic inflammation and repeated skin injury from scratching. The co-existence of Th2 and Th1 signals in chronic plaques adds another layer of complexity to the inflammatory milieu.[20]

The Neuroimmune Interface and the Pruritus Cycle

Pruritus is the hallmark symptom of AD, and its intensity does not always correlate perfectly with the degree of visible inflammation, suggesting independent pathophysiological contributors. The neuroimmune axis is a critical source of heterogeneity in symptom perception and disease chronicity.

Pruritogenic Cytokines: Multiple cytokines can directly or indirectly activate cutaneous sensory nerve fibers. IL-31 is the most directly linked, signaling through the IL-31 receptor A (IL-31RA) and oncostatin M receptor (OSMR) heterodimer on neurons.[12] TSLP can also sensitize sensory neurons to respond to other pruritogens. Furthermore, IL-4 can directly sensitize itch-sensing neurons, and JAK-STAT signaling within neurons appears to be a common pathway for cytokine-induced itch.[21]

Non-Cytokine Mediators: Other factors contribute to the neurogenic inflammation and itch in AD. Substance P, calcitonin gene-related peptide (CGRP), and nerve growth factor (NGF) are released from sensory nerves and can perpetuate inflammation. Mast cell-derived histamine, while less critical in AD than in urticaria, can contribute to itch in some patients. The relative importance of these different pruritogenic pathways likely varies between individuals, influencing their response to anti-itch therapies.

The Microbiome as a Modifier of Pathology

The skin microbiome is not a passive bystander but an active modulator of the cutaneous immune and barrier environment. *Staphylococcus aureus* colonization is prevalent in both lesional and non-lesional AD skin.

*S. aureus Virulence Factors:** S. aureus* exacerbates AD pathophysiology through multiple mechanisms. It secretes superantigens (e.g., SEA, SEB) that polyclonally activate T cells, and delta-toxin that directly induces mast cell degranulation.[22] Furthermore, *S. aureus* proteases can cleave corneodesmosomal proteins and activate PAR-2, directly damaging the barrier and driving inflammation. The degree of microbial dysbiosis and the specific strains of *S. aureus*present can thus introduce significant variation in disease activity and severity between patients.

Table 2: Sources of Pathophysiological Heterogeneity in Atopic Dermatitis

Pathophysiological Domain	Key Sources of Heterogeneity	Molecular/Clinical Consequences
Epidermal Barrier	- Presence/Absence of *FLG* mutations - Ceramide profile abnormalities - Tight junction protein integrity	- Varying degrees of TEWL and xerosis - Differential alarmin (TSLP) production - Altered antigen penetration
Immune Response	- Dominance of Th2 vs. Th22/Th17 cytokines - Relative contribution of ILC2s vs. Th cells - Degree of Th1 infiltration in chronic disease	- Classic flexural eczema vs. psoriasiform morphology - High vs. normal IgE levels - Differential response to Th2-targeted biologics

Neuroimmune System	- Relative expression of IL-31, TSLP, and other pruritogens - Neuronal sensitization via JAK-STAT signaling	- Severity of pruritus independent of lesion severity - Response to neuromodulatory agents (e.g., JAK inhibitors)
Skin Microbiome	- Degree of *S. aureus* colonization and strain virulence - Overall diversity of the microbial community	- Susceptibility to skin infections - Superantigen-driven T-cell activation and inflammation

Decoding the IL-4/IL-13/IL-31 Axis, TSLP, and JAK-STAT Signaling

While the broad categorization of atopic dermatitis (AD) into endotypes provides a crucial taxonomic framework, a deep understanding of disease pathogenesis and therapeutic action requires decoding the specific molecular circuitry that drives inflammation and symptoms. At the heart of the most prevalent AD endotype lies a powerfully interconnected network comprising the cytokines IL-4, IL-13, and IL-31, the alarmin TSLP, and the ubiquitous JAK-STAT intracellular signaling pathway. This network is not a simple linear cascade but a highly integrated, self-amplifying system whose detailed elucidation has directly enabled the development of targeted precision therapies.

