Volume 4, Issue 5, May 2026 ISSN (E): 2938-3765

IMMUNE-MEDIATED PATHOGENETIC MECHANISMS OF ATOPIC DERMATITIS IN CHILDREN

Sobirjonova Shakhzodakhon Gofforjon kizi
Fergana Medical Institute of Public Health
Assistant of the Department of Dermatovenereology and Allergology

Abstract
Atopic dermatitis (AD) affects up to 20% of children globally and is the most prevalent chronic inflammatory skin disease in pediatric populations. Its pathogenesis is governed by a bidirectional interaction between innate and adaptive immune dysfunction: keratinocyte-derived alarmins (TSLP, IL-33, IL-25) prime type 2 innate lymphoid cells and Th2 lymphocytes, which produce IL-4, IL-13, IL-31, and IL-5, driving IgE class switching, eosinophilia, barrier disruption, and neurogenic pruritus through JAK1-mediated signaling cascades.

Keywords: atopic dermatitis, Th2 lymphocytes, interleukin-4, interleukin-13, IgE hypersensitivity, type 2 innate lymphoid cells, TSLP alarmin, filaggrin deficiency, eosinophilia, JAK/STAT pathway, Staphylococcus aureus colonization, IL-31 pruritus, SCORAD index, epidermal differentiation complex, pediatric immunology

Introduction

Atopic dermatitis is the most common chronic inflammatory skin disease in childhood, with a global prevalence reaching 15-20% among children under the age of 14 and approximately 25% in certain high-income populations. The condition typically manifests within the first two years of life - in 60% of affected individuals before twelve months of age - and its onset in early childhood carries prognostic significance far beyond the skin: longitudinal cohort studies confirm that AD initiates the so-called "atopic march," in which progressive sensitization leads to food allergy in 35% of children with moderate-to-severe disease, followed by allergic asthma in 30-40% and allergic rhinoconjunctivitis in up to 66% by school age. Despite its clinical familiarity, the immunopathogenesis of pediatric AD is considerably more complex than a simple Th2-dominant hypersensitivity reaction. The disease integrates genetic susceptibility, epidermal barrier insufficiency, dysregulated innate immune signaling, maladaptive adaptive immune activation, microbial dysbiosis, and aberrant neuroimmune communication into a self-reinforcing inflammatory circuit. A clear understanding of each of these components and the molecular pathways connecting them is essential for selecting appropriate therapeutic targets and for anticipating the natural trajectory of disease in individual pediatric patients.

Literature review

The foundational understanding of AD immunopathogenesis in children was established through the early work of Leung and Bieber, who identified the Th1/Th2 imbalance as the core immunological

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aberration. Subsequent refinements have been contributed by Guttman-Yassky et al., whose transcriptomic profiling of pediatric AD skin lesions demonstrated a more pronounced Th2/Th22 bias in children compared with adults, with relatively less Th1 polarization, explaining the distinct clinical phenotype of infantile disease. The pivotal roles of IL-4 and IL-13 in epidermal barrier disruption and IgE class switching were quantitatively defined in a series of mechanistic studies consolidated in a comprehensive review by Cabanillas et al. (2022). The alarmin cascade - TSLP, IL-25, and IL-33 - as the upstream initiator of innate type 2 responses was described by Ziegler and Artis, with subsequent clinical validation through trials of anti-TSLP agents. Correlation between pediatric disease severity (SCORAD index) and quantitative immunological parameters was established in a prospective study of 345 children by Laske et al., which confirmed a significant positive correlation between SCORAD and serum IgE levels ($R = 0.31$, $p < 0.001$). The role of Staphylococcus aureus colonization as both a consequence and a driver of immune dysregulation in AD children was reviewed comprehensively by Totté et al. and Geoghegan et al. Together, these sources provide the mechanistic and clinical quantitative framework synthesized in this article.

Methodology

A structured narrative review was conducted. Databases searched included PubMed/MEDLINE, Scopus, Web of Science, Cochrane Library, and eLIBRARY.ru, covering publications from January 2010 through April 2025, with priority given to studies published after 2018. Key search terms used were: "atopic dermatitis children pathogenesis," "pediatric AD Th2 immune mechanism," "ILC2 atopic dermatitis," "TSLP IL-33 IL-25 alarmin skin," "IL-4 IL-13 filaggrin barrier," "IgE eosinophil SCORAD pediatric," "Staphylococcus aureus AD colonization children," "JAK STAT atopic dermatitis signaling," and "IL-31 pruritus neuroimmune." Studies were included if they reported original experimental or clinical data on immunological parameters in pediatric AD patients, defined as patients aged 0-18 years, or if they provided mechanistic evidence directly applicable to this age group. In vitro studies were included where they provided quantitative cytokine or enzyme expression data not available from clinical datasets. Patient cohort characteristics in key referenced studies. Across the principal referenced clinical datasets, the pediatric AD population showed the following characteristics: mean age of disease onset of 4.55 years (range 0.5-12 years); male-to-female ratio of approximately 1:1.4 in childhood AD; family history of atopy present in 55-75% of patients; comorbid food sensitization in 38.8-90.7% depending on disease severity; comorbid bronchial asthma in 30-54%; and comorbid allergic rhinitis in 45-66%.

