Review

Atopic Dermatitis Beyond the Skin Barrier: Precision Medicine Approaches to Immunological Profiling and Therapeutic Innovation

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Atopic Dermatitis Beyond the Skin Barrier: Precision Medicine Approaches to Immunological Profiling and Therapeutic Innovation

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Abstract

Atopic dermatitis (AD) is a chronic, relapsing inflammatory skin disease characterized by substantial clinical and immunological heterogeneity. Traditionally considered a disorder of epidermal barrier dysfunction primarily, AD is now increasingly recognized as a complex systemic inflammatory condition involving dysregulated immune responses, epithelial-derived signaling, neuroimmune interactions, and diverse molecular endotypes. Advances in molecular immunology have significantly expanded current understanding of the cytokine networks underlying disease pathogenesis and have accelerated the transition toward precision medicine approaches in AD. This narrative review summarizes current evidence regarding the immunopathogenesis of AD, with particular emphasis on the interplay between classical and emerging cytokines, biomarker development, and recent therapeutic innovations. Classical type 2 cytokines, including interleukin (IL)-4 and IL-13, remain central drivers of allergic inflammation and epidermal barrier impairment, whereas emerging mediators such as IL-31, IL-33, IL-22, thymic stromal lymphopoietin (TSLP), and OX40/OX40L signaling pathways contribute significantly to chronic inflammation, neuroimmune activation, epidermal remodeling, and pruritus. Comparative analysis of these cytokine pathways highlights the molecular heterogeneity of AD and supports the identification of distinct immunological endotypes. The review additionally discusses current and emerging biomarkers associated with disease severity, therapeutic responsiveness, and inflammatory profiling, including cytokine signatures, serum biomarkers, and transcriptomic approaches. Furthermore, major therapeutic advances involving biologic agents and Janus kinase (JAK) inhibitors are examined within the context of mechanism-based and biomarker-guided therapeutic strategies. Importantly, this review proposes a conceptual precision medicine framework integrating immunopathogenesis, cytokine profiling, molecular endotyping, and targeted therapeutic innovation in AD. Continued advances in biomarker discovery, multi-omics technologies, and individualized therapeutic algorithms may further refine disease stratification and improve personalized management strategies for patients with AD.

Keywords: atopic dermatitis; precision medicine; cytokines; biomarkers; Th2 inflammation; biologics; JAK inhibitors; immunopathogenesis

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1. Introduction

Atopic dermatitis (AD) has evolved from being considered primarily an epidermal barrier disorder to a highly heterogeneous systemic inflammatory disease characterized by complex immune dysregulation, diverse molecular endotypes, and variable therapeutic responses [1,2]. As one of the most common chronic inflammatory skin diseases worldwide, AD affects both pediatric and adult populations and represents a major public health burden due to its chronic relapsing course, intense pruritus, sleep disturbance, psychosocial impact, and reduced quality of life [1,3].

Although epidermal barrier dysfunction remains a central component of AD pathogenesis, growing evidence demonstrates that the disease extends far beyond structural skin abnormalities [1,4]. Contemporary models emphasize dynamic interactions between keratinocyte dysfunction, type 2 immune activation, neuroimmune signaling, environmental triggers, and systemic inflammatory pathways. This paradigm shift has substantially transformed the understanding of AD and has accelerated the emergence of precision medicine approaches aimed at identifying individualized disease mechanisms and therapeutic targets [4,5].

The immunological landscape of AD is predominantly driven by T helper 2 (Th2)-mediated inflammation, with interleukin (IL)-4 and IL-13 playing key roles in epidermal barrier impairment, immunoglobulin E (IgE) production, eosinophilic inflammation, and chronic itch [1,2]. However, recent studies have demonstrated that additional immune pathways, including Th17-, Th22-, and Th1-associated responses, contribute significantly to disease chronicity, lesion heterogeneity, and ethnic or age-related phenotypes [1,4]. Consequently, AD is increasingly recognized as a spectrum of immunological endotypes rather than a single disease entity [3,5].

Within this evolving framework, cytokine profiling has emerged as a promising strategy for improving disease stratification and therapeutic personalization [3,5]. Classical cytokines such as IL-4, IL-13, IL-5, and thymic stromal lymphopoietin (TSLP) remain fundamental to AD immunopathogenesis, but emerging mediators, including IL-31, IL-33, IL-22, IL-25, and OX40/OX40L signaling pathways, have gained increasing attention due to their roles in pruritus, epidermal remodeling, chronic inflammation, and neuroimmune interactions [1,6]. In particular, IL-31 has been closely associated with itch severity, whereas IL-33 acts as an epithelial alarmin that can amplify type 2 inflammatory responses [6]. These findings have stimulated growing interest in identifying cytokine-based biomarkers that can predict disease severity, monitor therapeutic response, and define clinically relevant endotypes [3,5].

The transition toward precision medicine has been further accelerated by major therapeutic advances in moderate-to-severe AD [5,7]. The introduction of biologic agents targeting IL-4/IL-13 signaling pathways, alongside Janus kinase inhibitors (JAKi) that modulate multiple cytokine cascades, has revolutionized treatment strategies and significantly improved clinical outcomes [7,8]. Nevertheless, considerable interindividual variability in treatment response persists, highlighting the need for reliable immunological profiling tools and biomarker-guided therapeutic algorithms [3,5].

In this context, precision medicine in AD seeks to integrate clinical phenotypes with molecular and immunological signatures in order to optimize individualized management strategies [4,5]. Understanding the interplay between established and emerging cytokines may not only clarify disease heterogeneity but also facilitate the development of novel targeted therapies and personalized therapeutic approaches [5–7].

Therefore, this narrative review aims to summarize current advances in the immunopathogenesis of AD, with particular emphasis on cytokine-mediated mechanisms, immunological profiling, biomarker development, and recent therapeutic innovations within the evolving framework of precision medicine.

In addition to providing an updated overview of current evidence, this review seeks to highlight the evolving roles of emerging cytokines relative to established inflammatory mediators and to explore their potential integration into precision medicine algorithms. By comparatively analyzing classical and novel cytokine pathways, the review aims to identify potential immunological biomarkers associated with disease severity, pruritus intensity, therapeutic response, and disease

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heterogeneity [3,5,6]. Furthermore, this work aims to highlight current gaps in translational research and to discuss future perspectives on individualized therapeutic strategies and biomarker-guided management in AD.

2. Immunopathogenesis of Atopic Dermatitis: Beyond the Skin Barrier

The contemporary understanding of AD has undergone a substantial transformation over the past decade. Historically regarded as predominantly a disease caused by epidermal barrier dysfunction, AD is now recognized as a highly heterogeneous and systemic inflammatory disorder characterized by complex interactions among epithelial abnormalities, innate and adaptive immune responses, neuroimmune pathways, environmental exposures, and molecular endotypes [1,2,4]. This evolving paradigm has shifted the focus of research from isolated structural defects to integrated immunological mechanisms that can explain the remarkable variability observed in disease severity, clinical phenotype, chronicity, and therapeutic response.

The concept of AD as a multifactorial inflammatory disease is supported by the observation that patients exhibit considerable heterogeneity in cytokine expression, immune activation patterns, serum biomarker profiles, and responsiveness to targeted therapies [3,5]. Such variability has fueled growing interest in precision medicine approaches that identify individualized molecular signatures and translate them into personalized therapeutic strategies.

2.1. Epidermal Barrier Dysfunction and the Active Role of Keratinocytes

Epidermal barrier impairment remains one of the earliest pathogenic events in AD and represents a critical interface between environmental stimuli and immune activation [1,2]. The healthy epidermis functions as both a physical and an immunological barrier that protects against allergens, microbial antigens, and pollutants, and helps prevent transepidermal water loss. In AD, disruption of this protective function facilitates increased penetration of environmental triggers, thereby initiating and perpetuating chronic cutaneous inflammation.

Several structural abnormalities contribute to epidermal barrier dysfunction in AD, including reduced filaggrin expression, altered ceramide composition, impaired tight junction integrity, and defective keratinocyte differentiation [1,4]. Although filaggrin deficiency has been strongly associated with impaired barrier integrity, contemporary evidence indicates that barrier dysfunction in AD cannot be explained solely through structural protein abnormalities. Instead, inflammatory cytokines themselves actively contribute to epidermal damage by suppressing the expression of proteins essential for epidermal differentiation and barrier maintenance.

Among the major cytokines involved in this process, IL-4 and IL-13 exert profound inhibitory effects on filaggrin, loricrin, and involucrin synthesis, thereby perpetuating epidermal fragility and increasing susceptibility to environmental insults [1,4]. This reciprocal relationship between inflammation and barrier dysfunction establishes a self-amplifying pathogenic cycle in which epidermal disruption promotes immune activation, while inflammatory mediators further aggravate barrier impairment.

Keratinocytes are now recognized as active immunological participants rather than passive structural cells. Following epidermal injury or exposure to allergens and irritants, keratinocytes release epithelial-derived cytokines known as alarmins, including TSLP, IL-25, and IL-33 [4,6]. These mediators initiate and amplify type 2 inflammatory responses by activating dendritic cells, innate lymphoid cells, eosinophils, mast cells, and Th2 lymphocytes.

TSLP has emerged as one of the most important epithelial cytokines in AD pathogenesis. Increased TSLP expression has been demonstrated in lesional AD skin and correlates with disease activity [9]. By activating dendritic cells and promoting Th2 differentiation, TSLP contributes to the early initiation of allergic inflammation and facilitates chronic immune polarization [4,9]. Similarly, IL-33 acts as an epithelial alarm signal released following tissue injury and plays a critical role in amplifying type 2 immune responses by activating type 2 innate lymphoid cells (ILC2s) and mast

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cells [6]. Recent evidence additionally suggests that IL-33 contributes to pruritus signaling and chronic tissue remodeling, further emphasizing its relevance as a potential therapeutic target [6,10].

These findings support the concept that the epidermis in AD functions as an active immunological organ capable of initiating and perpetuating inflammatory cascades. Consequently, epidermal barrier dysfunction should no longer be interpreted exclusively as a structural abnormality but rather as a dynamic immunologically driven process.

2.2. Type 2 Inflammation as the Central Immunological Axis

Type 2 immune activation is the dominant immunological hallmark of AD and is primarily mediated by interactions among Th2 lymphocytes, ILC2s, dendritic cells, eosinophils, mast cells, and keratinocytes [1,2]. Cytokines, including IL-4, IL-13, and IL-5, orchestrate most acute inflammatory responses observed in AD and directly contribute to epidermal barrier disruption, eosinophilic inflammation, IgE synthesis, and chronic pruritus.

IL-4 and IL-13 are considered the principal drivers of AD immunopathogenesis and have become central therapeutic targets in modern biologic therapy [7,8]. These cytokines signal through shared receptor pathways and activate JAK and activator of transcription (JAK-STAT) signaling cascades, leading to amplification of type 2 inflammation and suppression of antimicrobial defense mechanisms [11]. Both IL-4 and IL-13 impair epidermal differentiation by downregulating structural proteins essential for barrier integrity while simultaneously promoting B-cell class switching toward IgE production [1,4].