The IL-4/IL-13 Dyad: Master Regulators of Immune and Barrier Pathology

The cytokines IL-4 and IL-13 are the cornerstone effectors of type 2 immunity in AD. They share a common receptor subunit, the IL-4 receptor alpha (IL-4Rα), which pairs with different partners to form two primary receptor complexes. The Type I receptor, formed by IL-4Rα and the common gamma chain (γc), binds only IL-4 and is primarily expressed on hematopoietic cells, mediating T-cell differentiation and IgE class switching. The Type II receptor, formed by IL-4Rα and the IL-13 receptor alpha 1 (IL-13Rα1), is more broadly expressed and can be activated by both IL-4 and IL-13.[22] This shared usage of the IL-4Rα subunit is the fundamental reason why dual blockade is so therapeutically effective.

The pathological influence of this dyad is extensive. Signaling through the Type II receptor on keratinocytes activates the JAK-STAT pathway (primarily JAK1/JAK2 and STAT6), leading to the direct transcriptional suppression of key epidermal differentiation genes, including filaggrin (*FLG*), loricrin (*LOR*), and involucrin (*IVL*).[23] This results in a structurally deficient stratum corneum. Concurrently, IL-4 and IL-13 alter the lipid profile of the epidermis by downregulating enzymes involved in the synthesis of long-chain ceramides, thereby disrupting the lamellar lipid bilayers essential for barrier integrity.[17] Beyond the barrier, these cytokines promote IgE production by B cells, enhance vascular cell adhesion molecule-1 (VCAM-1) expression to facilitate eosinophil recruitment, and polarize naïve T cells towards a Th2 phenotype, creating a powerful positive feedback loop.

IL-31: The Neuroimmune Pruritogen

IL-31 is a distinct cytokine primarily produced by Th2 cells that provides the critical link between the immune system and the sensory nervous system, directly mediating the debilitating pruritus of AD. It signals through a heterodimeric receptor composed of the IL-31 receptor A (IL-31RA) and the oncostatin M receptor (OSMR).[24] This receptor is expressed on a subset of cutaneous sensory neurons and, to a lesser extent, on keratinocytes and immune cells.

Upon binding its receptor, IL-31 activates a JAK-STAT signaling cascade (primarily JAK1/JAK2 and STAT3/STAT5) within sensory neurons, leading to immediate depolarization and the sensation of itch.[25] This direct neurostimulatory effect explains why the severity of pruritus in AD does not always correlate perfectly with the visual extent of inflammation. The subsequent scratching behavior causes mechanical damage to the epidermis, further breaching the barrier and releasing more alarmins and cytokines, including IL-31 itself, thus perpetuating the infamous "itch-scratch cycle." The critical role of IL-31 makes its receptor and associated JAKs a prime therapeutic target for antipruritic therapy.

TSLP: The Epithelial Alarmin at the Apex

Thymic stromal lymphopoietin (TSLP) is an IL-7-like cytokine produced mainly by keratinocytes in response to barrier damage, proteases (from allergens like house dust mites or endogenous KLKs), and microbial exposure. It acts as a master switch positioned at the interface between the external environment and the immune system.[26] TSLP exerts its effects by binding to a receptor complex composed of the TSLP receptor (TSLPR) and IL-7Rα, which signals through JAK1 and JAK2 to activate STAT5.

TSLP-primed dendritic cells drive the differentiation of naïve T cells into pro-inflammatory Th2 cells that produce IL-4, IL-5, IL-13, and TNF-α. Furthermore, TSLP can directly activate mast cells and ILC2s, and it has been shown to directly sensitize sensory neurons to other pruritogens, lowering the threshold for itch.[27] By initiating and amplifying the type 2 response and contributing to neuroimmune crosstalk, TSLP sits at the apex of the pathological cascade, making it a highly attractive target for upstream intervention.

The JAK-STAT Pathway: The Central Signaling Hub

The Janus kinase–signal transducer and activator of transcription (JAK-STAT) pathway is the indispensable intracellular signaling mechanism that transduces the extracellular signals from all the cytokines discussed above into a transcriptional response within the cell. Each cytokine receptor pair associates with specific JAK kinases (JAK1, JAK2, JAK3, TYK2). Upon cytokine binding, the JAKs phosphorylate each other and then phosphorylate tyrosine residues on the receptor cytoplasmic tails, creating docking sites for STAT proteins. The STATs are then phosphorylated by JAKs, dimerize, and translocate to the nucleus to regulate gene expression.[28]

The specificity within this network is remarkable:

IL-4/IL-13 (Type II receptor): Primarily activates JAK1/JAK2 and STAT6.

