Research Article

The Neuro-Immune-Barrier Axis in Atopic Dermatitis: Pathophysiologic Insights and Targeted Therapeutic Breakthroughs

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ABSTRACT

Atopic dermatitis (AD) is an inflammatory skin condition that lasts for a long time and causes the skin's protective barrier to break down, leading to immune dysregulation and constant itching. In this review, we look at the neuro-immune-barrier axis that is involved in the development of Atopic dermatitis (AD), specifically at abnormalities in the barrier, type 2 inflammation, microbial dysbiosis, and neuronal sensitization. Flaws in filaggrin, epidermal lipids, and tight junctions elevate transepidermal water loss and promote allergen infiltration. Epithelial alarmins facilitate type 2 immune responses, especially through interleukin (IL)-4 and IL-13, whereas IL-31 and additional neuroimmune factors play a role in persistent pruritus and the itch-scratch cycle. The proliferation of Staphylococcus aureus intensifies inflammation and compromises barrier integrity. Targeted treatments, such as biologics and Janus kinase inhibitors, have enhanced disease management; nevertheless, ongoing pruritus, inconsistent treatment outcomes, and long-term safety issues persist. Innovative approaches, including aryl hydrocarbon receptor agonists, OX40/OX40L-targeted treatments, microbiome-centric interventions, and biomarker-driven precision medicine, could present novel therapeutic avenues. Improving long-term disease control and patient quality of life and supporting the development of personalized treatments could be achieved by understanding the interactions between neural, immune, microbial, and epidermal components.

Keywords: Atopic dermatitis, neuroimmune crosstalk, epidermal barrier dysfunction, chronic pruritus, skin microbiome, targeted therapy.

INTRODUCTION

Atopic dermatitis (AD) signifies a fundamental transformation in dermatological comprehension, evolving from a fundamental perspective of eczema to a multifaceted, systemic condition characterized by the Neuro-Immune-Barrier Triad. This triad embodies the reciprocal and self-perpetuating relationships between skin barrier impairment, immune system dysregulation, and neural hyperreactivity [1,2]. Historically, the etiology of AD was disputed through two opposing theories: the "outside-in" model, which suggested that primary barrier deficiencies permit environmental allergens to infiltrate and incite inflammation, and the "inside-out" model, which contended that inherent immune dysfunction leads to barrier failure [3,4]. Recent studies have integrated these perspectives, revealing that barrier dysfunction and immune activation occur simultaneously, mutually enhancing each other, and are further complicated by significant neuroimmune interactions [5,6].

The clinical impact of AD is significant, influencing around 171 million people worldwide, which constitutes 2.23% of the global population. Atop the hierarchy of skin disorders, atopic dermatitis (AD) holds the greatest disease burden as indicated by disability-adjusted life-years (DALYs), primarily owing to the persistent and intense itching that defines the ailment. Pruritus in atopic dermatitis is not simply a symptom; it is a fundamental catalyst of the disease, frequently diminishing quality of life more significantly than the observable skin lesions [7]. The pruritus in atopic dermatitis is primarily non-histaminergic, making conventional antihistamines mostly ineffective, and is driven by a complex network of cytokines and neuropeptides that heighten the sensitivity of peripheral nerve endings [8,9]. This persistent itching results in considerable sleep disruption, with nocturnal pruritus exacerbated by the circadian fluctuations in cortisol levels, skin temperature, and cytokine synthesis. The resulting lack of sleep leads to a series of neuropsychiatric comorbidities, such as anxiety, depression, and a heightened risk of attention-deficit/hyperactivity disorder (ADHD) in children [10].

The dynamics of the detrimental cycle initiate with the epidermal barrier. In numerous patients, genetic alterations in the filaggrin gene undermine the skeletal stability of the stratum corneum, resulting in increased transepidermal water loss and an increased skin pH. This faulty barrier permits the penetration of allergens and microbes, including Staphylococcus aureus, which incite the secretion of alarmins such as thymic stromal lymphopoietin (TSLP) from keratinocytes [11,12]. These alarmins trigger a Type 2 immune response, marked by the prevalence of T helper 2 (Th2) cells and the secretion of cytokines including interleukin-4 (IL-4), interleukin-13 (IL-13), and interleukin-31 (IL-31). Significantly, IL-4 and IL-13 not only promote inflammation but also inhibit the expression of filaggrin and other barrier proteins, exacerbating the initial barrier impairment and establishing a positive feedback loop [13,14].

Concurrently, these immune mediators directly interact with the nervous system. IL-31, frequently referred to as the "itch cytokine," attaches to its receptor on sensory neurons, initiating downstream signaling cascades that involve Janus kinase 1 (JAK1) and transient receptor potential (TRP) channels, including TRPV1 and TRPA1. This interaction

diminishes the threshold for neuronal activation, resulting in peripheral sensitization where typically non-itchy stimuli elicit severe itching [15,16]. Additionally, neuropeptides emitted from stimulated nerve endings, like substance P, can further activate immune cells and keratinocytes, connecting neural activity with inflammatory responses [17]. The action of scratching offers momentary alleviation by utilizing pain to inhibit itch signals in the spinal cord, yet it inflicts mechanical harm to the skin barrier, resulting in the release of additional alarmins and sustaining the cycle. This scratch-induced injury additionally encourages epidermal hyperplasia and lichenification, further modifying the skin's neuroimmune environment [18].