Although IL-4 and IL-13 exhibit overlapping functions, emerging evidence suggests that they may contribute differently to disease pathogenesis. IL-4 appears particularly important in early immune polarization and initiation of Th2 responses, whereas IL-13 is more strongly associated with chronic tissue inflammation, epidermal remodeling, and sustained disease activity [4,11]. Increased IL-13 expression has consistently been identified in lesional skin and is strongly correlated with disease severity [12].

IL-5 also contributes significantly to eosinophilic inflammation by activating, recruiting, and sustaining eosinophils within cutaneous tissues [1]. Elevated eosinophil counts frequently correlate with severe disease phenotypes and may reflect systemic type 2 inflammatory activation.

In addition to adaptive immunity, innate immune mechanisms play a crucial role in amplifying type 2 inflammation. ILC2s are rapidly activated by epithelial-derived cytokines such as TSLP and IL-33 and represent an important source of IL-5 and IL-13 independent of antigen-specific adaptive immune responses [6,13]. The interaction between epithelial cells and innate lymphoid pathways is therefore increasingly recognized as a critical mechanism in the early stages of AD development.

The importance of type 2 inflammation in AD is further supported by the remarkable efficacy of biologic agents targeting IL-4 and IL-13 pathways. The introduction of dupilumab, tralokinumab, and lebrikizumab has significantly improved disease control in moderate-to-severe AD and has validated the pathogenic relevance of these cytokines in clinical practice [7,8].

2.3. Beyond Th2 Dominance: Additional Inflammatory Pathways and Disease Heterogeneity

Although type 2 inflammation remains the dominant immunological axis in AD, recent studies have demonstrated that the disease involves substantially more complex inflammatory networks than previously recognized [1,4]. Chronic AD lesions often exhibit simultaneous activation of Th1-, Th17-, and Th22-associated pathways, contributing to disease chronicity, epidermal hyperplasia, treatment resistance, and phenotypic diversity.

Th22 cells and their signature cytokine IL-22 have emerged as particularly important contributors to epidermal remodeling and lichenification [6]. IL-22 promotes keratinocyte proliferation while impairing terminal epidermal differentiation, leading to acanthosis and chronic skin thickening [14]. Elevated IL-22 expression has been associated with severe chronic AD and may represent a potential biomarker of disease progression.

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Similarly, Th17-related cytokines appear to contribute to specific AD phenotypes, particularly pediatric and Asian variants characterized by enhanced IL-17 signaling and neutrophilic inflammation [4]. IL-17 may additionally influence antimicrobial peptide expression and contribute to microbial dysregulation within the epidermal microenvironment.

Chronic lesions also exhibit increased expression of interferon-γ (IFN-γ), reflecting progressive Th1 activation during the prolonged evolution of the disease [1]. This transition toward mixed inflammatory profiles may partially explain why some patients exhibit incomplete responses to therapies targeting isolated type 2 pathways.

Importantly, these observations support the concept that AD comprises multiple immunological endotypes rather than a single homogeneous disease entity [3,5]. Distinct cytokine signatures may therefore explain variations in disease severity, age-related presentation, ethnic phenotypes, treatment responsiveness, and progression toward chronic inflammation.

Recent molecular profiling studies have identified significant differences between intrinsic and extrinsic AD phenotypes, pediatric and adult disease, and acute versus chronic lesions [3,15]. Such findings reinforce the need for biomarker-driven patient stratification and provide the foundation for precision medicine approaches in AD.

2.4. Neuroimmune Interactions and the Molecular Basis of Pruritus

Pruritus represents the hallmark symptom of AD and is increasingly recognized as a consequence of highly complex neuroimmune interactions involving cytokines, epidermal inflammation, peripheral sensory neurons, and central nervous system signaling pathways [6]. Chronic itch significantly contributes to sleep disturbance, psychological stress, impaired quality of life, and perpetuation of the itch-scratch cycle.

Among emerging cytokines implicated in AD, IL-31 has attracted particular attention due to its direct association with pruritus intensity [6,10]. Produced predominantly by activated Th2 lymphocytes, IL-31 exerts its effects through interaction with IL-31 receptors expressed on keratinocytes, immune cells, and peripheral sensory neurons.

Activation of IL-31 signaling pathways induces neuronal hypersensitivity and directly stimulates itch transmission, thereby establishing IL-31 as a central neuroimmune mediator in AD [10]. Elevated serum IL-31 levels have been associated with severe pruritus, sleep impairment, and increased disease activity [6]. Furthermore, chronic scratching induced by IL-31-mediated itch contributes to epidermal damage, enhanced alarmin release, and amplification of cutaneous inflammation.

In addition to IL-31, epithelial cytokines such as TSLP and IL-33 also participate in neuroimmune signaling by directly activating sensory neurons and promoting neuronal sensitization [6]. This bidirectional communication between the immune and nervous systems contributes substantially to chronic disease and symptom persistence.

The recognition of neuroimmune pathways as central pathogenic mechanisms has generated significant therapeutic interest in cytokines associated with pruritus signaling. Nemolizumab, an anti-IL-31 receptor monoclonal antibody, has demonstrated promising antipruritic effects in moderate-to-severe AD, highlighting the translational relevance of targeting neuroimmune cytokine pathways [16].

2.5. Immunological Endotypes and Precision Medicine Perspectives

The substantial heterogeneity observed in AD has accelerated the transition from conventional symptom-based treatment strategies toward precision medicine approaches centered on immunological profiling and individualized therapeutic selection [3,5]. Precision medicine in AD seeks to integrate clinical phenotypes, cytokine signatures, serum biomarkers, and molecular pathways to identify disease endotypes that predict prognosis and therapeutic responsiveness.

Recent advances in transcriptomic and immunological profiling have demonstrated that cytokine expression patterns vary significantly according to age, ethnicity, disease chronicity, and

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treatment exposure [5,15]. These findings suggest that individualized cytokine signatures may provide clinically meaningful information regarding disease severity and optimal therapeutic targeting.

Biomarkers, including TARC/CCL17, periostin, eosinophil counts, serum IgE, IL-13, IL-22, and IL-31, are increasingly investigated as potential tools for disease stratification and treatment monitoring [3]. Nevertheless, the lack of standardized biomarker panels currently limits routine clinical implementation.

The emergence of targeted therapies has further reinforced the importance of precision medicine in AD. Biologic agents targeting the IL-4/IL-13 pathways, JAKi that modulate multiple cytokine cascades, and investigational therapies directed against IL-31, IL-33, TSLP, and OX40/OX40L signaling pathways collectively illustrate the rapid therapeutic evolution in the field [7,8,16,17].

Ultimately, integrating immunological profiling into clinical practice may facilitate earlier identification of severe disease phenotypes, optimize therapeutic selection, reduce unnecessary treatment exposure, and improve long-term disease control. Consequently, understanding the complex immunological architecture of AD represents a fundamental prerequisite for the successful implementation of precision medicine strategies.

3. Cytokine Networks and Emerging Immunological Targets

The immunopathogenesis of AD is orchestrated by a highly complex cytokine network that involves interactions among epithelial cells, innate immune pathways, adaptive immune responses, and neuroimmune signaling [1,4,10,14,18]. Cytokines not only mediate inflammatory responses but also directly influence epidermal barrier integrity, pruritus signaling, tissue remodeling, and therapeutic responsiveness. Over the past decade, advances in molecular profiling have revealed that AD is characterized by dynamic, heterogeneous cytokine signatures that vary by disease stage, age, ethnicity, severity, and treatment exposure [3,5].

Historically, AD was considered predominantly a Th2-driven disease mediated by cytokines such as IL-4, IL-13, and IL-5. However, recent evidence demonstrates that additional inflammatory mediators, including IL-31, IL-33, IL-22, IL-25, TSLP, and OX40/OX40L signaling pathways, contribute significantly to disease chronicity, epidermal remodeling, neuroimmune activation, and therapeutic resistance [6,10]. The identification of these emerging cytokines has fundamentally expanded the understanding of AD immunobiology and has created new opportunities for biomarker development and targeted therapeutic intervention.

Importantly, cytokines in AD should not be interpreted as isolated mediators but rather as components of interconnected inflammatory circuits that can amplify and sustain chronic disease activity. Consequently, comparative analysis of classical and emerging cytokine pathways has become increasingly relevant in the context of precision medicine and individualized therapeutic selection.

3.1. Classical Th2 Cytokines: IL-4, IL-13, and IL-5

Type 2 inflammation remains the central immunological hallmark of AD and is largely mediated through IL-4, IL-13, and IL-5 signaling pathways [1,2]. These cytokines are predominantly produced by Th2 lymphocytes, although additional cellular sources include ILC2s, mast cells, eosinophils, and basophils.

IL-4 is considered a primary initiator of Th2 polarization and exerts multiple downstream effects on both immune and structural skin cells [11]. Through activation of the JAK-STAT pathway, IL-4 promotes B-cell class switching toward IgE production, suppresses antimicrobial peptide synthesis, and enhances eosinophilic inflammation [1,4]. Furthermore, IL-4 directly impairs epidermal barrier integrity by downregulating the expression of filaggrin, involucrin, and loricrin, thereby perpetuating epidermal dysfunction.

IL-13 shares substantial functional overlap with IL-4 but appears to play a particularly important role in chronic inflammation and tissue remodeling [12]. Increased IL-13 expression has consistently

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been demonstrated in lesional AD skin and correlates strongly with disease severity [12]. Experimental studies have shown that IL-13 contributes to epidermal hyperplasia, fibrosis, and persistent inflammatory activation, highlighting its central role in chronic disease progression.

The pathogenic significance of IL-4 and IL-13 is further supported by the remarkable efficacy of biologic agents targeting these pathways. Dupilumab, a monoclonal antibody targeting the IL-4 receptor α subunit, inhibits signaling by both IL-4 and IL-13 and has substantially improved clinical outcomes in moderate-to-severe AD [7]. Similarly, tralokinumab and lebrikizumab selectively target IL-13 and have demonstrated significant efficacy in reducing disease severity and pruritus [7,8].

IL-5 also contributes to AD pathogenesis by activating, recruiting, and sustaining eosinophils [1]. Elevated eosinophil counts are frequently observed in severe disease phenotypes and may reflect systemic type 2 inflammatory activity. Although IL-5-targeted therapies have demonstrated more limited efficacy in AD compared with asthma, eosinophilic inflammation remains an important component of the disease process.

Collectively, these findings establish IL-4 and IL-13 as core pathogenic cytokines in AD and validate their importance as both therapeutic targets and biomarkers of type 2 immune activation.

3.2. Epithelial Alarmins and Early Immune Activation

Increasing evidence indicates that epithelial-derived cytokines, commonly referred to as alarmins, play a central role in initiating and amplifying inflammatory responses in AD [4,6]. Among these mediators, TSLP, IL-25, and IL-33 have emerged as key regulators of early immune activation and epithelial-immune communication.

TSLP is produced predominantly by keratinocytes following epidermal injury, allergen exposure, or microbial stimulation [9]. Elevated TSLP expression has been identified in lesional AD skin and appears to correlate with disease activity and Th2 polarization [4]. TSLP activates dendritic cells and promotes differentiation of naïve T cells into Th2 lymphocytes, thereby initiating downstream production of IL-4, IL-5, and IL-13.