IL-31 (IL-31RA/OSMR): Primarily activates JAK1/JAK2 and STAT3/STAT5.

TSLP (TSLPR/IL-7Rα): Primarily activates JAK1/JAK2 and STAT5.

This convergence of multiple pathogenic cytokine signals on the JAK-STAT pathway explains the therapeutic rationale for small-molecule JAK inhibitors. Unlike biologic agents that target a single cytokine or receptor, a JAK inhibitor can simultaneously dampen signaling from IL-4, IL-13, IL-31, TSLP, and other cytokines that utilize this pathway (e.g., IL-22, IFN-γ), offering a broader anti-inflammatory and antipruritic effect.[29]

Therapeutic Integration: From Molecular Decoding to Clinical Application

The decoding of this intricate network has been directly translated into clinical therapeutics, validating the molecular model.

Anti-IL-4Rα (Dupilumab): By blocking the shared IL-4Rα subunit, dupilumab simultaneously inhibits signaling from both IL-4 and IL-13, leading to dramatic improvements in both skin inflammation and barrier function.[30]

Anti-TSLP (Tezepelumab): By targeting the upstream alarmin TSLP, this approach aims to prevent the initial activation of the downstream inflammatory cascade, showing efficacy in clinical trials.[27]

JAK Inhibitors (e.g., Upadacitinib, Abrocitinib): These oral and topical agents provide a "small-molecule blockade" of the intracellular hub itself. By inhibiting JAK1, they effectively mute the signals from IL-4, IL-13, IL-31, and TSLP, resulting in rapid and potent improvement of both signs and symptoms of AD, particularly pruritus.[29]

Interrogating the Type 2 and Non-Type 2 Immune Circuits

The longstanding characterization of atopic dermatitis (AD) as a purely T-helper 2 (Th2) cell-mediated disease has been fundamentally challenged by molecular profiling, revealing a complex immunological landscape where non-Type 2 circuits significantly contribute to disease heterogeneity and therapeutic response. While the Type 2 axis, driven by IL-4, IL-13, and IL-31, is undeniably central to a majority of patients, a significant subset exhibits immune polarizations that diverge from this classic pathway. Interrogating these distinct but sometimes co-existing immune circuits—specifically the Th22, Th17, and Th1 pathways—is critical for understanding the full spectrum of AD pathogenesis and for developing comprehensive treatment strategies that address all relevant inflammatory drivers.[30]

Refining the Type 2 Circuit

The Type 2 immune response in AD is a coordinated effort involving both adaptive and innate immunity. Beyond CD4+ Th2 cells, group 2 innate lymphoid cells (ILC2s) are now recognized as potent and rapid responders to epithelial-derived alarmins like TSLP, IL-25, and IL-33.[25] Upon activation, ILC2s produce large quantities of IL-5 and IL-13, initiating inflammation even before adaptive immune responses are fully engaged. This circuit is characterized by a well-defined molecular signature, including high expression of CCL17 (TARC), CCL18 (PARC), and CCL26 (eotaxin-3), which serve as biomarkers for this endotype. The clinical success of therapies targeting IL-4/IL-13 signaling has robustly validated this pathway. However, the variable response to these biologics, with some patients achieving only partial improvement, provided the first clinical clue that non-Type 2 circuits were operating in a meaningful subset of individuals.[31]

The Th22 Circuit:

The Th22 pathway represents a distinct immune axis characterized by the production of IL-22, a cytokine that primarily targets keratinocytes. Unlike the Type 2 cytokines that suppress epidermal differentiation, IL-22 induces keratinocyte proliferation and inhibits terminal differentiation, leading to epidermal hyperplasia (acanthosis) and impaired barrier function through a different mechanism.[32] Transcriptomic studies have consistently identified a Th22 signature in AD skin, often co-expressed with the Th2 signature but with variable strength.