The incorporation of the nervous system into this framework emphasizes the concept of the "multi-axial neuro-immune regulatory network," which transcends localized skin interactions to encompass central nervous system processing and the gut-brain-skin axes. Chronic pruritus results in central sensitization, causing the spinal cord and brain to become excessively responsive to itch signals, maintaining the sensation of itch even without peripheral stimuli [19]. This neuroplasticity elucidates the persistent and resistant characteristics of AD pruritus. Recent therapeutic advances, including biologics that focus on the IL-4/IL-13 pathway (e.g., dupilumab) and JAK inhibitors, proficiently disrupt this triad by concurrently diminishing inflammation, reinstating barrier function, and relieving pruritus [20,21]. By inhibiting the particular cytokines that promote immune activation and neuronal sensitization, these therapies disrupt the detrimental cycle, presenting a translational success narrative grounded in the thorough comprehension of the Neuro-Immune-Barrier Triad [22].

STRUCTURAL BARRIER DEFECTS

Gene Mutations (FLG, LOR, and IVL)

The primary genetic factor contributing to epidermal barrier dysfunction in atopic dermatitis (AD) is the presence of loss-of-function (LoF) mutations in the Filaggrin (FLG) gene, situated within the Epidermal Differentiation Complex (EDC) on chromosome 1q21.3 [23,24]. Filaggrin is first synthesized as a substantial precursor, profilaggrin, which is sequestered in keratohyalin granules prior to its progressive enzymatic degradation into active filaggrin monomers. Under physiological circumstances, filaggrin consolidates keratin intermediate filaments into tightly packed parallel bundles, enhancing corneocyte density and structural integrity. The proteolytic breakdown of filaggrin produces Natural Moisturizing Factors (NMFs) mainly hygroscopic amino acids, pyrrolidone carboxylic acid (PCA), and trans-urocanic acid (UCA) that preserve hydration in the stratum corneum (SC) and uphold an acidic pH on the skin's surface [25,26].

In individuals with FLG loss-of-function mutations, a deficiency in filaggrin results in corneocytes that are structurally underdeveloped, inadequately hydrated, and exhibit altered surface characteristics, alongside abnormal retention of corneodesmosomes. This retention interferes with proper desquamation and undermines the integrity of the physical "outside-in" permeability barrier [27]. As a result, FLG null variants lower the barrier for environmental allergens and haptens, heightening the likelihood of early-onset, severe, and chronic atopic dermatitis, along with associated asthma and allergic rhinitis. In addition to FLG, modifications in other EDC-encoded cornified envelope proteins, such as Loricrin (LOR) and Involucrin (IVL), additionally compromise the structural integrity of the SC. Essentially, although genetic mutations are responsible for primary baseline defects, type 2 inflammatory cytokines (IL-4 and IL-13) subsequently diminish the expression of FLG, LOR, and IVL in both affected and unaffected skin through STAT6 signaling, resulting in a functional deficiency of filaggrin even in individuals with a normal genotype [25].

Dysregulation of Tight Junction Proteins

Just beneath the stratum corneum, the nucleated granular layer contains tight junctions (TJs) formed by transmembrane claudins, occludins, and cytosolic zonula occludens (ZOs) which create an uninterrupted paracellular barrier that controls the movement of water, ions, and solutes [5]. In AD, the structural integrity of tight junctions is significantly impaired, evidenced by a pronounced reduction in Claudin-1 (CLDN1), Claudin-4, and Occludin in both affected and unaffected skin. Single nucleotide polymorphisms and loss-of-function variants in CLDN1 are directly associated with the susceptibility to AD and its severity. Reduced Claudin-1 expression undermines epithelial integrity, enhances paracellular permeability to external antigens, and induces atypical keratinocyte proliferation. Moreover, mechanical interference from the itch-scratch cycle diminishes Claudin-1 expression through Akt/Erk signaling pathways. Simultaneously, Th2 cytokines and the TSLP/OX40-OX40L inflammatory pathway further diminish tight junction expression, worsening barrier disruption and promoting systemic allergic sensitization [27,28].

Lipidome Alterations

Reduced Ceramide Levels and Subclass Alterations

The extracellular matrix of the stratum corneum is comprised of a structured lipid bilayer made up of ceramides, free fatty acids (FFAs), and cholesterol in a nearly equal ratio, serving as the protective "mortar" between corneocyte "bricks. In individuals with AD, the overall ceramide
levels are significantly diminished. This decrease is particularly evident in esterified ω-hydroxy ceramides (EOS, EOH, EOP) and non-hydroxy phytosphingosine/hydroxy ceramides (NP, NH). Simultaneously, there exists an unusual change in the distribution of ceramide subclasses, characterized by a relative increase in non-hydroxy sphingosine (NS) ceramides [29,30].