Beyond adaptive immunity, TSLP also influences innate inflammatory pathways by activating ILC2s, mast cells, and basophils [13]. Recent studies additionally suggest that TSLP may directly stimulate peripheral sensory neurons, thereby contributing to pruritus signaling and neuroimmune activation [10].

IL-33 functions as an epithelial alarm cytokine released during tissue injury and cellular stress [6]. Once released, IL-33 amplifies type 2 inflammation by activating mast cells, eosinophils, basophils, and ILC2s. Elevated IL-33 expression has been associated with severe AD phenotypes, enhanced eosinophilic inflammation, and increased itch intensity [6]. Importantly, IL-33 may represent a molecular link between epithelial barrier disruption and chronic immune activation. Experimental models have demonstrated that IL-33 promotes epidermal inflammation, fibrosis, and neuronal sensitization, supporting its role in both inflammatory and neuroimmune pathways [10].

IL-25 also contributes to Th2 polarization by activating ILC2s and enhancing type 2 cytokine production [4]. Although less extensively studied than TSLP and IL-33, IL-25 is increasingly recognized as an important mediator of epithelial-driven inflammation in AD.

The pathogenic relevance of epithelial alarmins has generated substantial interest in novel biologic therapies targeting these pathways. Anti-TSLP and anti-IL-33 agents are currently under investigation and may represent future therapeutic options for patients with severe or treatment-resistant disease [7].

3.3. IL-31 and the Neuroimmune Axis

Among emerging cytokines implicated in AD, IL-31 has gained particular attention due to its strong association with chronic pruritus and neuroimmune dysregulation [6,10]. IL-31 is produced predominantly by activated Th2 cells, although mast cells, macrophages, eosinophils, and dendritic cells may also contribute to its production.

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IL-31 exerts its biological effects by interacting with IL-31 receptor A and oncostatin M receptor β, which are expressed on keratinocytes, immune cells, and sensory neurons [6]. Activation of neuronal IL-31 signaling pathways induces intense itch transmission and neuronal hypersensitivity, thereby establishing IL-31 as a key mediator of chronic pruritus in AD. Elevated serum IL-31 concentrations have been consistently associated with increased disease severity, sleep disturbance, and pruritus intensity [6]. Furthermore, IL-31 may directly contribute to epidermal barrier impairment by reducing keratinocyte differentiation and enhancing the production of inflammatory cytokines.

The itch-scratch cycle induced by IL-31 represents a critical pathogenic mechanism in AD. Chronic scratching aggravates epidermal damage, promotes release of epithelial alarmins, and amplifies inflammatory activation, thereby sustaining chronic disease activity [10].

The therapeutic relevance of IL-31 has been highlighted by the development of nemolizumab, a monoclonal antibody targeting IL-31 receptor signaling [16,17]. Clinical trials have demonstrated rapid and significant reductions in pruritus severity following nemolizumab treatment, supporting the concept that neuroimmune pathways represent highly relevant therapeutic targets in AD. Importantly, the emergence of IL-31-targeted therapy has expanded the therapeutic focus beyond classical inflammation toward direct modulation of neuroimmune signaling and symptom control.

3.4. IL-22, Th22 Responses, and Epidermal Remodeling

IL-22 has emerged as a major cytokine involved in epidermal remodeling, lichenification, and chronic tissue inflammation in AD [14]. Primarily produced by Th22 cells, IL-22 promotes keratinocyte proliferation while impairing terminal epidermal differentiation. Increased IL-22 expression has been consistently identified in chronic AD lesions and correlates with epidermal hyperplasia and disease severity [14]. Unlike IL-4 and IL-13, which primarily drive type 2 immune polarization, IL-22 appears particularly involved in structural skin remodeling and chronic tissue changes. Experimental studies have demonstrated that IL-22 suppresses expression of filaggrin and other epidermal differentiation proteins while simultaneously enhancing acanthosis and epidermal thickening [14]. These findings suggest that IL-22 may contribute significantly to chronic lichenified AD phenotypes.

Recent molecular profiling studies have also shown that IL-22 expression varies by ethnicity and disease phenotype, with particularly strong activation observed in Asian AD populations [15,19,20]. Such observations reinforce the concept of immunological heterogeneity and support the need for endotype-specific therapeutic approaches. Although IL-22-targeted therapies remain investigational, increasing evidence supports their potential utility as both a biomarker of chronic inflammation and a future therapeutic target.

3.5. OX40/OX40L Signaling and T-Cell Activation

The OX40/OX40L signaling pathway has recently emerged as another important immunological target in AD [21–23]. OX40 is a co-stimulatory receptor expressed on activated T lymphocytes, whereas OX40 ligand (OX40L) is primarily expressed on antigen-presenting cells, including dendritic cells. Activation of the OX40/OX40L axis promotes T-cell survival, expansion, and sustained production of inflammatory cytokines, thereby contributing to chronic immune activation [21–23]. Elevated OX40/OX40L expression has been identified in AD skin lesions and appears associated with persistent Th2 polarization.

Importantly, inhibition of OX40 signaling may simultaneously suppress multiple downstream inflammatory pathways, including IL-4-, IL-13-, and IL-31-mediated responses. Consequently, OX40-targeted therapies have attracted considerable attention as potential treatments for severe AD. Early clinical trials of anti-OX40 monoclonal antibodies have demonstrated encouraging reductions in inflammatory biomarkers and disease severity, although further studies are needed to establish long-term efficacy and safety profiles [21–23].

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3.6. Cytokine Networks, Biomarkers, and Precision Medicine

The expanding understanding of cytokine interactions in AD has substantially accelerated the development of precision medicine approaches centered on immunological profiling and biomarker-guided therapy [3,5]. Rather than representing isolated inflammatory mediators, cytokines function as components of interconnected molecular networks that define disease endotypes and therapeutic responsiveness.

Recent studies have demonstrated that specific cytokine signatures may correlate with disease severity, treatment response, chronicity, and pruritus intensity [3,5]. Elevated IL-13 expression has been associated with severe chronic inflammation, whereas increased IL-31 levels correlate strongly with itch severity and sleep disturbance [6,12]. Similarly, IL-22 may reflect chronic epidermal remodeling, while TSLP and IL-33 may indicate enhanced epithelial-driven immune activation.

These observations support the potential integration of cytokine profiling into clinical decision-making algorithms to optimize individualized therapeutic selection. Patients with dominant type 2 inflammation may respond particularly well to IL-4/IL-13 blockade, whereas individuals exhibiting strong neuroimmune activation may benefit from IL-31-targeted therapies.

JAKis represent another important component of precision medicine in AD, as they can modulate multiple cytokine pathways simultaneously [7,8,24,25]. Agents such as upadacitinib, abrocitinib, and baricitinib inhibit intracellular signaling downstream of several cytokine receptors, including IL-4, IL-13, IL-31, and interferon pathways.

Despite these advances, several challenges remain regarding the routine implementation of cytokine-based precision medicine in AD. Standardized biomarker panels have not yet been universally established, and substantial overlap exists among inflammatory endotypes [3,5]. Nevertheless, ongoing advances in molecular profiling technologies continue to improve understanding of disease heterogeneity and may ultimately facilitate more personalized therapeutic strategies.

Collectively, the evolving characterization of cytokine networks in AD has transformed the disease from a relatively uniform inflammatory disorder into a highly heterogeneous immunological spectrum requiring individualized diagnostic and therapeutic approaches.

Given the substantial immunological complexity and multidirectional interactions underlying AD, a mechanistic overview integrating epidermal barrier disruption, cytokine networks, neuroimmune signaling, and targeted therapeutic implications is presented in Figure 1.