This circuit is particularly relevant in specific patient subgroups. For instance, patients with intrinsic AD (characterized by normal IgE levels) often show a stronger Th22 component compared to their extrinsic counterparts. Furthermore, the Th22 signal is markedly elevated in chronic versus acute AD lesions, suggesting a role in disease persistence.[23] Therapeutically, this circuit may explain the limited efficacy of pure Th2-blockade in some patients. While a trial of fezakinumab (an anti-IL-22 monoclonal antibody) did not meet its primary endpoint in an unselected AD population, post-hoc analysis suggested potential benefit in patients with the highest baseline IL-22 levels, highlighting the need for endotype-driven patient

selection.[33]

The Th17 Circuit:

Perhaps the most striking deviation from the classic AD model is the activation of the Th17/IL-23 axis. This circuit is defined by cytokines IL-17A, IL-17C, and IL-23, which are traditionally associated with psoriasis. Their presence in AD underscores the disease's immunological plasticity. IL-17 promotes the recruitment of neutrophils and induces the expression of antimicrobial peptides (e.g., β-defensins) and pro-inflammatory mediators like IL-36γ.[34]

This Th17 signature is not uniformly present across all AD patients but is a defining feature of certain ethnic and phenotypic subgroups. Seminal work by Noda et al. demonstrated that Asian AD patients, particularly those from Japan and Korea, frequently exhibit a robust Th17 signature alongside Th2 and Th22 activation, correlating with a more psoriasiform clinical morphology.[35] This molecular overlap between AD and psoriasis in these patients blurs the traditional diagnostic boundaries and suggests a shared pathophysiological element in a subset of cases. The clinical implication is profound: patients with a strong Th17 component may respond suboptimally to Th2-targeted therapies and might theoretically benefit from agents used in psoriasis, such as anti-IL-23 or anti-IL-17 biologics, though this remains an area of active investigation.

The Th1 Circuit:

The role of the Th1 circuit, driven by interferon-gamma (IFN-γ), has been reinterpreted in the context of molecular taxonomy. Initially thought to be a key driver of chronic AD, it is now understood that while IFN-γ levels are indeed elevated in chronic lesions, this often represents a secondary immune response rather than a primary pathogenic driver.[36] The transition from an acute, Th2-dominated lesion to a chronic, lichenified plaque is associated with an increased infiltration of IFN-γ-producing CD4+ and CD8+ T cells. This Th1 signal likely contributes to the persistent inflammation and further tissue remodeling seen in long-standing disease, but it is rarely the initiating event.

Integrated Immune Circuits and Clinical Implications

The modern view of AD immunology is not of isolated circuits but of an integrated network where the relative balance of Type 2, Th22, and Th17 activation defines the individual's disease signature. A patient can be classified as having a "high Th2/Th22" or "high Th2/Th17" or even a "low Th2/high Th17" endotype. This molecular stratification has direct clinical utility, as summarized in Table 3.

Table 3: Interrogating Immune Circuits in Atopic Dermatitis

Immune Circuit	Key Effector Cytokines	Primary Cellular Sources	Main Pathological Effects	Potential Therapeutic Targets
Type 2	IL-4, IL-13, IL-5, IL-31	Th2 cells, ILC2s	Barrier suppression, IgE synthesis, eosinophilia, pruritus	IL-4Rα, IL-13, IL-31RA, JAK1
Th22	IL-22	Th22 cells	Keratinocyte proliferation, impaired differentiation, acanthosis	IL-22, JAK1/TYK2
Th17	IL-17A, IL-17C, IL-23	Th17 cells, Tc17 cells	Neutrophil recruitment, antimicrobial peptide expression	IL-23, IL-17, JAK2/TYK2
Th1	IFN-γ	Th1 cells, CD8+ T cells (in chronic disease)	Sustained inflammation, lichenification	JAK1/JAK2

The practical application of this knowledge is in guiding treatment. For a patient with a dominant Type 2 signature, an IL-4Rα antagonist is a rational first-line biologic. For a patient with a mixed Th2/Th22 profile, a JAK inhibitor, which can block signaling from both IL-4/IL-13 (via JAK1) and IL-22 (via JAK1/TYK2), may offer a broader mechanism of action.[37]