Carbon Chain Length Shortening and ELOVL Inhibition

In addition to quantitative reduction, a significant qualitative abnormality in the Atopic dermatitis lipidome is the shortening of fatty acid acyl chain length. Lipids in a healthy stratum corneum are characterized by a prevalence of very-long-chain fatty acids (VLCFAs ≥ C24) and ultra-long-chain variants, which facilitate compact hydrophobic arrangement and form a dense, well-organized orthorhombic lamellar structure. In AD, inflammatory signals prompt a transition toward short-chain fatty acid variants (C14–C20) within ceramides and free fatty acids. This reduction in chain length diminishes hydrophobic interactions, destabilizes intercellular lipid layers, and alters lipid organization into a less protective, disordered hexagonal phase.This lipid anomaly is fundamentally induced by Th2 cytokine signaling (IL-4 and IL-13), which operates via STAT6-dependent mechanisms to inhibit essential fatty acid elongases, namely ELOVL3 and ELOVL6. Moreover, IL-4 and IL-13 obstruct essential ceramide-synthesizing enzymes, such as sphingomyelinase and β-glucocerebrosidase, thereby exacerbating lipid metabolism and lamellar body excretion [25,30].

Accelerated Transepidermal Water Loss (TEWL)

The permeability barrier is seriously disrupted by the combination of short-chain lipid predominance, subclass imbalances, and total ceramide depletion. Effective stratum corneum water retention is hindered by this structural collapse, which directly causes severe cutaneous xerosis, accelerated Transepidermal Water Loss (TEWL), and increased susceptibility to environmental allergens and irritants [30].

Microbial Dysbiosis

Shift from Commensals to Staphylococcus aureus Overcolonization

Optimal skin sustains a varied microbiome wherein commensal microorganisms—like advantageous Staphylococcus epidermidis and Roseomonas mucosa shield the host by releasing antimicrobial peptides (AMPs), bacteriocins, and protective ceramides, in addition to generating Esp protease to obstruct pathogenic biofilm formation [31]. In AD, the deterioration of barriers, increased skin surface pH, diminished natural moisturizing factors, and depletion of antimicrobial lipids (such as sphingosine) lead to significant microbial dysbiosis. This setting results in a reduction of beneficial commensals and a significant overgrowth of Staphylococcus aureus, which inhabits 60–90% of individuals with atopic dermatitis. Impaired keratinocytes exhibit heightened surface accumulation of fibronectin and fibrinogen, offering direct adhesion points for S. aureus surface adhesins like ClfB and fibronectin-binding proteins [26].

Virulence Factors: Enterotoxins, Superantigens, and Cytotoxins

Upon establishment, S. aureus releases an potent array of virulence factors that promote skin inflammation and intensify barrier disruption:Superantigens and Staphylococcal Enterotoxins: Staphylococcus aureus synthesizes staphylococcal enterotoxins (SEA, SEB, SEC) and Toxic Shock Syndrome Toxin-1 (TSST-1). These superantigens circumvent traditional antigen processing by directly linking Major Histocompatibility Complex (MHC) class II molecules on antigen-presenting cells to specific variable beta (Vβ) regions of T-cell receptors. This induces extensive polyclonal T-cell activation, leading to significant Th2 cytokine secretion (IL-4, IL-13, IL-31), IgE production, and the degranulation of mast cells/basophils accompanied by histamine release.
Alpha-toxin (α-toxin/Hla) and Phenol-Soluble Modulins (PSMs): Alpha-toxin creates cytolytic pores in the membranes of keratinocytes, leading to cell death and initiating IL-1-mediated skin inflammation. Keratinocytes lacking filaggrin demonstrate heightened vulnerability to -toxin-induced cytolysis as a result of diminished sphingomyelinase secretion [32,33,34].

Protease-Mediated Keratinocyte Cleavage and Barrier Destruction

S. aureus systematically breaks down the structural integrity of the epidermis by releasing external bacterial proteases (including V8 serine protease and exfoliative toxins A and B) while concurrently enhancing the activity of endogenous keratinocyte serine protease/kallikrein. These proteases specifically identify and sever crucial cell-adhesion proteins, such as desmoglein-1 found in corneodesmosomes and essential tight junction proteins. This enzymatic disintegration obliterates intercellular connections, deteriorates the stratum corneum, induces loss of

tissue integrity, and hastens the failure of the epidermal barrier [32,33].