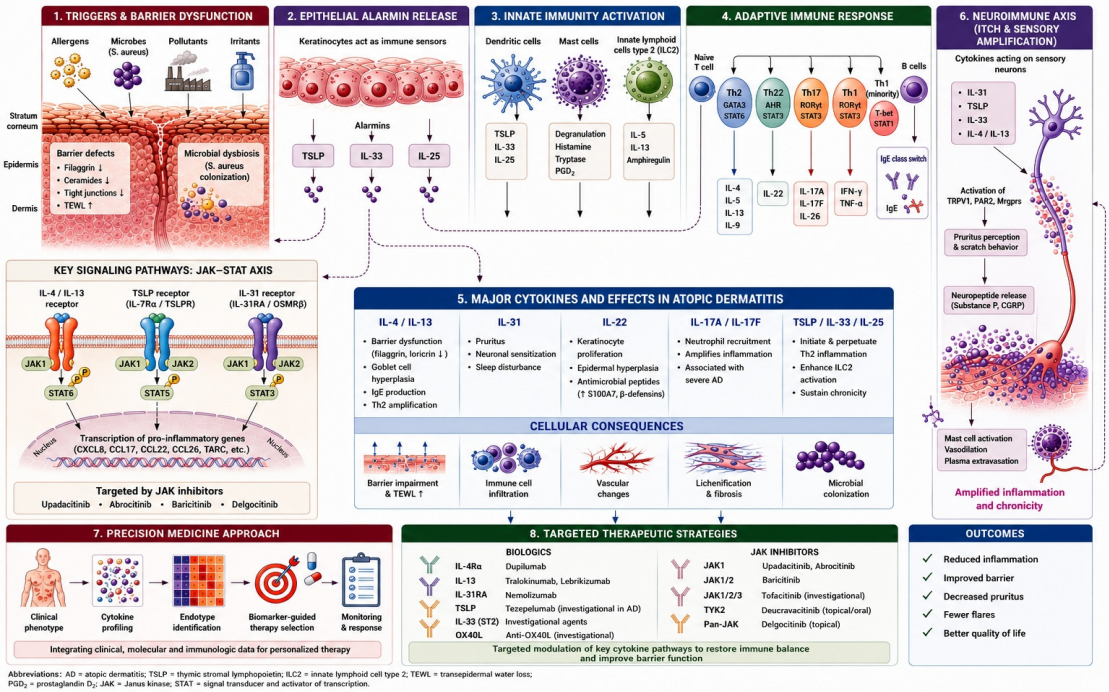

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Figure 1. Mechanistic immunopathogenic pathways and precision medicine targets in atopic dermatitis. Environmental triggers, including allergens, microbial antigens, pollutants, and irritants, initiate epidermal barrier disruption characterized by filaggrin deficiency, altered lipid composition, impaired tight junction integrity, and increased transepidermal water loss (TEWL). Barrier dysfunction facilitates enhanced penetration of external antigens and promotes keratinocyte activation. Activated keratinocytes function as immune sensors and release epithelial-derived alarmins, including thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, and IL-33, which initiate and amplify type 2 immune responses by activating dendritic cells, mast cells, basophils, and type 2 innate lymphoid cells (ILC2s). Adaptive immune activation is predominantly mediated by T helper 2 (Th2) cells producing IL-4, IL-5, and IL-13, leading to immunoglobulin E (IgE) class switching, eosinophilic inflammation, suppression of epidermal differentiation proteins, and amplification of barrier dysfunction. Additional inflammatory pathways involving Th22-, Th17-, and Th1-associated cytokines contribute to disease heterogeneity and chronic inflammation. IL-22 promotes keratinocyte proliferation, epidermal hyperplasia, and lichenification, whereas IL-17A/F enhances neutrophilic inflammation and inflammatory amplification. Interferon-γ (IFN-γ) derived from Th1 cells contributes to persistent chronic immune activation. Neuroimmune interactions represent a major pathogenic component of atopic dermatitis. Cytokines such as IL-31, TSLP, IL-33, and IL-4/IL-13 directly stimulate sensory neurons through activation of itch-associated signaling pathways, including TRPV1, PAR2, and Mas-related G protein-coupled receptors (Mrgprs). IL-31-mediated neuronal sensitization promotes chronic pruritus and perpetuates the itch-scratch cycle, leading to further keratinocyte injury, mast cell activation, neurogenic inflammation, and disease chronicity. Central intracellular signaling pathways involved in atopic dermatitis include Janus kinase-signal transducer and activator of transcription (JAK-STAT) cascades activated downstream of IL-4/IL-13, TSLP, and IL-31 receptor signaling. Activation of these pathways induces transcription of pro-inflammatory genes, including CXCL8, CCL17, CCL22, CCL26, and thymus and activation-regulated chemokine (TARC). The lower panels illustrate the integration of cytokine profiling and immunological endotyping into precision medicine approaches. Identification of dominant inflammatory pathways may facilitate biomarker-guided therapeutic selection and individualized treatment strategies. Current targeted therapies include biologic agents targeting IL-4Rα, IL-13, IL-31 receptor α, TSLP, and OX40/OX40L signaling, as well as JAK inhibitors that suppress multiple cytokine-mediated inflammatory pathways. Collectively, these mechanisms highlight the transition of atopic dermatitis from a traditionally barrier-centered disease toward a highly heterogeneous systemic inflammatory disorder amenable to precision medicine interventions.

The increasing recognition of atopic dermatitis as a highly heterogeneous inflammatory disorder has highlighted the central role of complex cytokine interactions in shaping disease pathogenesis, chronicity, neuroimmune activation, epidermal remodeling, and therapeutic responsiveness. While classical type 2 cytokines remain dominant drivers of allergic inflammation, emerging mediators such as IL-31, IL-33, IL-22, and epithelial-derived alarmins have further expanded the current understanding of AD immunobiology and contributed to the identification of distinct inflammatory endotypes. To provide a comparative overview of the principal cytokines implicated in AD, Table 1 summarizes the major classical and emerging cytokines involved in AD pathogenesis, including their cellular origin, immunological pathways, biological functions, clinical significance, and corresponding targeted therapeutic strategies.

Table 1. Classical and emerging cytokines involved in the immunopathogenesis of atopic dermatitis (AD).

Cytokine	Main Cellular Source	Signaling Pathway	Major Biological Effects	Clinical Relevance	Targeted Therapy
IL-4	Th2 cells, ILC2s	JAK1/STAT6	IgE switching, Th2 polarization, barrier dysfunction	Acute inflammation	Dupilumab
IL-13	Th2 cells, ILC2s	JAK1/TYK2/STAT6	Epidermal remodeling, chronic	Disease severity	Tralokinumab,

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			inflammation		Lebrikizumab
IL-5	Th2 cells	JAK/STAT	Eosinophil activation and survival	Eosinophilic inflammation	Investigational
IL-31	Th2 cells	JAK1/STAT3	Pruritus, neuronal sensitization	Itch severity	Nemolizumab
IL-22	Th22 cells	STAT3	Keratinocyte proliferation, lichenification	Chronic lesions	Investigational
IL-17A/F	Th17 cells	ACT1/NF-κB	Neutrophilic inflammation	Specific endotypes	Investigational
IFN-γ	Th1 cells	JAK1/JAK2/STAT1	Chronic inflammation	Long-standing disease	None approved
TSLP	Keratinocytes	TSLPR/JAK-STAT	Th2 initiation, dendritic activation	Early inflammation	Tezepelumab (investigational)
IL-33	Keratinocytes	ST2/NF-κB/MAPK	Alarmin amplification, neuroinflammation	Severe AD, pruritus	Investigational
IL-25	Keratinocytes	IL-17RB/NF-κB	ILC2 activation	Early allergic inflammation	Investigational
OX40/OX40L	T cells/DCs	NF-κB	T-cell survival and cytokine amplification	Chronic inflammation	Anti-OX40 agents

This table summarizes the principal cytokines implicated in the pathogenesis of AD, including both classical type 2 inflammatory mediators and emerging cytokines associated with neuroimmune activation, epithelial-derived signaling, epidermal remodeling, and chronic inflammatory amplification. For each cytokine, the major cellular source, immunological pathway, biological effects, clinical relevance, and corresponding targeted therapeutic strategies are presented. Comparative evaluation of these cytokine pathways highlights the substantial immunological heterogeneity of AD and supports the development of biomarker-driven precision medicine approaches. AD, atopic dermatitis; IL, interleukin; ILC2s, type 2 innate lymphoid cells; IFN-γ, interferon gamma; TSLP, thymic stromal lymphopoietin; IgE, immunoglobulin E; OX40L, OX40 ligand.

4. Biomarkers in Atopic Dermatitis: Toward Precision Medicine and Personalized Therapeutic Stratification

The growing recognition of AD as a highly heterogeneous inflammatory disorder has accelerated interest in identifying reliable biomarkers that can improve disease stratification, predict therapeutic response, monitor disease activity, and facilitate precision medicine approaches [3,5]. Although clinical severity scores remain fundamental to routine assessment, increasing evidence suggests that integrating molecular and immunological biomarkers may substantially improve understanding of disease heterogeneity and support individualized treatment strategies.

Biomarkers in AD encompass a broad spectrum of clinical, serological, cellular, transcriptomic, and cytokine-associated parameters reflecting different aspects of disease pathophysiology, including type 2 inflammation, epidermal barrier dysfunction, neuroimmune activation, and chronic tissue remodeling [3,18]. However, despite major advances in biomarker research, no single biomarker has yet demonstrated sufficient sensitivity and specificity to comprehensively capture the complexity of AD.

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4.1. Clinical Biomarkers and Disease Severity Assessment

Clinical scoring systems remain the cornerstone of AD severity evaluation and continue to represent essential tools in both clinical practice and research settings [26,27]. Among the most widely used instruments are the Scoring Atopic Dermatitis (SCORAD) index, the Eczema Area and Severity Index (EASI), the Investigator's Global Assessment (IGA), and the Dermatology Life Quality Index (DLQI). SCORAD integrates objective signs of inflammation with subjective symptoms such as pruritus and sleep disturbance, thereby providing a multidimensional assessment of disease burden [28,29]. In contrast, EASI primarily assesses objective inflammatory skin findings and is widely used in clinical trials evaluating biologic agents and JAKi [7].

Although clinical scoring systems provide valuable information regarding disease severity and treatment response, they exhibit several limitations. Considerable interobserver variability exists, and clinical scores frequently fail to reflect underlying immunological heterogeneity [3]. Patients with similar EASI or SCORAD scores may demonstrate markedly different cytokine profiles, inflammatory pathways, and therapeutic responsiveness [28,29].

Consequently, increasing attention has been directed toward integrating molecular biomarkers with clinical phenotyping to define more precise disease endotypes and improve therapeutic stratification [5].

4.2. Serum Biomarkers and Systemic Immune Activation

Several circulating biomarkers have been investigated as indicators of systemic inflammatory activity in AD [3]. Among the most extensively studied are total IgE, peripheral eosinophil counts, lactate dehydrogenase (LDH), thymus and activation-regulated chemokine (TARC/CCL17), and periostin.

Elevated serum IgE levels are a classical hallmark of extrinsic AD and reflect enhanced type 2 immune activation, primarily mediated by IL-4 and IL-13 signaling [1,18]. However, total IgE exhibits substantial variability between patients and does not consistently correlate with disease severity, limiting its utility as an isolated biomarker [3].

Peripheral eosinophilia similarly reflects systemic type 2 inflammation and is frequently associated with severe disease phenotypes, increased pruritus intensity, and higher rates of atopic comorbidities [18]. Nevertheless, eosinophil counts may fluctuate considerably over time and may be influenced by concomitant allergic disorders.

Among currently available biomarkers, TARC/CCL17 has emerged as one of the most promising indicators of AD disease activity [30,31]. TARC is a chemokine involved in the recruitment of CCR4-positive Th2 lymphocytes into inflamed skin and has been shown to correlate strongly with SCORAD and EASI scores [32,33]. Several studies have additionally shown that TARC levels decrease significantly following effective biologic therapy, suggesting potential utility for treatment monitoring [3].

Periostin, an extracellular matrix protein induced predominantly by IL-13, has also gained attention as a biomarker associated with chronic inflammation, fibrosis, and tissue remodeling [34–37]. Elevated periostin concentrations have been linked to severe AD phenotypes and persistent disease activity.

Collectively, these findings indicate that serum biomarkers may provide valuable insights into systemic immune activation; however, substantial overlap between inflammatory endotypes continues to limit their specificity in clinical practice.

4.3. Cytokine-Based Biomarkers and Immunological Endotyping

Recent advances in molecular immunology have highlighted cytokine profiling as one of the most promising approaches for biomarker development in AD [3,5]. Cytokine signatures may reflect distinct inflammatory endotypes and provide clinically relevant information regarding disease severity, chronicity, pruritus intensity, and therapeutic responsiveness.

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Among classical cytokines, IL-13 has emerged as a particularly important biomarker associated with chronic inflammation and severe disease phenotypes [12]. Elevated IL-13 expression has consistently been identified in lesional skin and serum samples from patients with moderate-to-severe AD [12]. Moreover, reductions in IL-13 activity correlate closely with clinical improvement following biologic therapy targeting IL-4/IL-13 pathways.

IL-31 has gained considerable interest as a biomarker associated specifically with neuroimmune activation and chronic pruritus [6]. Increased serum IL-31 concentrations correlate strongly with itch severity, sleep impairment, and disease activity [10]. Consequently, IL-31 may represent both a mechanistic and clinically relevant biomarker for identifying patients with dominant neuroimmune disease phenotypes.

Similarly, IL-22 has emerged as a potential marker of chronic epidermal remodeling and lichenification [14]. Elevated IL-22 expression has been associated with severe chronic AD lesions characterized by epidermal hyperplasia and tissue remodeling.

Epithelial-derived cytokines such as TSLP and IL-33 are increasingly investigated as biomarkers of early epithelial immune activation [6]. Elevated expression of these alarmins may reflect enhanced barrier dysfunction and activation of innate type 2 inflammatory pathways.

Importantly, cytokine expression profiles appear to vary according to age, ethnicity, disease chronicity, and treatment exposure [15,19,20]. Pediatric AD phenotypes frequently demonstrate stronger Th17/Th22 activation, whereas adult chronic disease is more strongly associated with IL-13- and IL-31-mediated pathways [4].

These observations strongly support the concept that AD consists of multiple immunological endotypes rather than a single homogeneous disease entity. Consequently, cytokine profiling may facilitate more precise disease classification and individualized therapeutic selection.