Linking Pathogenic Drivers to Targeted Biologic and Small Molecule Therapies

The molecular deconstruction of atopic dermatitis (AD) into distinct endotypes, defined by dominant pathogenic drivers, has fundamentally shifted the therapeutic landscape from empiric, broad-spectrum immunosuppression toward a precision-based paradigm. The core principle of this approach is the direct linkage between a defined pathological pathway and a therapeutic agent engineered to specifically interrupt it. The development and clinical success of biologics and small-molecule inhibitors have not only provided new treatment options but have also served as definitive "proof-of-concept" validation for the underlying pathophysiological models, confirming the causal roles of specific cytokines and intracellular signaling pathways in the disease process.[37]

Targeting the Type 2 Axis:

The IL-4/IL-13 pathway, as a central driver in the majority of AD patients, has been the most fruitful target for therapeutic intervention.

IL-4 Receptor α (IL-4Rα) Blockade: Dupilumab, a fully human monoclonal antibody that binds to the IL-4Rα subunit, represents a cornerstone of precision therapy in AD. By blocking the shared receptor for IL-4 and IL-13, it simultaneously inhibits signaling from both cytokines. This dual antagonism translates directly into clinical efficacy: rapid improvement in skin inflammation, pruritus, and barrier function. Molecular studies confirm that dupilumab treatment normalizes the AD transcriptome, reducing the expression of Th2-associated genes (e.g., *CCL17*, *CCL18*), Th22-associated genes (*S100A's*), and epidermal hyperplasia markers, while promoting the expression of barrier proteins like filaggrin.[31, 38] This broad downstream effect underscores the upstream, master-regulator position of the IL-4/IL-13 dyad.

IL-13 Specific Inhibition: Tralokinumab, a fully human monoclonal antibody that specifically neutralizes IL-13, provides a more refined tool for dissecting the contributions of individual cytokines. While IL-13 shares many functions with IL-4, its specific role in promoting IgE production and fibrosis may be particularly relevant in a subset of patients. The efficacy of tralokinumab in phase III trials confirms that IL-13 is a non-redundant, pivotal cytokine in AD pathogenesis.[39] The slightly differentiated clinical profile compared to dupilumab offers clinicians a choice in targeting the Type 2 axis, potentially allowing for therapy matching based on a patient's specific biomarker profile (e.g., high periostin levels, which are more directly linked to IL-13 activity).

Intercepting Pruritus and Innate Immunity: The IL-31 and TSLP Pathways

Beyond the core IL-4/IL-13 axis, targeting upstream and parallel circuits has emerged as a successful strategy.

Anti-IL-31 Therapy: Nemolizumab, a humanized monoclonal antibody against the IL-31 receptor A (IL-31RA), directly addresses the neuroimmune component of AD. By blocking the signaling of the key pruritogen IL-31, nemolizumab has demonstrated a rapid and profound reduction in pruritus, often within days, preceding significant improvements in skin lesions.[40] This dissociation between itch relief and visual inflammation highlights the direct link between the IL-31 pathway and sensory neuron activation, validating it as a primary driver of patient-reported symptoms.

TSLP Inhibition: As an epithelial-derived alarmin that sits at the apex of the inflammatory cascade, TSLP is a logical target for upstream intervention. Tezepelumab, an anti-TSLP monoclonal antibody, demonstrated efficacy in a phase 2b trial for moderate-to-severe AD, significantly improving disease severity scores.[41] By preventing the initial dendritic cell activation and neuronal sensitization triggered by TSLP, this approach aims to dampen the entire downstream Type 2 response, including the production of IL-4, IL-13, and IL-31.

The JAK-STAT Pathway: Intracellular Small Molecule Blockade

While biologics target extracellular cytokines and receptors, small-molecule Janus kinase (JAK) inhibitors act intracellularly to block the signal transduction of multiple cytokines simultaneously. This offers a broader mechanism of action within a targeted framework.

Oral JAK Inhibitors: Agents like upadacitinib (JAK1-selective) and abrocitinib (JAK1-selective) have shown remarkable efficacy in phase III trials, often with a rapid onset of action, particularly for pruritus.[37, 42] Their mechanism is a direct consequence of their molecular target: by inhibiting JAK1, they block signaling from a suite of cytokines implicated in AD, including IL-4, IL-13, IL-31, TSLP, and IL-22. This allows a single agent to address multiple pathogenic circuits—Type 2 immunity, pruritus, and Th22 activation—explaining their potent and comprehensive clinical effect.