TH2 SIGNALING

Epithelial Barrier Injury & Alarmin-Mediated Innate Activation

When the epidermal barrier is compromised due to mechanical trauma (like scratching), environmental allergens, or microbial imbalance, injured keratinocytes emit crucial upstream stress indicators referred to as epithelial alarmins: Thymic Stromal Lymphopoietin (TSLP), Interleukin-33 (IL-33), and Interleukin-25 (IL-25). These alarmins serve as the principal agents that connect the initial breach of physical barriers to subsequent immune activation.TSLP transmits signals via a heterodimeric receptor complex comprising the IL-7 receptor alpha chain (IL-7R) and the TSLP receptor (TSLPR) chain. It primarily influences local dendritic cells (DCs) to enhance the expression of OX40 ligand (OX40L), which then interacts with OX40 on naive CD4+ T cells to guide their differentiation into allergen-specific Th2 helper cells [35,36]. In response to IL-33 and IL-25 stimulation, ILC2s swiftly generate significant quantities of type 2 cytokines (such as IL-4, IL-5, and IL-13) without requiring antigen recognition, simultaneously enhancing OX40L expression on their surface to expedite T-cell priming.TSLP, IL-33, and IL-25 collectively establish an initial pro-inflammatory environment that prepares both innate and adaptive antigen-presenting systems [37,5].

The Central Role of the IL-4/IL-13 Axis

The Th2 Cytokine PathwayThe stimulation of dendritic cells (DCs) and innate lymphoid cells type 2 (ILC2s) initiates a self-reinforcing Th2 cytokine cascade predominantly driven by Interleukin-4 (IL-4) and Interleukin-13 (IL-13). These dual cytokines propel the primary pathological characteristics of acute atopic dermatitis: B-Cell Class Switching to IgE: IL-4 (mainly generated by T helper cells and T follicular helper cells) and IL-13 interact with type I (IL-4Rα/γC) and type II (IL-4Rα/IL-13Rα1) receptors to initiate intracellular JAK1/STAT6 signaling cascades in B cells. This facilitates immunoglobulin class-switch recombination, producing antigen-specific IgE antibodies. The released IgE attaches to high-affinity FcεRI receptors on mast cells, basophils, and inflammatory dendritic epidermal cells (IDECs), priming them for swift degranulation, mediator discharge, and increased allergen uptake during future encounters.

Eosinophil Recruitment and Activation: In conjunction with IL-5, which significantly influences eosinophil development and longevity, IL-4 and IL-13 promote adjacent cells to secrete specific chemokines such as CCL11 (eotaxin-1), CCL26 (eotaxin-3), CCL17 (TARC), and CCL22 (MDC). These chemokines methodically attract circulating eosinophils and Th2 cells to affected skin. Reduction of Epidermal Barrier Proteins: In keratinocytes, IL-4 and IL-13 activate the type II receptor complex (IL-4Rα/IL-13Rα1), initiating JAK1/TYK2/JAK2-STAT6/STAT3 phosphorylation. This signaling cascade directly inhibits the nuclear relocation of OVOL1 (a crucial transcription factor for barrier proteins) and promotes autocrine IL-24 synthesis, resulting in the significant downregulation of structural differentiation proteins—particularly filaggrin (FLG), loricrin (LOR), and involucrin (IVL)23more_horiz.Interruption of Lipid Equilibrium: Alongside the inhibition of structural proteins, the activation of STAT6 leads to the downregulation of fatty acid elongases (ELOVL3 and ELOVL6), causing a shortage of very-long-chain fatty acids (VLCFAs) and a transition toward shorter-chain ceramides. This disrupts the lipid arrangement of the stratum corneum, elevates transepidermal water loss (TEWL), and establishes a feedback mechanism that facilitates additional allergen and microbial infiltration [38,39,40].

Th22/Th1 Axes and Endotypic Heterogeneity

As atopic dermatitis evolves from acute lesions to persistent inflammatory plaques, or when assessing patients with various ancestral endotypes, the immunological profile broadens beyond traditional Th2 signaling.Th22 Pathway Participation and Epidermal Hyperplasia: Chronic dermal inflammation attracts Th22 cells, along with Th17 cells to a lesser extent, are responsible for the secretion of Interleukin-22 (IL-22) [35]. IL-22 interacts with the IL-22R1/IL-10R2 receptor complex on keratinocytes, activating STAT3 to promote keratinocyte hyperproliferation, which leads to significant epidermal acanthosis, elongation of rete ridges, and thickening (lichenification) of persistent lesions. Simultaneously, IL-22 additionally inhibits the terminal differentiation of keratinocytes, exacerbating the filaggrin deficiency induced by IL-4 and IL-13. Persistent Phase Transition Toward Th1 Pathways: In chronic lesions, the secretion of IL-12 by local macrophages and dendritic cells promotes the influx of Th1 cells, resulting in increased levels of Interferon-gamma (IFN-γ) [40,41].