4.4. Transcriptomic and Molecular Biomarkers

Beyond serum cytokines, advances in transcriptomic technologies have substantially expanded understanding of molecular heterogeneity in AD [5]. High-throughput RNA sequencing and lesional skin transcriptomics have revealed distinct inflammatory signatures associated with disease severity, ethnicity, treatment response, and chronicity.

Transcriptomic analyses have demonstrated that lesional AD skin exhibits increased expression of genes associated with type 2 inflammation, epidermal hyperplasia, chemokine signaling, and neuroimmune activation [38–41]. Genes including CCL17, CCL22, IL13, IL31, S100A proteins, and periostin-related pathways are frequently upregulated in severe disease phenotypes.

Importantly, transcriptomic biomarkers may additionally predict therapeutic responsiveness. Patients exhibiting dominant IL-13-driven molecular signatures appear particularly responsive to IL-4/IL-13 blockade, whereas broader inflammatory activation may favor therapeutic responses to JAKi that simultaneously suppress multiple cytokine pathways [5].

Despite these promising findings, transcriptomic profiling remains limited primarily to research settings due to high costs, technical complexity, and a lack of standardized methodologies.

4.5. Biomarkers and Therapeutic Response Prediction

One of the most clinically relevant applications of biomarkers in AD is predicting therapeutic response and optimizing individualized treatment strategies [5,24,25]. The rapid expansion of biologic therapies and JAKi has highlighted the urgent need for biomarkers to identify patients most likely to benefit from specific therapeutic pathways.

Emerging evidence suggests that patients with strong type 2 inflammatory signatures characterized by elevated IL-13, TARC, periostin, and eosinophilia may respond particularly well to IL-4/IL-13-targeted biologic therapies [24,25]. In contrast, individuals with broader inflammatory activation involving IL-22-, IL-17-, or IFN-γ-associated pathways may demonstrate variable therapeutic responses and may benefit from broader immunomodulatory approaches such as JAKi.

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Similarly, elevated IL-31 levels may predict enhanced antipruritic responses to IL-31 receptor blockade with nemolizumab [16]. Such findings underscore the growing relevance of cytokine-based therapeutic stratification in precision medicine.

Biomarkers may additionally facilitate monitoring of therapeutic efficacy and early identification of treatment resistance [3]. Dynamic changes in TARC, IL-13, eosinophil counts, and transcriptomic signatures have all demonstrated potential utility in longitudinal disease monitoring.

Nevertheless, substantial challenges remain regarding standardization, reproducibility, accessibility, and cost-effectiveness of biomarker implementation in routine clinical practice. Large prospective studies remain necessary to validate biomarker-guided treatment algorithms and establish clinically applicable endotype classification systems.

4.6. Future Perspectives and Challenges in Biomarker Integration

The integration of biomarkers into precision medicine frameworks represents one of the most important future directions in AD research [2]. Advances in molecular profiling, artificial intelligence-assisted data integration, and multi-omics technologies may ultimately enable highly individualized therapeutic strategies informed by combined clinical, immunological, and molecular signatures.

Future biomarker panels will likely require integrating multiple parameters rather than relying on isolated inflammatory mediators. Combined approaches incorporating cytokine profiles, serum biomarkers, transcriptomics, and clinical phenotyping may improve diagnostic precision and therapeutic prediction accuracy.

However, significant barriers remain before biomarker-driven precision medicine can be fully implemented in routine dermatologic practice. Standardization of laboratory methodologies, validation across diverse populations, cost reduction, and establishment of universally accepted endotype classifications remain essential priorities for future research.

Despite these limitations, ongoing advances in biomarker discovery continue to redefine the understanding of AD as a dynamic and molecularly heterogeneous inflammatory disorder. Consequently, biomarker-guided precision medicine is expected to play an increasingly central role in the future management of AD.

Given the increasing importance of biomarker-driven precision medicine in AD, the principal biomarkers associated with disease activity, immunological profiling, and therapeutic response are summarized in Table 2.

Table 2. Potential biomarkers associated with disease severity and therapeutic response in atopic dermatitis.

Biomarker	Biological Source	Pathophysiological Role	Clinical Association	Potential Therapeutic Implications
Total IgE	B cells	Type 2 immune activation	Extrinsic AD, allergic sensitization	Predictive of Th2-dominant disease
Eosinophils	Peripheral blood	Eosinophilic inflammation	Severe disease phenotypes	Response to type 2-targeted therapies
TARC/CCL17	Dendritic cells, keratinocytes	Th2 cell recruitment	Correlates with SCORAD/EASI	Monitoring treatment response
Periostin	Fibroblasts, keratinocytes	Tissue remodeling, fibrosis	Chronic AD	Predictor of IL-13-driven inflammation
IL-13	Th2 cells	Chronic type 2 inflammation	Severe AD, chronic lesions	Response to IL-13 inhibitors
IL-31	Th2 cells	Neuroimmune pruritus signaling	Severe itch, sleep disturbance	Response to nemolizumab

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IL-22	Th22 cells	Epidermal hyperplasia	Lichenified/chronic AD	Marker of remodeling phenotype
TSLP	Keratinocytes	Epithelial alarmin activation	Early inflammation	Candidate for upstream targeted therapy
IL-33	Keratinocytes	Amplification of Th2 inflammation	Severe inflammatory phenotype	Emerging therapeutic target
LDH	Serum biomarker	Tissue inflammation and turnover	Disease activity	General inflammatory marker
Transcriptomic signatures	Lesional skin	Molecular endotyping	Disease heterogeneity	Precision therapeutic stratification
JAK-STAT activation profile	Multiple immune cells	Cytokine signaling amplification	Broad inflammatory activation	Candidate for JAK inhibitor responsiveness

This table summarizes major serum, cytokine-associated, cellular, and molecular biomarkers currently investigated in atopic dermatitis. The presented biomarkers are associated with different aspects of disease pathophysiology, including type 2 inflammation, neuroimmune activation, epidermal remodeling, and systemic inflammatory activity. Their potential utility for disease stratification, immunological endotyping, therapeutic response prediction, and biomarker-guided precision medicine approaches is also highlighted. AD, atopic dermatitis; IgE, immunoglobulin E; TARC/CCL17, thymus and activation-regulated chemokine/C-C motif chemokine ligand 17; IL, interleukin; TSLP, thymic stromal lymphopoietin; LDH, lactate dehydrogenase; JAK-STAT, Janus kinase-signal transducer and activator of transcription.

5. Precision Medicine and Therapeutic Innovation in Atopic Dermatitis

The therapeutic landscape of AD has undergone a profound transformation over the last decade, driven largely by advances in molecular immunology and the increasing recognition of disease heterogeneity [5,7]. Historically, treatment strategies for moderate-to-severe AD relied predominantly on nonspecific immunosuppressive agents, including systemic corticosteroids, cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil. Although these therapies may reduce inflammatory activity, their long-term use is frequently limited by toxicity, inconsistent efficacy, and lack of selectivity [24,25].

The emergence of precision medicine has fundamentally reshaped therapeutic approaches in AD by promoting individualized treatment strategies based on immunological profiling, cytokine signatures, and molecular endotypes [5]. Advances in understanding type 2 inflammation, epithelial alarmin signaling, neuroimmune pathways, and intracellular cytokine cascades have facilitated the development of targeted biologic therapies and small-molecule inhibitors that selectively modulate key pathogenic mechanisms.

Importantly, therapeutic innovation in AD now extends beyond simple suppression of inflammation to modulate disease-specific molecular pathways that contribute to barrier dysfunction, chronic pruritus, neuroimmune activation, and tissue remodeling. This evolving therapeutic paradigm represents one of the clearest clinical applications of precision medicine in inflammatory dermatology.

5.1. Biologic Therapies Targeting Type 2 Inflammation

The development of biologic agents targeting IL-4 and IL-13 signaling pathways represents a major milestone in AD management and has validated type 2 inflammation as the dominant pathogenic axis in moderate-to-severe disease [7,8].

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Dupilumab, a fully human monoclonal antibody targeting the IL-4 receptor α (IL-4Rα) subunit, inhibits signaling by both IL-4 and IL-13 [42–44]. Clinical trials have demonstrated substantial improvements in EASI scores, pruritus severity, sleep quality, and quality of life following dupilumab therapy [42–44]. Importantly, dupilumab additionally reduces markers of epidermal barrier dysfunction and systemic type 2 immune activation, highlighting the close relationship between cytokine signaling and structural skin abnormalities.

Long-term extension studies have confirmed sustained efficacy and favorable safety profiles associated with dupilumab treatment [45–47]. Nevertheless, conjunctivitis, facial erythema, and partial treatment responses remain clinically relevant limitations in certain patient populations.

Selective IL-13 inhibition has emerged as another important therapeutic strategy in AD. Tralokinumab [48–56] and lebrikizumab [57–68] selectively neutralize IL-13 and have demonstrated significant efficacy in reducing chronic inflammation, pruritus, and epidermal remodeling. These findings reinforce the central role of IL-13 in chronic disease activity and support the concept that distinct cytokine pathways may contribute differently to disease phenotypes.

Importantly, the efficacy of IL-4/IL-13 blockade has provided strong clinical validation for cytokine-targeted precision medicine approaches. Patients exhibiting dominant type 2 inflammatory signatures characterized by elevated IL-13, TARC, eosinophilia, and periostin expression appear particularly responsive to these therapies [3,5].

5.2. JAK Inhibitors and Broad Cytokine Modulation

JAKi represent another major therapeutic innovation in AD and differ fundamentally from biologic therapies in that they simultaneously inhibit intracellular signaling downstream of multiple cytokine receptors [7,24,25].

Cytokines implicated in AD pathogenesis, including IL-4, IL-13, IL-31, TSLP, and interferon-associated pathways, signal predominantly through JAK-STAT cascades [11]. Consequently, pharmacologic inhibition of JAK signaling provides broader anti-inflammatory effects compared with selective cytokine blockade.

Upadacitinib [65–69] and abrocitinib [70–74], both selective JAK1 inhibitors, have demonstrated rapid and substantial reductions in disease severity and pruritus intensity. Clinical improvement frequently occurs within days to weeks of treatment initiation, particularly regarding itch reduction, emphasizing the importance of JAK-dependent neuroimmune signaling pathways.

Baricitinib, a JAK1/JAK2 inhibitor, has also shown efficacy in moderate-to-severe AD, although responses may be somewhat less pronounced compared with highly selective JAK1 inhibitors [75–79].

One of the major advantages of JAKi involves their ability to simultaneously suppress multiple inflammatory pathways, including type 2-, Th22-, Th17-, and interferon-mediated signaling [24,25]. Such broad immunomodulatory activity may prove particularly beneficial in patients exhibiting mixed inflammatory endotypes or incomplete responses to biologic monotherapy. However, safety considerations remain highly relevant. Potential adverse effects associated with JAKi include infections, acneiform eruptions, laboratory abnormalities, thromboembolic events, and cardiovascular risk concerns [70–74]. Consequently, careful patient selection and long-term pharmacovigilance remain essential components of JAKi therapy.

5.3. Targeting Neuroimmune Pathways and Pruritus

Pruritus remains one of the most debilitating symptoms in AD and represents a major therapeutic target within precision medicine frameworks [6,10]. Traditional anti-inflammatory therapies often fail to completely control chronic itch, highlighting the importance of direct neuroimmune modulation.