Topical JAK Inhibitors: Ruxolitinib cream, a JAK1/JAK2 inhibitor, provides a highly targeted approach for localized AD. Its efficacy demonstrates that even topical blockade of the JAK-STAT pathway is sufficient to resolve inflammation and itch at the site of application, confirming the pathway's critical role in maintaining the local inflammatory milieu.[42]

Targeting the Non-Type 2 Circuits

The linkage of drivers to therapies for non-Type 2 endotypes is still evolving. For patients with a dominant Th17 signature, the logical therapeutic link would be to agents targeting the IL-23/IL-17 axis, such as secukinumab (anti-IL-17A) or risankizumab (anti-IL-23p19). While clinical trials of these agents in AD are limited, their proven efficacy in psoriasis, a Th17-mediated disease, provides a strong rationale for their investigation in the Th17-high AD subpopulation.[43]

Table 4: Linking Pathogenic Drivers to Targeted Therapies in Atopic Dermatitis

Pathogenic Driver / Pathway	Therapeutic Class	Prototype Agent(s)	Mechanism of Action

IL-4/IL-13 Signaling	Biologic (monoclonal antibody)	Dupilumab	Blocks shared IL-4Rα subunit, inhibiting both IL-4 and IL-13 signaling.
IL-13	Biologic (monoclonal antibody)	Tralokinumab, Lebrikizumab	Selectively neutralizes IL-13 cytokine.
IL-31 Signaling	Biologic (monoclonal antibody)	Nemolizumab	Blocks IL-31 receptor, inhibiting neuroimmune pruritus.
TSLP Signaling	Biologic (monoclonal antibody)	Tezepelumab	Neutralizes the epithelial alarmin TSLP.
JAK-STAT Signaling (Multiple Cytokines)	Small Molecule (Oral JAKi)	Upadacitinib, Abrocitinib	Inhibits intracellular JAK1, blocking signaling from IL-4, IL-13, IL-31, TSLP, et al.
JAK-STAT Signaling (Local)	Small Molecule (Topical JAKi)	Ruxolitinib cream	Inhibits JAK1/JAK2 in the skin, resolving local inflammation.
IL-23/Th17 Pathway	Biologic (Investigational in AD)	Secukinumab, Risankizumab	Target IL-17A or IL-23, potentially for Th17-high endotype.

3. SUMMARY AND CONCLUSION

The journey from a phenotypically-described to a mechanistically-defined understanding of atopic dermatitis represents a transformative leap in dermatology. The delineation of AD into distinct endotypes—primarily the T2-high, barrier-defective, and non-T2 (T22/T17) subgroups—provides a critical framework for deconstructing the disease's profound heterogeneity. This review has elucidated how each endotype is driven by a unique constellation of molecular pathways, from the canonical IL-4/IL-13/IL-31 axis and JAK-STAT signaling to intrinsic barrier defects and alternative Th17/Th22 immune polarizations.

The clinical translation of this molecular knowledge is already underway, marking the dawn of precision medicine in AD. The development and success of targeted biologic therapies and small-molecule JAK inhibitors are direct validations of the endotype concept. These agents allow clinicians to move beyond nonspecific immunosuppression and instead match the mechanism of action of a drug to the dominant pathogenic drivers in an individual patient. For instance, a patient with a strong T2-high signature is ideally suited for IL-4Rα or IL-13 blockade, whereas one with debilitating pruritus may benefit most from anti-IL-31 therapy. The broad intracellular blockade offered by JAK inhibitors presents a powerful option for patients with mixed inflammatory signals.

However, the full implementation of this paradigm requires overcoming a significant challenge: the translation of complex molecular signatures into practical, accessible biomarkers for clinical use. The ultimate goal is to have reliable tools—whether serum biomarkers, genetic tests, or non-invasive skin measurements—that can accurately assign an endotype at the point of care.

Conflict of interest: none declared

Fund: non-fundable.

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