European AD: Predominantly defined by a Th2 and Th22 immune profile, with a significant occurrence of loss-of-function FLG gene mutations present in as many as 50% of European patients. Asian AD Phenotype: Merges vigorous Th2 and Th22 stimulation with a notable expansion of the Th17 axis (marked by increased levels of IL-17A, IL-19, and S100A12) while exhibiting diminished Th1 activity. This results in a composite "AD-psoriasis" endotype, characterized by pronounced psoriasiform epidermal hyperplasia, parakeratosis, and distinctly defined plaques [42]. African/African American AD Phenotype: Exhibits pronounced Th2/Th22 polarization alongside a significant reduction in Th1 and Th17 pathways, characterized by a minimal occurrence of FLG loss-of-function mutations and unique structural changes including marked loricrin depletion [37].

NEURO-IMMUNE CROSSTALK AND THE PATHOPHYSIOLOGY OF CHRONIC PRURITUS

Pruriceptive Sensory Neurons and DRG Activation

Pruriception is chiefly facilitated by a distinct group of unmyelinated C-fibers that possess particular receptors for pruritogenic substances [43]. These sensory neurons arise from the neural crest and conclude in the epidermis, where they are adeptly situated to sense chemical, mechanical, and thermal stimuli [44]. Upon stimulation, these neurons convey signals to the dorsal root ganglion and then to the spinal cord, triggering the sensation of itch [45]. The sensitization of these neurons is a defining characteristic of chronic pruritic conditions, wherein the activation threshold is markedly diminished, resulting in spontaneous itching or increased sensitivity to minor stimuli, referred to as alloknesis [46]. Recent progress in generating peripheral sensory neurons from human induced pluripotent stem cells has enhanced our understanding of the developmental and functional traits of these itch-specific pathways, addressing prior ethical and technical constraints in the examination of human DRG neurons [47].

The Primary "Itch Cytokine"

Interleukin-31 (IL-31) is extensively acknowledged as a principal activator of itching in type 2 inflammatory disorders, establishing a direct connection between immune stimulation and neuronal activation. IL-31 is primarily synthesized by Th2 cells, macrophages, dendritic cells, and eosinophils, and it functions by interacting with a heterodimeric receptor complex consisting of IL-31 receptor A (IL-31RA) and Oncostatin M receptor β (OSMRβ). This receptor complex is abundantly present on sensory neurons, especially in the DRG, enabling IL-31 to directly stimulate these cells without requiring intermediary immune cell involvement [48,49]. The interaction of IL-31 with its receptor activates the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling cascade, particularly engaging JAK1 and JAK2 [35]. This intracellular pathway results in the swift sensitization of transient receptor potential (TRP) channels, including TRPV1 and TRPA1, consequently reducing the firing threshold of sensory neurons. As a result, IL-31 not only triggers acute pruritus but also plays a role in the prolonged sensitization of the nervous system, establishing it as a vital target for treatment. Monoclonal antibodies aimed at the IL-31 receptor or its ligand have shown considerable effectiveness in alleviating pruritus in clinical studies, confirming the pivotal function of this cytokine in the itch pathway [50,51].

Neuronal Hypersensitization

IL-31 functions as a direct pruritogen, whereas Interleukin-4 (IL-4) and Interleukin-13 (IL-13) primarily induce pruritus via neuronal hypersensitivity and impairment of the barrier. These type 2 cytokines communicate via a common receptor complex that includes the IL-4 receptor alpha subunit (IL-4Rα), present on both immune cells and sensory neurons. The stimulation of IL-4Rα on sensory neurons increases their sensitivity to various pruritogens, such as IL-31 and histamine, thus intensifying the itch response [52,1]. Moreover, IL-4 and IL-13 are crucial in impairing the epidermal barrier by diminishing the expression of essential structural proteins like filaggrin, loricrin, and claudin-1. This compromised barrier permits the infiltration of environmental allergens and microbes, subsequently triggering the secretion of further pruritogenic mediators from keratinocytes and immune cells. The combined effects of IL-4 and IL-13—both direct neuronal sensitization and indirect barrier compromise—produce a synergistic influence that perpetuates chronic pruritus. Pharmaceuticals aimed at the IL-4/IL-13 pathway, like dupilumab, have demonstrated a swift alleviation of pruritus, frequently occurring before observable enhancements in skin inflammation, underscoring the immediate influence of these cytokines on neuronal activity [3,53].

TSLP and the TRPA1 Axis

Thymic Stromal Lymphopoietin (TSLP) is a cytokine originating from epithelial cells that serves as a principal regulator of type 2 immune responses and a strong pruritogen [54]. In the realm of pruritus, TSLP is secreted by keratinocytes as a reaction to barrier impairment or environmental stimuli, including particulate matter. In contrast to IL-31, which necessitates a particular receptor complex, TSLP can directly stimulate sensory neurons by attaching to TRPA1 ion channels on C-fibers [55]. This engagement circumvents conventional histamine routes, elucidating the restricted effectiveness of antihistamines in addressing TSLP-induced pruritus. The stimulation of TRPA1 by TSLP induces a calcium ion influx, causing neuronal depolarization and the conveyance of itch signals to the central nervous system. Moreover, TSLP facilitates the transformation of naive T cells into Th2 cells, which enhances the synthesis of IL-4, IL-13, and IL-31, thereby establishing a self-perpetuating cycle of inflammation and itchiness. Focusing on TSLP using monoclonal antibodies has surfaced as a potential therapeutic approach, especially for individuals with severe AD unresponsive to standard therapies [56,57].