IL-31 has emerged as one of the most important cytokines involved in itch signaling and neuronal sensitization [6]. Nemolizumab, a monoclonal antibody targeting the IL-31 receptor α subunit, has demonstrated rapid and significant antipruritic effects in moderate-to-severe AD [16].

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Clinical trials have shown that IL-31 blockade substantially reduces itch severity, sleep disturbance, and scratching behavior, further validating the pathogenic relevance of neuroimmune cytokine pathways [16]. Importantly, improvement in pruritus frequently precedes visible reductions in skin inflammation, suggesting partially independent neuroimmune mechanisms.

Additional therapeutic strategies targeting neuroimmune pathways remain under active investigation. Cytokines such as TSLP and IL-33 may directly stimulate sensory neurons and contribute to chronic neuronal hypersensitivity [6,10]. Consequently, therapies targeting epithelial alarmins may provide both anti-inflammatory and antipruritic benefits.

These findings collectively reinforce the concept that AD should not be regarded solely as an inflammatory skin disease but rather as a complex neuroimmune disorder requiring multidimensional therapeutic approaches.

5.4. Emerging Therapeutic Targets Beyond Type 2 Immunity

Although type 2 inflammation remains central to AD pathogenesis, increasing evidence suggests that additional inflammatory pathways contribute significantly to chronic disease activity and therapeutic variability [1,4]. Consequently, several emerging therapies aim to target pathways beyond classical IL-4/IL-13 signaling.

Among these targets, OX40/OX40L signaling has attracted substantial attention due to its role in sustaining T-cell activation and amplifying chronic inflammation [21–23]. Anti-OX40 monoclonal antibodies have demonstrated encouraging reductions in inflammatory biomarkers and clinical severity in early-phase studies [21–23].

Similarly, therapies targeting epithelial alarmins, such as TSLP and IL-33, are currently undergoing clinical investigation [7]. By targeting upstream inflammatory initiators, these agents may, in theory, suppress multiple downstream cytokine cascades simultaneously.

Additional investigational approaches involve modulation of IL-22 signaling, Th17-associated pathways, and microbiome-associated immune regulation [14]. Such strategies may prove particularly relevant for patients exhibiting nonclassical or mixed inflammatory endotypes.

Importantly, the increasing diversification of therapeutic targets reflects the growing recognition that AD comprises multiple immunological subtypes that require individualized therapeutic strategies rather than universal treatment algorithms.

5.5. Biomarker-Guided Therapy and Precision Medicine Algorithms

One of the principal goals of precision medicine in AD involves integration of biomarkers into therapeutic decision-making algorithms [5]. The identification of cytokine signatures, serum biomarkers, and molecular endotypes may facilitate the prediction of therapeutic response and the optimization of individualized treatment strategies.

Patients with dominant IL-13-driven inflammation may demonstrate superior responses to IL-4/IL-13 blockade, whereas individuals with broader inflammatory activation may benefit from JAKi [5,24,25]. Similarly, elevated IL-31 expression may identify patients likely to respond favorably to neuroimmune-targeted therapies such as nemolizumab.

Emerging transcriptomic studies additionally suggest that molecular profiling may predict treatment responsiveness prior to therapeutic initiation [38–41]. Such approaches could ultimately reduce therapeutic failure, minimize unnecessary immunosuppression, and improve long-term disease control.

Artificial intelligence-assisted biomarker integration and machine learning-based predictive modeling may further enhance precision medicine strategies in the future [80–83]. Combined analysis of clinical phenotypes, serum biomarkers, cytokine profiles, and transcriptomic signatures may facilitate highly individualized therapeutic algorithms.

Nevertheless, substantial challenges remain before precision medicine can be fully implemented in routine clinical practice. Standardization of biomarker panels, cost reduction, validation across

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diverse populations, and accessibility of molecular profiling technologies remain essential priorities for future research.

5.6. Future Perspectives in Therapeutic Innovation

The future of AD management will likely involve increasingly individualized therapeutic strategies that integrate immunological profiling, molecular endotyping, and targeted interventions [5]. Combination therapies that simultaneously target multiple inflammatory pathways may be particularly relevant in severe or treatment-resistant disease phenotypes.

Advances in single-cell transcriptomics, spatial immunology, and multi-omics integration continue to improve understanding of disease heterogeneity and may ultimately facilitate real-time monitoring of inflammatory activity and therapeutic response [84–87].

Furthermore, early intervention strategies targeting epithelial alarmins and neuroimmune pathways may potentially alter disease progression and prevent chronic inflammatory remodeling. Such approaches could shift AD management from reactive symptom control toward proactive disease modification.

Collectively, these therapeutic advances illustrate the ongoing transition of AD from a traditionally empirical treatment model toward a biomarker-driven precision medicine framework centered on individualized molecular targeting and personalized disease management.

To synthesize the central concepts explored throughout this review, Figure 2 presents a conceptual precision medicine framework integrating immunopathogenesis, biomarker-driven immunological profiling, molecular endotyping, and mechanism-based therapeutic innovation in AD.

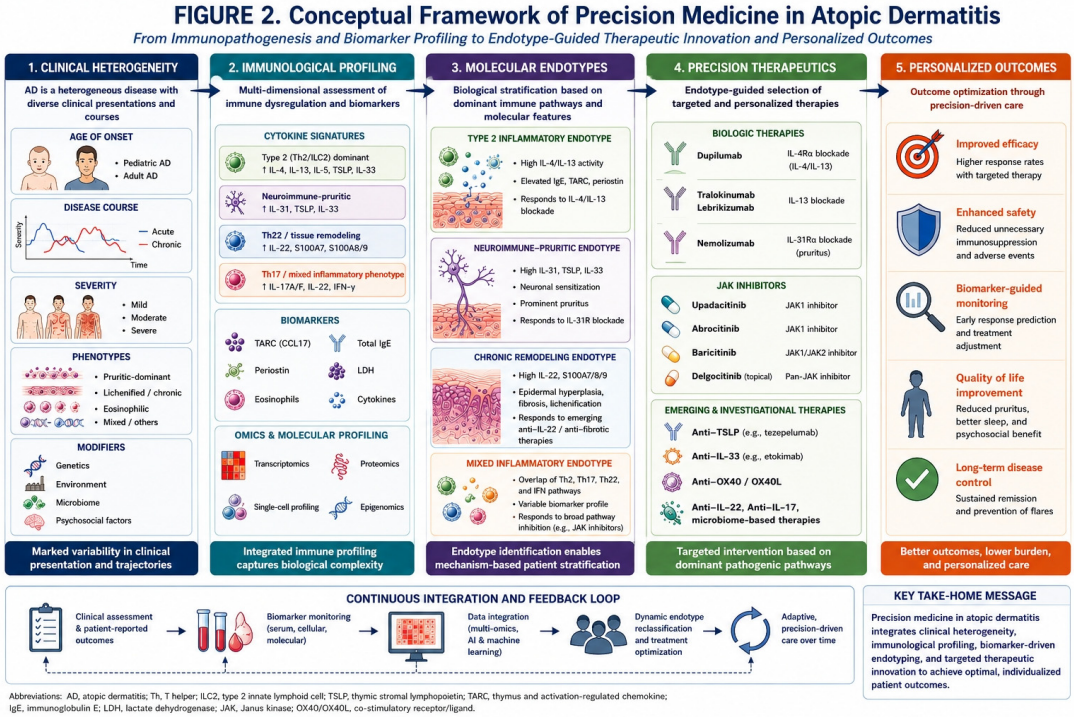

Figure 2. Conceptual framework of precision medicine in atopic dermatitis: from immunopathogenesis and biomarker profiling to endotype-guided therapeutic innovation and personalized outcomes. This figure illustrates an integrated precision medicine model for atopic dermatitis (AD), emphasizing the transition from conventional phenotype-based management toward biomarker-driven and endotype-guided therapeutic strategies. (1) The framework begins with the recognition of substantial clinical heterogeneity in AD, including variations in age of onset, disease course, severity, inflammatory phenotype, and environmental or genetic modifiers. These factors contribute to marked interindividual variability in disease presentation and progression. (2) *The second panel* highlights immunological profiling as a central component of precision medicine

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in AD. Cytokine signatures associated with type 2 inflammation, neuroimmune activation, tissue remodeling, and mixed inflammatory responses are integrated with serum biomarkers, including thymus and activation-regulated chemokine (TARC/CCL17), immunoglobulin E (IgE), eosinophils, lactate dehydrogenase (LDH), and periostin. Advanced molecular approaches, including transcriptomics, proteomics, epigenomics, and single-cell profiling, further characterize disease-specific immune dysregulation and the underlying biological complexity. (3) *The third panel* demonstrates the identification of distinct molecular endotypes based on dominant immunological pathways. The type 2 inflammatory endotype is characterized by increased IL-4/IL-13 activity, elevated IgE, TARC, and periostin expression, and favorable responses to IL-4/IL-13 blockade. The neuroimmune-pruritic endotype is associated with enhanced signaling by IL-31, TSLP, and IL-33, neuronal sensitization, and severe chronic pruritus. The chronic remodeling endotype is characterized by IL-22-driven epidermal hyperplasia, fibrosis, and lichenification, whereas the mixed inflammatory endotype involves overlapping Th2-, Th17-, Th22-, and interferon-associated pathways with broader inflammatory activation and variable therapeutic responsiveness. (4) *The fourth panel* illustrates precision therapeutics targeting specific pathogenic pathways. Biologic agents, including dupilumab, tralokinumab, lebrikizumab, and nemolizumab, selectively inhibit major cytokine axes involved in AD immunopathogenesis. Small-molecule therapies such as JAK inhibitors suppress multiple downstream inflammatory signaling pathways simultaneously. Emerging and investigational therapies targeting TSLP, IL-33, OX40/OX40L, IL-22, IL-17, and microbiome-associated pathways reflect the ongoing expansion of mechanism-based therapeutic approaches. (5) *The final panel* summarizes the principal objectives of precision medicine in AD, including improved therapeutic efficacy, enhanced safety through reduction of unnecessary immunosuppression, biomarker-guided monitoring, improved quality of life, and sustained long-term disease control. *The lower section* emphasizes the importance of integrating clinical assessment, biomarker monitoring, multi-omics analysis, and dynamic endotype reclassification to optimize adaptive, individualized therapeutic strategies over time.

6. Therapeutic Innovations in Atopic Dermatitis

The therapeutic management of AD has undergone a profound transformation over the last decade, driven primarily by advances in molecular immunology and the identification of cytokine-specific inflammatory pathways [5,7,88–90]. Historically, treatment strategies for moderate-to-severe AD relied predominantly on broad immunosuppressive agents such as systemic corticosteroids, cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil. Although these therapies may reduce inflammatory activity, their long-term use is frequently limited by toxicity, variable efficacy, and lack of immunological selectivity [24,25].