Immunological assessment parameters used. Serum total IgE levels were measured by chemiluminescent immunoassay; age-adjusted upper normal limits used were: <1 year 15 IU/mL, 1-5 years 60 IU/mL, 6-10 years 90 IU/mL. Absolute eosinophil counts (AEC) were obtained from complete blood counts; normal range defined as 100-450 cells/μL. Blood CD4 Th2 cell proportions, IL-4 and IL-13 CD4 cell fractions, and TSLP serum levels were assessed by flow cytometry and ELISA in experimental cohorts. Disease severity was quantified using the SCORAD index (range 0-103; mild <25, moderate 25-50, severe >50) and the EASI (range 0-72). Three interlocking immune pathways were evaluated: (1) the innate alarmin-ILC2 axis initiating type 2 polarization; (2) the adaptive Th2 cytokine network driving IgE production, eosinophil recruitment, and barrier suppression; (3) the JAK1/JAK2-STAT6 signal transduction cascade mediating the biological effects of IL-4 and IL-13 at the level of the keratinocyte and the sensory neuron.

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Results

Epidemiological and clinical immunological data. In the largest pediatric cohort studied for immunological correlates of disease severity (n = 304 patients, mean age 6.3 years), a significant negative correlation was established between SCORAD score and age at disease onset ($r = 0.474$, $p < 0.001$), confirming that earlier onset predicts greater immunological dysregulation and clinical severity. Food sensitization rates were dramatically higher in moderate-to-severe disease (90.7%) compared with mild disease (23.1%), $p < 0.001$. Among 395 pediatric AD patients assessed for serum immunological markers, total serum IgE levels were markedly elevated above age-adjusted norms, with a mean value of 1,127.11 731.69 IU/mL; 65.9% of patients demonstrated abnormal IgE elevation. Absolute eosinophil counts exceeded the normal range in 69.7% of patients, with a mean AEC of 1,004.1 596.2 cells/μL (range 325-2,510). A significant correlation between SCORAD and serum IgE was confirmed across cohorts ($R = 0.31$, $p < 0.001$), while children with high-SCORAD disease showed significantly more frequent sensitization to aeroallergens compared with low-SCORAD patients ($p < 0.02$). Innate immune activation - the alarmin cascade. The initiating event in pediatric AD lesional development is physical disruption of the epidermal barrier - driven by filaggrin (FLG) gene mutations present in 30-40% of extrinsic AD patients and amplified by environmental irritants and S. aureus-derived proteases - which triggers the release of three epithelial alarmins from stressed keratinocytes: TSLP, IL-25 (also known as IL-17E), and IL-33. TSLP, binding to the heterodimeric TSLPR/IL-7Rα receptor complex on dendritic cells, drives their maturation into OX40L inflammatory DCs that prime naïve CD4 T cells toward a Th2 phenotype. Simultaneously, IL-33 activates tissue-resident type 2 innate lymphoid cells (ILC2s) via the ST2 receptor, inducing rapid secretion of IL-5 and IL-13 in a T cell-independent manner. Cutaneous ILC2s express relatively low levels of ST2 compared with pulmonary ILC2s, but markedly upregulate IL-18R1, indicating that IL-18 - released during keratinocyte mechanical injury from scratching - serves as a particularly important ILC2-activating signal in pediatric skin lesions. This innate inflammatory burst establishes the cytokine milieu that subsequently recruits and polarizes adaptive immune cells.

Adaptive immune activation - Th2 cytokine network. CD4 memory Th2 cells, differentiated under the influence of IL-4 and TSLP-conditioned DCs, constitute the dominant adaptive immune effector population in acute pediatric AD lesions. These cells secrete IL-4, IL-13, IL-31, and IL-22 in a coordinated fashion. IL-4 and IL-13 operate through two converging mechanisms with respect to epidermal barrier integrity: (1) they suppress transcription of FLG, loricrin, and involucrin - the principal structural proteins of the stratum corneum - in keratinocytes via STAT6-dependent chromatin remodeling; (2) they inhibit sphingomyelinase (SMASE) mRNA expression by 50% and glucocerebrosidase (GBA) by 70%, directly depleting stratum corneum ceramide levels and increasing transepidermal water loss (TEWL). IL-4 additionally promotes IgE class switching in B cells by providing the co-stimulatory signal for isotype recombination to the ε heavy chain, while IL-5 acts on eosinophil precursors in bone marrow to expand and mobilize the eosinophil pool. In children with AD, CD4 IL-4 and CD4 IL-13 T cell fractions in peripheral blood are significantly elevated compared with non-atopic controls, correlating with SCORAD severity. IL-31 and neuroimmune pruritus signaling. IL-31, produced primarily by CLACD4 Th2 cells in lesional skin, acts on sensory dorsal root ganglion neurons expressing IL-31RA/OSMR heterodimeric receptors. Receptor binding activates JAK1 kinase signaling in sensory fibers, transmitting itch signals to the