Neuropeptides and Neurogenic Inflammation

The communication between the nervous and immune systems is reciprocal, as sensory neurons both receive signals from immune cells and secrete neuropeptides that influence immune reactions. Upon stimulation, pruriceptive

neurons secrete neuropeptides including Substance P (SP) and Calcitonin Gene-Related Peptide (CGRP). These neuropeptides induce neurogenic inflammation by facilitating mast cell degranulation, vasodilation, and the influx of supplementary immune cells to the inflammatory region [19]. Substance P specifically attaches to the neurokinin-1 receptor (NK1R) on mast cells, initiating the secretion of histamine and additional pro-inflammatory agents [8]. CGRP, conversely, increases vascular permeability and facilitates the movement of immune cells, thereby intensifying local inflammation. This mutual engagement between neurons and immune cells establishes a localized inflammatory milieu that perpetuates and amplifies the sensation of itch [58].

The Self-Perpetuating Itch-Scratch Cycle

At the top of these neuro-immune interactions is the itch-scratch cycle, a detrimental feedback loop that defines chronic pruritic conditions. Mechanical scratching offers transient alleviation by stimulating inhibitory pain pathways that diminish itch signals in the spinal cord. Nonetheless, scratching causes physical harm to the skin barrier, resulting in the secretion of alarmins like TSLP, IL-33, and IL-25 from keratinocytes. These alarmins additionally stimulate immune cells and sensory neurons, leading to heightened synthesis of pruritogenic cytokines and neuropeptides [59,1]. Persistent scratching leads to morphological alterations in the skin, such as lichenification and neural hyperplasia, characterized by a heightened concentration of nerve fibers within the dermis. This neural reorganization enhances peripheral sensitization, rendering the skin more vulnerable to pruritic stimuli. Moreover, continuous itch signals induce central sensitization within the spinal cord and brain, leading to modified sensory information processing and increased itch perception. Disrupting this cycle necessitates a comprehensive therapeutic strategy that tackles both the foundational inflammation and neuronal sensitization, emphasizing the significance of focusing on particular cytokines and neuronal receptors in managing chronic pruritus [60,6].

TRANSLATIONAL ADVANCES IN ATOPIC DERMATITIS MANAGEMENT

The therapeutic landscape for atopic dermatitis (AD) has transformed significantly with the introduction of targeted biologics and small molecule inhibitors, transitioning from generalized immunosuppression to the precise modulation of specific inflammatory pathways [61]. These highly advanced therapies predominantly focus on the Type 2 immune pathway, distinguished by the cytokines interleukin-4 (IL-4) and interleukin-13 (IL-13), along with the itch-inducing cytokine interleukin-31 (IL-31) and the intracellular Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway [52,62]. The clinical application of these mechanisms has led to notable enhancements in skin barrier efficacy, swift alleviation of itching, and sustained disease management for individuals with moderate-to-severe atopic dermatitis [63,64].

Comparative Analysis of Targeted Therapies in Atopic Dermatitis

The table presents comparative analysis of the mechanistic functions, clinical effectiveness, and translational benefits of the main targeted therapies that are either approved or in advanced stages of development for Atopic dermatitis.

Therapeutic Class	Agent(s)	Primary Mechanism of Action	Key Clinical & Translational Advantages
IL-4/IL-13 Dual Inhibitor	Dupilumab	Monoclonal antibody binding to the IL-4 receptor alpha (IL-4Rα) subunit, blocking signaling of both IL-4 and IL-13 [63,65].	Restores epidermal barrier integrity by downregulating IL-4/IL-13-driven suppression of filaggrin and other barrier proteins; highly effective across multiple Type 2 comorbidities (e.g., asthma, CRSwNP) [5,36].
Selective IL-13 Inhibitors	Tralokinumab, Lebrikizumab	Monoclonal antibodies specifically neutralizing circulating IL-13, preventing its interaction with the Type II IL-4 receptor complex.	Offers an alternative for patients who may not tolerate dupilumab; lebrikizumab demonstrates rapid onset of action and high efficacy in achieving clear or almost clear skin [21].

IL-31 Receptor Antagonist	Nemolizumab	Monoclonal antibody targeting the IL-31 receptor alpha (IL-31RA), directly interrupting the primary neuro-immune itch pathway [66].	Provides superior and rapid relief from pruritus (itch), addressing the most debilitating symptom of AD; highly effective in breaking the itch-scratch cycle [67,68].