The emergence of targeted biologic agents and JAKi has fundamentally reshaped the therapeutic landscape of AD and represents one of the clearest clinical applications of precision medicine in inflammatory dermatology [7,80–87,91–93]. Unlike conventional immunosuppressive therapies, modern targeted treatments selectively modulate specific cytokine pathways involved in disease pathogenesis, including type 2 inflammation, neuroimmune activation, epithelial alarmin signaling, and chronic inflammatory amplification.

Importantly, therapeutic innovation in AD now extends beyond suppression of cutaneous inflammation alone and increasingly aims to improve epidermal barrier integrity, reduce chronic pruritus, prevent tissue remodeling, and optimize long-term disease control through individualized therapeutic approaches.

6.1. Biologic Therapies Targeting IL-4 and IL-13 Signaling

The introduction of biologic therapies targeting IL-4 and IL-13 pathways represented a major breakthrough in AD treatment and validated type 2 inflammation as the dominant pathogenic axis in moderate-to-severe disease [42–47].

Dupilumab, a fully human monoclonal antibody targeting the IL-4 receptor α (IL-4Rα) subunit, inhibits signaling by both IL-4 and IL-13 [42–44]. By suppressing downstream JAK-STAT activation and type 2 cytokine amplification, dupilumab improves epidermal barrier function, reduces eosinophilic inflammation, and significantly decreases pruritus intensity.

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Large phase III clinical trials demonstrated substantial improvements in EASI scores, SCORAD, sleep quality, and patient-reported outcomes following dupilumab therapy [42–44]. Long-term extension studies also confirmed sustained efficacy and a favorable safety profile over extended treatment periods [45–47].

Importantly, dupilumab also reduces biomarkers associated with type 2 inflammation, including TARC/CCL17, periostin, serum IgE, and eosinophilic activation, supporting the concept of biomarker-guided therapeutic monitoring [3,80–87].

Selective IL-13 inhibition has subsequently emerged as another important therapeutic strategy. Tralokinumab and lebrikizumab selectively neutralize IL-13 signaling and have demonstrated significant efficacy in reducing chronic inflammation, epidermal remodeling, and itch severity. These findings reinforce the central role of IL-13 in sustaining chronic disease activity and support the concept that IL-13 represents a key therapeutic target in chronic AD inflammation [27,28,37]. Furthermore, differential responses to IL-4/IL-13 blockade among patients further emphasize the importance of individualized immunological profiling in therapeutic decision-making.

6.2. JAK Inhibitors and Intracellular Cytokine Signaling Modulation

JAKi represent another major therapeutic innovation in AD and differ fundamentally from biologic agents in that they simultaneously inhibit intracellular signaling downstream of multiple cytokine receptors [48–62,94–96].

Several cytokines implicated in AD pathogenesis, including IL-4, IL-13, IL-31, thymic stromal lymphopoietin (TSLP), IFN-γ, and IL-22, signal predominantly through JAK-STAT pathways [11]. Consequently, pharmacologic inhibition of JAK signaling enables broader immunomodulation than selective extracellular cytokine blockade.

Upadacitinib and abrocitinib, both selective JAK1 inhibitors, have demonstrated rapid and substantial improvements in inflammatory skin lesions and pruritus severity [65–74]. Clinical improvement frequently occurs within days of treatment initiation, particularly regarding itch reduction, emphasizing the importance of JAK-dependent neuroimmune signaling pathways in AD.

Baricitinib, a JAK1/JAK2 inhibitor, has also demonstrated efficacy in moderate-to-severe disease, although clinical responses may be somewhat less pronounced than those observed with highly selective JAK1 inhibitors [75–79].

An important advantage of JAKi involves their ability to simultaneously suppress multiple inflammatory axes, including Th2-, Th17-, Th22-, and interferon-associated pathways [24,25]. This broader anti-inflammatory activity may prove particularly beneficial in patients exhibiting mixed inflammatory endotypes or incomplete responses to biologic monotherapy.

Nevertheless, safety considerations remain highly relevant in the context of JAKi. Potential adverse effects include infections, acneiform eruptions, laboratory abnormalities, thromboembolic events, and cardiovascular risk concerns [70–74]. Consequently, careful patient selection and long-term pharmacovigilance remain essential components of therapeutic management.

6.3. Neuroimmune-Targeted Therapies and Pruritus Modulation

Pruritus represents one of the most debilitating clinical manifestations of AD and remains a major therapeutic challenge [6,10]. Conventional anti-inflammatory therapies often fail to fully control chronic itch, underscoring the importance of direct neuroimmune modulation.

IL-31 has emerged as a principal cytokine involved in neuronal sensitization and itch transmission [6]. Produced predominantly by activated Th2 lymphocytes, IL-31 directly stimulates sensory neurons through IL-31 receptor signaling pathways and amplifies chronic pruritus and scratching behavior.

Nemolizumab, a monoclonal antibody targeting the IL-31 receptor α subunit, has demonstrated rapid and significant antipruritic effects in moderate-to-severe AD. Clinical trials showed marked reductions in itch severity, sleep disturbance, and scratching behavior, often preceding visible improvement in inflammatory skin lesions [16,97–100].

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These findings strongly support the concept that neuroimmune pathways represent partially independent therapeutic targets in AD and reinforce the importance of symptom-specific precision medicine strategies.

Additional therapeutic targets involved in neuroimmune signaling include TSLP and IL-33, both of which may directly activate sensory neurons and contribute to neuronal hypersensitivity [6]. Emerging therapies directed against epithelial alarmins may therefore provide combined anti-inflammatory and antipruritic effects.

6.4. Emerging Therapeutic Targets Beyond Classical Type 2 Inflammation

Although type 2 inflammation remains central to AD pathogenesis, increasing evidence suggests that additional inflammatory pathways contribute substantially to disease chronicity, tissue remodeling, and therapeutic variability [1,4]. Consequently, several emerging therapeutic strategies aim to target pathways beyond classical IL-4/IL-13 signaling.

Among these targets, OX40/OX40L signaling has attracted considerable attention due to its role in sustaining T-cell activation and amplifying chronic inflammation [17,21–23]. OX40-targeted therapies may suppress multiple downstream cytokine pathways simultaneously and potentially reduce persistent immune activation.

Similarly, therapies targeting epithelial alarmins, such as TSLP and IL-33, are currently under active clinical investigation [7]. By targeting upstream inflammatory initiators released by keratinocytes, these therapies may theoretically inhibit broader inflammatory cascades before full immune amplification occurs.

IL-22-targeted therapies are also being explored, given IL-22's role in epidermal hyperplasia, chronic tissue remodeling, and lichenification [14]. Such approaches may prove particularly relevant for chronic AD phenotypes characterized by severe epidermal thickening and fibrosis.

Additional investigational strategies include modulation of Th17-associated pathways, restoration of epidermal barrier integrity, microbiome-directed therapy, and epigenetic regulation [101–103]. These emerging approaches reflect the growing recognition that AD consists of multiple overlapping inflammatory and structural disease mechanisms.

6.5. Precision Therapeutics and Endotype-Guided Treatment Strategies

The increasing diversification of therapeutic options in AD has accelerated the development of endotype-guided therapeutic approaches [5,80–87]. Precision therapeutics aims to integrate clinical phenotypes, cytokine signatures, serum biomarkers, and molecular profiling in order to optimize individualized treatment selection.

Patients exhibiting dominant type 2 inflammatory signatures characterized by elevated IL-13, TARC, periostin, and eosinophilia may respond particularly well to IL-4/IL-13-targeted biologic therapy [3,5]. In contrast, patients demonstrating broader inflammatory activation involving IL-22-, IL-17-, or interferon-associated pathways may benefit more substantially from broader immunomodulatory approaches such as JAKi.

Similarly, elevated IL-31 expression and severe chronic pruritus may identify patients likely to respond favorably to neuroimmune-targeted therapies such as nemolizumab [16].

The future integration of transcriptomic profiling, single-cell analysis, and artificial intelligence-assisted biomarker interpretation may further refine therapeutic stratification and facilitate highly individualized therapeutic algorithms [80–87].

Importantly, precision therapeutics in AD extend beyond maximizing efficacy alone and also aim to minimize unnecessary immunosuppression, reduce adverse effects, improve long-term adherence, and optimize patient quality of life.

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6.6. Challenges and Future Perspectives in Therapeutic Innovation

Despite remarkable therapeutic progress, several important challenges remain regarding the implementation of precision therapeutics in routine clinical practice [5]. Significant overlap exists between inflammatory endotypes, and dynamic cytokine expression patterns may complicate therapeutic prediction.

Additionally, substantial variability in treatment responsiveness persists even among patients with apparently similar immunological profiles. The lack of universally standardized biomarker panels currently limits precise therapeutic stratification.

Long-term safety monitoring also remains essential, particularly regarding chronic JAKi exposure and prolonged cytokine suppression [70–74]. Further studies are required to clarify optimal sequencing strategies, combination therapies, and the long-term disease-modifying potential of emerging agents.

Nevertheless, ongoing advances in molecular immunology continue to expand the therapeutic possibilities available for AD. The progressive integration of immunological profiling, biomarker-guided therapy, and mechanism-based interventions strongly supports a transition in AD management from generalized empirical treatment to highly individualized precision medicine strategies.

The expanding understanding of cytokine-mediated inflammatory pathways and molecular heterogeneity in atopic dermatitis has profoundly transformed the therapeutic landscape of the disease over the last decade. Increasing recognition of distinct immunological endotypes and biomarker-associated inflammatory signatures has accelerated the transition from broad nonspecific immunosuppressive strategies toward highly selective, mechanism-based therapeutic approaches targeting specific cytokines, intracellular signaling cascades, neuroimmune pathways, and epithelial-derived inflammatory mediators. The introduction of biologic agents targeting IL-4-, IL-13-, and IL-31-associated pathways, together with JAKi that simultaneously modulate multiple cytokine signaling networks, represents one of the most important advances in precision dermatology. Furthermore, emerging therapies targeting epithelial alarmins, co-stimulatory immune pathways, and chronic inflammatory amplification mechanisms continue to expand therapeutic options for patients with moderate-to-severe AD. Table 3 summarizes the main therapeutic innovations in contemporary AD management, including currently approved and investigational targeted therapies, their molecular targets, mechanisms of action, principal clinical effects, and major therapeutic limitations.

Table 3. Targeted therapies and molecular pathways in atopic dermatitis (AD).

Therapy	Molecular Target	Mechanism of Action	Main Clinical Effects	Limitations/Safety Concerns
Dupilumab	IL-4Rα	Blocks IL-4/IL-13 signaling	Reduces inflammation and pruritus	Conjunctivitis
Tralokinumab	IL-13	Selective IL-13 inhibition	Improves chronic lesions	Partial responders
Lebrikizumab	IL-13	IL-13 neutralization	Reduces EASI and itch	Long-term data limited
Nemolizumab	IL-31RA	Inhibits neuroimmune itch signaling	Rapid antipruritic effect	Injection-site reactions
Upadacitinib	JAK1	Broad cytokine signaling inhibition	Rapid disease control	Infection risk
Abrocitinib	JAK1	Suppresses multiple inflammatory pathways	Fast itch reduction	Thromboembolic warnings
Baricitinib	JAK1/JAK2	Multi-cytokine inhibition	Moderate efficacy	Laboratory abnormalities

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Delgocitinib	Pan-JAK	Topical cytokine inhibition	Local inflammation control	Limited availability
Tezepelumab	TSLP	Alarmin inhibition	Experimental disease modulation	Investigational
Anti-OX40 agents	OX40/OX40 L	T-cell co-stimulation blockade	Reduces chronic inflammation	Early clinical phase

Overview of currently approved and emerging targeted therapies for atopic dermatitis, including biologic agents and Janus kinase (JAK) inhibitors. The table summarizes the principal molecular targets, mechanisms of action, major clinical effects, and important safety considerations associated with each therapeutic class. These therapies illustrate the transition from broad immunosuppressive approaches toward mechanism-based and endotype-guided precision therapeutics in AD. AD, atopic dermatitis; IL, interleukin; IL-4Rα, interleukin-4 receptor alpha; IL-31RA, interleukin-31 receptor alpha; JAK, Janus kinase; TYK2, tyrosine kinase 2; EASI, Eczema Area and Severity Index.