central nervous system. In pediatric AD, IL-31 levels in lesional skin biopsies and serum correlate directly with SCORAD-derived itch subscores. The itch-scratch cycle generated by this neuroimmune loop is not merely symptomatic: mechanical skin trauma from scratching induces additional keratinocyte alarmin release (particularly IL-33 and IL-18), amplifying the innate immune cascade and sustaining the self-reinforcing inflammatory circuit. Staphylococcus aureus - immunological disruption. S. aureus colonizes lesional skin in approximately 90% of children with AD, compared with 5-30% of healthy pediatric controls. Its exotoxins - particularly staphylococcal enterotoxins A and B (SEA, SEB) - act as superantigens, cross-linking MHC class II molecules with Vβ-specific T cell receptors on a scale that activates 5-30% of all T cells simultaneously, bypassing antigen-specific restriction. This superantigenic stimulation drives massive IL-4 and IL-13 secretion, further potentiating Th2 polarization and IgE synthesis. Separately, α-toxin (α-hemolysin) induces keratinocyte apoptosis through intrinsic caspase activation and cytochrome c release, directly worsening barrier disruption. IL-31 levels are further elevated in S. aureus-colonized AD skin, amplifying itch intensity and the scratch-induced secondary alarm response. JAK/STAT signal transduction. The biological effects of IL-4 and IL-13 on keratinocytes, B cells, and sensory neurons are mediated through the JAK1/JAK2-STAT6 axis. IL-4 binding to the type I receptor complex (IL-4Rα/γc) or the type II complex (IL-4Rα/IL-13Rα1) phosphorylates JAK1 and TYK2, activating STAT6, which translocates to the nucleus and suppresses barrier gene expression while upregulating IgE heavy chain germline transcription in B cells. IL-13, operating exclusively through the type II receptor, achieves equivalent STAT6 activation in keratinocytes and is increasingly recognized as the dominant cytokine mediating chronic barrier disruption - IL-13 mRNA and protein levels are consistently higher than IL-4 in both lesional and non-lesional AD skin in pediatric patients.

Discussion

The immune pathogenesis of pediatric AD cannot be adequately framed as a simple Th2 allergic reaction. The data reviewed here reveal a cascade architecture in which barrier failure, innate immune alarmin secretion, ILC2 activation, Th2 polarization, IgE-mediated sensitization, eosinophil recruitment, IL-31-driven neuroimmune pruritus, and microbial superantigen-mediated immune amplification operate in a mutually reinforcing network. Each node in this network both responds to and reinforces the others, explaining why the disease is so difficult to control with single-target interventions directed at any one pathway.

The quantitative immunological data from pediatric cohorts are instructive in this regard. The mean total serum IgE of 1,127 IU/mL in pediatric AD patients - compared with age-adjusted norms below 90 IU/mL - reflects not simply increased B cell activity but the cumulative downstream effect of sustained IL-4 and IL-13 cytokine production by a large, activated Th2 cell pool. The 90.7% rate of food sensitization in moderate-to-severe pediatric AD confirms that the compromised epidermal barrier is functioning as an active route of allergen entry and sensitization, generating systemic immune responses to food proteins that would not penetrate an intact stratum corneum. The age dependence of disease severity (earlier onset predicts higher SCORAD, $r = 0.474$, $p < 0.001$) has an important immunological interpretation: infants possess a naturally Th2-skewed immune environment as a physiological baseline, reflecting evolutionary pressure to maintain maternal-fetal tolerance and to resist parasitic infection. In the context of AD-predisposing filaggrin mutations and microbial colonization, this pre-existing Th2 bias is dramatically amplified, explaining why infantile

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AD is characterized by more intense inflammatory activity and higher IgE levels relative to later-onset disease. From a therapeutic standpoint, these mechanistic data provide a clear rationale for targeting the IL-4Rα axis with dupilumab - which simultaneously neutralizes both IL-4 and IL-13 signaling - as the most logically comprehensive pharmacological strategy currently available. The 91.3-91.8% SCORAD-50 rates achieved with dupilumab in pediatric patients at week 52 confirm that blocking the shared receptor of both principal Th2 cytokines normalizes the immune aberration at its most downstream measurable expression. The residual disease activity in approximately 8-9% of dupilumab-treated children may reflect Th17 or Th22 contributions to the inflammatory phenotype, suggesting that molecular phenotyping of pediatric AD could further individualize and improve therapeutic outcomes.

Pediatric atopic dermatitis is driven by a multilayered immune cascade initiated by epidermal barrier failure and alarmin-mediated ILC2 activation, amplified by Th2-derived IL-4, IL-13, and IL-31 through JAK/STAT signaling, and perpetuated by IgE sensitization, eosinophilia, and S. aureus superantigen stimulation. Elevated serum IgE exceeding 1,100 IU/mL, eosinophilia in nearly 70% of patients, and SCORAD correlating directly with immunological severity underscore the quantifiable nature of this immune dysfunction and the precision required in its therapeutic management.

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