Oral JAK1 Inhibitors	Upadacitinib, Abrocitinib	Small molecules selectively inhibiting JAK1, thereby blocking the intracellular signaling of multiple pro-inflammatory cytokines (IL-4, IL-13, IL-31, TSLP) [69].	Demonstrates the fastest onset of itch relief (often within days) and highest rates of complete skin clearance (EASI 90/100) due to simultaneous blockade of multiple downstream pathways [70,71].
Topical JAK Inhibitor	Ruxolitinib	Topical cream inhibiting JAK1 and JAK2 locally within the skin, reducing local inflammation without significant systemic exposure [64].	Provides targeted relief for mild-to-moderate AD or as an adjunctive therapy, avoiding the systemic safety monitoring required for oral JAK inhibitors.

IL-4 and IL-13 Axis Modulation: Barrier Recovery and Selective Inhibition

Dupilumab, the first biologic approved for atopic dermatitis, operates by binding to the IL-4Rα subunit, which is common to both the Type I (IL-4 specific) and Type II (responsive to IL-4 and IL-13) receptor complexes [65]. By inhibiting this common receptor, dupilumab proficiently interrupts the downstream STAT6 signaling cascade that propels Type 2 inflammation. A pivotal element of dupilumab's clinical application is its capacity to rejuvenate the epidermal barrier. IL-4 and IL-13 significantly inhibit the expression of essential structural proteins, including filaggrin, loricrin, and claudin-1, resulting in the typical barrier impairment observed in atopic dermatitis. Dupilumab counteracts this suppression, resulting in enhanced skin hydration and diminished transepidermal water loss, which fundamentally transforms the disease course instead of merely alleviating symptoms. Empirical research substantiates that dupilumab facilitates a substantial percentage of patients in attaining Treat-to-Target objectives, encompassing notable decreases in eczema area and severity [72].

Conversely, tralokinumab and lebrikizumab are monoclonal antibodies that specifically attach to and inhibit IL-13, while ostensibly preserving IL-4 signaling. This targeted methodology was established to ascertain whether IL-13 is the primary instigator of skin inflammation in atopic dermatitis. Clinical studies have shown that both substances are remarkably effective in diminishing disease severity and enhancing quality of life. Lebrikizumab, specifically, has demonstrated a positive efficacy profile with a swift onset of action, establishing it as a strong contender within the anti-IL-13 category [21]. The availability of selective IL-13 inhibitors offers healthcare professionals further alternatives for patients who might suffer from adverse effects, like conjunctivitis, linked to extensive IL-4/IL-13 blockade, despite conjunctivitis also being noted with selective IL-13 inhibition [73].

IL-31 Receptor Antagonism

Pruritus, also known as chronic itch, is the defining symptom of atopic dermatitis and is predominantly driven by non-histaminergic mechanisms, making conventional antihistamines mostly ineffective. IL-31, a cytokine primarily generated by Th2 cells, attaches to its receptor complex (IL-31RA and OSMR β) on sensory neurons, thereby directly initiating itch signals. Nemolizumab, an antagonist of IL-31RA, directly disrupts this neuro-immune pathway. Meta-analyses of randomized controlled trials demonstrate that nemolizumab markedly enhances pruritus numerical rating scales and investigator global evaluations, delivering swift and substantial itch alleviation [67]. By precisely focusing on the itch pathway, nemolizumab disrupts the detrimental itch-scratch cycle, thereby facilitating skin barrier repair and diminishing secondary inflammatory stimuli. This method is especially beneficial for individuals suffering from intense, unmanageable itching, and it is currently under investigation for additional pruritic disorders such as prurigo nodularis [74,75].

JAK-STAT Pathway Blockade

Janus kinase (JAK) inhibitors constitute a unique category of therapeutics that function within cells to inhibit the signaling of various cytokines concurrently. Cytokines crucial to the pathogenesis of Atopic dermatitis, such as IL-4, IL-13, IL-31, and thymic stromal lymphopoietin (TSLP), utilize the JAK-STAT pathway to convey their signals from the cell membrane to the nucleus. Oral JAK1-selective inhibitors, including upadacitinib and abrocitinib, impede the phosphorylation of STAT proteins, thus inhibiting the transcription of pro-inflammatory genes [69].

The concurrent inhibition of various upstream cytokines leads to an extraordinarily swift therapeutic effect, with

numerous patients reporting considerable alleviation of itching within days of commencement. Moreover, JAK inhibitors have exhibited enhanced effectiveness in attaining complete or nearly complete skin clearance (EASI 90 and EASI 100) relative to certain biologics in direct and network meta-analyses. Abrocitinib has demonstrated effectiveness in individuals who have not responded to prior systemic treatments, such as biologics and other JAK inhibitors, underscoring its value in resistant cases [70,71]. The extensive mechanism of JAK inhibition requires meticulous patient selection and monitoring for possible adverse effects, including infections and laboratory irregularities, setting their risk-benefit profile apart from more targeted biologics. Topical JAK inhibitors, like ruxolitinib cream, provide a targeted method that reduces systemic absorption, rendering them appropriate for mild-to-moderate conditions or as adjunctive treatment [64].