7. Future Directions and Emerging Perspectives in Precision Medicine for Atopic Dermatitis

The increasing understanding of AD as a biologically heterogeneous and immunologically complex inflammatory disorder has profoundly transformed both research priorities and therapeutic strategies over the last decade [5,80–87]. Advances in molecular immunology, biomarker discovery, transcriptomic profiling, and targeted therapy development have accelerated the transition from generalized treatment approaches toward individualized precision medicine frameworks. Nevertheless, despite substantial progress, several important scientific and clinical challenges remain unresolved.

Future perspectives in AD are expected to focus predominantly on deeper characterization of disease endotypes, integration of multi-omics technologies, identification of predictive biomarkers, and development of highly personalized therapeutic algorithms to optimize long-term disease control while minimizing unnecessary immunosuppression [3,5]. Importantly, the future of precision medicine in AD will likely depend on the ability to integrate clinical phenotypes with dynamic molecular and immunological signatures in real-world clinical practice.

7.1. Expanding the Concept of Immunological Endotypes

One of the most important future directions in AD research involves refinement of immunological endotype classification systems [5]. Current evidence strongly supports the concept that AD consists of multiple overlapping inflammatory subtypes characterized by distinct cytokine profiles, barrier abnormalities, neuroimmune activation patterns, and therapeutic responsiveness [3,15].

Although type 2 inflammation remains the dominant pathogenic axis in most patients, substantial variability exists regarding the relative contribution of IL-13-, IL-31-, IL-22-, IL-17-, and interferon-associated pathways [4,6]. Future studies are therefore expected to focus on identifying more stable and clinically relevant molecular endotypes that can guide therapeutic selection and predict disease progression.

Importantly, endotype characterization may additionally facilitate earlier identification of patients at increased risk for severe disease, treatment resistance, or progression toward chronic lichenified phenotypes [80–87]. Such approaches could ultimately support preventive therapeutic strategies and earlier intervention during critical stages of disease evolution.

Furthermore, increasing evidence suggests that endotypes may evolve dynamically over time in response to age, environmental exposures, microbiome alterations, and therapeutic intervention [5]. Consequently, future precision medicine frameworks will likely require continuous reassessment of molecular profiles rather than static classification systems.

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7.2. Multi-Omics Technologies and Systems Immunology

Rapid advances in multi-omics technologies are expected to substantially improve understanding of AD heterogeneity and inflammatory complexity [80–87]. Integrated analysis of transcriptomics, proteomics, metabolomics, epigenomics, lipidomics, and single-cell sequencing may provide deeper insights into the molecular architecture of disease pathogenesis.

Single-cell RNA sequencing has already demonstrated remarkable potential in identifying disease-specific immune cell populations, cytokine-producing cellular subsets, and spatial inflammatory microenvironments within lesional AD skin [104]. These technologies may facilitate the identification of previously unrecognized pathogenic pathways and novel therapeutic targets.

Spatial transcriptomics represents another rapidly evolving field with particular relevance for inflammatory skin diseases. By enabling simultaneous analysis of gene expression and tissue architecture, spatial profiling technologies may improve understanding of interactions between keratinocytes, immune cells, fibroblasts, endothelial cells, and peripheral sensory neurons within the AD microenvironment [105].

Importantly, integration of multi-omics datasets may ultimately facilitate the development of highly individualized inflammatory maps capable of predicting therapeutic response with significantly greater precision than currently available biomarkers.

7.3. Artificial Intelligence and Predictive Modeling

Artificial intelligence (AI) and machine learning technologies are increasingly recognized as important future tools in precision dermatology [80–87]. The integration of large-scale clinical, molecular, transcriptomic, imaging, and biomarker datasets may enable the development of predictive algorithms that improve diagnostic accuracy, disease stratification, and therapeutic selection.

Machine learning models may identify complex biomarker combinations associated with treatment responsiveness, disease progression, or therapeutic resistance that are not detectable with conventional statistical approaches [106]. Such technologies could facilitate real-time therapeutic optimization and dynamic reclassification of inflammatory endotypes during treatment. AI-assisted image analysis may additionally improve objective assessment of disease severity and longitudinal treatment monitoring. Integration of digital phenotyping with immunological profiling could represent a major future advancement in personalized AD management. Nevertheless, substantial challenges remain regarding data standardization, algorithm validation, interpretability, patient privacy, and integration into routine clinical workflows [106]. Ethical considerations surrounding AI-assisted decision-making will also require careful evaluation.

7.4. Future Biomarkers and Noninvasive Monitoring Strategies

One of the major limitations of current biomarker implementation in AD involves the lack of standardized, reproducible, and clinically accessible molecular monitoring tools [3]. Consequently, future research increasingly focuses on developing minimally invasive and noninvasive biomarker technologies.

Tape-strip sampling has emerged as a particularly promising approach for evaluating epidermal cytokine expression and barrier-associated molecular signatures without requiring invasive skin biopsies [38–41]. Such techniques may facilitate serial monitoring of inflammatory activity and treatment response in both pediatric and adult patients.

Additional future biomarker strategies may involve wearable biosensors, sweat analysis, microbiome-derived biomarkers, and real-time inflammatory monitoring technologies [107–110]. Integration of these approaches into routine practice could substantially improve longitudinal disease assessment and therapeutic adjustment.

Importantly, future biomarker panels will likely involve combined analysis of multiple parameters rather than isolated inflammatory mediators. Composite biomarker signatures

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integrating cytokine profiles, transcriptomic data, serum markers, and clinical characteristics may ultimately provide superior predictive accuracy.

7.5. Emerging Therapeutic Strategies and Disease Modification

The therapeutic future of AD extends beyond selective suppression of inflammation toward true disease modification and restoration of long-term immune tolerance [24,25]. Several emerging therapeutic strategies currently under investigation may substantially expand the precision medicine landscape in the coming years.

Upstream inhibition of epithelial alarmins such as TSLP and IL-33 may theoretically suppress multiple downstream inflammatory cascades simultaneously and potentially prevent early immune amplification [6,7]. Similarly, therapies targeting OX40/OX40L signaling may inhibit sustained T-cell activation and chronic inflammatory persistence [17,21–23].

Combination therapies targeting complementary inflammatory pathways may also become increasingly relevant in severe or treatment-resistant disease phenotypes. Simultaneous modulation of type 2 inflammation, neuroimmune activation, and epithelial dysfunction could potentially improve long-term therapeutic outcomes in complex endotypes.

Importantly, future therapeutic goals may progressively shift from temporary inflammatory suppression toward sustained disease remission, prevention of chronic remodeling, and interruption of the atopic march.

7.6. Challenges in Implementing Precision Medicine in Clinical Practice

Despite remarkable scientific progress, several important barriers continue to limit the implementation of precision medicine in routine AD management [5,80–87]. One of the principal challenges involves the substantial overlap between inflammatory endotypes and the dynamic nature of cytokine expression profiles.

Additionally, many molecular profiling technologies remain expensive, technically complex, and largely restricted to research environments. Standardization of laboratory methodologies and validation across ethnically diverse populations remain essential priorities before widespread clinical implementation becomes feasible.

Another important challenge involves the interpretation of complex biomarker datasets within routine clinical practice. Integration of transcriptomics, cytokine profiling, and multi-omics data requires substantial bioinformatic infrastructure and interdisciplinary collaboration between dermatologists, immunologists, molecular biologists, and computational scientists.

Furthermore, disparities in healthcare access may significantly influence the global applicability of precision medicine strategies. Ensuring equitable access to advanced molecular diagnostics and targeted therapies will remain an important ethical and public health consideration in the future.

7.7. Conclusion and Translational Perspective

The evolution of AD from a traditionally barrier-centered disease toward a highly heterogeneous systemic inflammatory disorder has fundamentally transformed contemporary dermatologic research and clinical practice. Increasing recognition of distinct cytokine signatures, neuroimmune interactions, epithelial alarmin pathways, and molecular endotypes has accelerated the development of biomarker-driven precision medicine strategies and targeted therapeutic innovation.

Future integration of immunological profiling, multi-omics technologies, artificial intelligence, and individualized therapeutic algorithms may substantially improve disease stratification, therapeutic responsiveness, and long-term patient outcomes. However, successful implementation of precision medicine in AD will require continued interdisciplinary collaboration, biomarker standardization, validation of molecular endotypes, and expansion of clinically accessible monitoring tools.

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Ultimately, the future management of AD will likely depend on the ability to dynamically integrate clinical phenotypes with evolving molecular signatures in order to provide highly individualized, mechanism-based therapeutic interventions tailored to each patient's unique immunological profile.

8. Conclusions

AD is increasingly recognized as a highly heterogeneous systemic inflammatory disorder that extends far beyond epidermal barrier dysfunction. Advances in molecular immunology have substantially improved understanding of the complex cytokine networks involved in disease pathogenesis and have highlighted the central role of immune dysregulation, neuroimmune activation, and epithelial-derived inflammatory signaling in shaping disease severity, chronicity, and therapeutic responsiveness. While IL-4 and IL-13 remain the dominant drivers of type 2 inflammation in AD, emerging cytokines, including IL-31, IL-33, IL-22, TSLP, and OX40/OX40L signaling pathways, have demonstrated important contributions to pruritus, epidermal remodeling, chronic inflammation, and disease heterogeneity. Comparative evaluation of classical and emerging cytokines may therefore improve immunological endotyping and facilitate identification of clinically relevant biomarkers associated with disease severity and treatment response. The rapid expansion of targeted therapies, including biologic agents and JAK inhibitors, has fundamentally transformed the therapeutic landscape of AD and represents one of the clearest applications of precision medicine in dermatology. Integration of cytokine profiling, biomarker identification, and molecular endotyping into therapeutic decision-making may support increasingly individualized treatment strategies and optimize long-term disease control. The conceptual framework proposed in this review integrates immunopathogenesis, biomarker-driven immunological profiling, molecular endotypes, and targeted therapeutic innovation within a precision medicine model for AD. Future advances in transcriptomics, multi-omics technologies, and predictive biomarker development are expected to further refine personalized therapeutic approaches and improve clinical outcomes. Ultimately, continued integration of immunological profiling with mechanism-based therapies may facilitate the transition from generalized empirical management toward truly individualized care for patients with AD.

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