Future Directions, Bispecific Antibodies and Personalized Medicine

Notwithstanding the efficacy of existing monotherapies, a portion of patients fail to achieve minimal disease activity, necessitating the advancement of next-generation biologics. Bispecific antibodies that concurrently target IL-4R α and IL-31RA seek to merge the barrier-repairing properties of IL-4/IL-13 inhibition with the direct antipruritic effects of IL-31 suppression [40]. Preliminary preclinical and clinical findings indicate that dual-targeting approaches might surpass the constraints of single-pathway inhibition, providing enhanced response rates and thorough symptom management [76]. The ongoing advancement of these targeted therapies highlights the significance of personalized medicine in AD, where treatment choices are progressively informed by distinct phenotypic and endotypic traits, guaranteeing optimal clinical results for diverse patient groups [77,78].

CHALLENGES & FUTURE PERSPECTIVES

The management of atopic dermatitis (AD) encounters numerous challenges such as ongoing itching, restrictions in treatment options, disease relapse, imbalances in the skin microbiome, and variability in clinical presentation. Pruritus can endure even when the skin appears clear,owing to peripheral neuronal sensitization and alterations in the central nervous system, with cytokines like interleukin-31 (IL-31) and thymic stromal lymphopoietin (TSLP) playing a role in neuroimmune communication [79,80]. While targeted therapies, such as aryl hydrocarbon receptor (AhR) agonists like tapinarof, present possible advantages in reestablishing skin barrier function and managing inflammation, their prolonged effectiveness and safety in atopic dermatitis necessitate additional research [81]. Moreover, the OX40/OX40L co-stimulatory pathway plays a role in T-cell activation and longevity, which may lead to chronic inflammation and underscores the necessity for more secure methods aimed at immune memory [82]. Dysbiosis of the skin microbiome, especially the proliferation of Staphylococcus aureus, exacerbates barrier impairment, inflammation, and pruritus, rendering the restoration of microbial equilibrium without harming beneficial microbes a significant therapeutic obstacle [84]. Moreover, discrepancies in immune pathways and neuroimmune mechanisms among individuals result in diverse treatment outcomes, highlighting the necessity for personalized therapeutic strategies and biomarker-driven methodologies to enhance sustained disease management.

Further research in atopic dermatitis (AD) should concentrate on formulating targeted and individualized treatment approaches to enhance disease management and prevent relapse. Neuroimmune-targeted treatments that adjust interleukin-31 (IL-31) signaling and neuronal sensitization could potentially reduce chronic itching, even in the absence of visible skin inflammation [2]. In a similar vein, aryl hydrocarbon receptor (AhR) agonists and sophisticated topical preparations present opportunities for reinstating skin barrier integrity while mitigating inflammation [85]. Employing next-generation inhibitors that target the OX40/OX40L pathway with enhanced safety profiles could facilitate prolonged disease management by adjusting pathogenic T-cell responses and immune memory [86]. Microbiome-centric strategies, such as bacteriophage therapy, live biotherapeutics, and pH-adjusted topical formulations, merit additional research to manage Staphylococcus aureus proliferation and reestablish microbial equilibrium [87]. Moreover, precision medicine strategies utilizing biomarkers linked to IL-31, IL-4, and IL-13 signaling could enhance personalized treatment choices, optimize therapeutic results, and reduce unwarranted exposure to systemic therapies [88]. Together, these emerging strategies may advance the development of safer, more effective and individualized approaches to long-term AD management.

CONCLUSION

Atopic dermatitis (AD) involves a complex interplay of epidermal barrier impairment, immune system irregularities, microbial dysbiosis, and neural sensitivity. Anomalies in epidermal proteins, lipids, and tight junctions facilitate allergen infiltration and inflammation, whereas type 2 cytokines, especially interleukin (IL)-4 and IL-13, exacerbate barrier dysfunction. IL-31 and various neuroimmune factors play a role in enduring pruritus and the itch-scratch cycle, resulting in chronic inflammation and disease relapse. Targeted biologics and Janus kinase inhibitors have enhanced the management of atopic dermatitis; however, ongoing symptoms, inconsistent treatment responses, financial implications, and long-term safety issues remain significant challenges. Neuroimmune pathway targeting

therapies, skin barrier strengthening therapies, and microbial balance restoration therapies should all be part of future research. Novel methodologies encompass aryl hydrocarbon receptor agonists, OX40/OX40L-targeted treatments, and microbiome-based strategies. Moreover, biomarker-driven precision medicine could facilitate personalized therapy. Additional longitudinal research and comparative clinical trials are crucial to determine the effectiveness and safety of treatments. Incorporating these methodologies could enhance long-term disease management, diminish relapse rates, and elevate patients' overall well-being.

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