

**THYMIC STROMAL LYMPHOPOIETIN-MEDIATED EPITHELIAL
ALARMIN SIGNALING AND SKIN-IMMUNE AXIS CROSSTALK IN
THE PATHOGENESIS OF PEDIATRIC ATOPIC DERMATITIS**

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Annotation: *This investigation examines the role of epithelial-derived alarmin cytokines - thymic stromal lymphopoietin, interleukin-25, and interleukin-33 - in orchestrating the skin-immune axis dysregulation that underlies pediatric atopic dermatitis pathogenesis. Through immunohistochemical quantification of alarmin expression, dendritic cell subset characterization, and mechanistic correlation with clinical severity indices, the study establishes alarmin-driven innate immune activation as the critical upstream amplifier connecting barrier dysfunction to adaptive Th2 inflammation in children.*

Keywords: *thymic stromal lymphopoietin, interleukin-33, interleukin-25, alarmin cytokines, epithelial barrier signaling, type 2 innate lymphoid cells, dendritic cell polarization, skin-immune axis, pediatric inflammation, Th2 amplification.*

Nowadays, the conceptual paradigm governing pediatric atopic dermatitis pathogenesis has evolved substantially beyond the classical Th1/Th2 imbalance model, incorporating the newly characterized alarmin cytokine network through which structurally damaged keratinocytes directly instruct the innate and adaptive immune systems to adopt a Th2-dominant inflammatory program. Thymic stromal lymphopoietin, interleukin-33, and interleukin-25 - collectively designated epithelial alarmins or type 2 cytokine initiators - are



released by keratinocytes in response to physical disruption, microbial products, and proteolytic allergens, and function as the earliest immunological signals linking environmental barrier insult to downstream lymphocytic inflammation. Notably, thymic stromal lymphopoietin expression is detectable in the epidermis of neonates with filaggrin loss-of-function mutations even before clinical atopic dermatitis manifestation, positioning alarmin signaling as a pre-clinical pathophysiological event with preventive therapeutic implications.

Thymic stromal lymphopoietin is produced by stressed keratinocytes upon protease-activated receptor 2 stimulation by serine proteases present in environmental allergens, house dust mite fecal particles, and *Staphylococcus aureus* virulence factors including V8 protease and staphopain. Upon secretion, thymic stromal lymphopoietin acts on dermal conventional dendritic cell type 2 populations, inducing their upregulation of the Th2-polarizing surface molecules OX40 ligand and programmed death ligand 2 while simultaneously suppressing interleukin-12 production, thereby converting dendritic cells from Th1-promoting to Th2-instructing antigen-presenting cells. Concurrently, thymic stromal lymphopoietin directly activates type 2 innate lymphoid cells residing in the dermis, inducing rapid interleukin-4, interleukin-5, and interleukin-13 secretion that amplifies the Th2 response independently of adaptive T-lymphocyte activation and within hours of barrier insult.

Immunohistochemical quantification in lesional scalp and flexural skin biopsies from 82 pediatric patients demonstrated thymic stromal lymphopoietin protein expression elevated 7.2-fold above healthy control values, with the highest expression recorded in infants aged 6-18 months presenting with early-onset facial and scalp involvement. Interleukin-33 nuclear-to-cytoplasmic translocation, indicating active secretory release from keratinocytes, was confirmed in 84.1% of lesional biopsy specimens. Double immunofluorescence staining established spatial co-localization of thymic stromal lymphopoietin-

expressing keratinocytes with OX40 ligand-positive dendritic cells at the dermo-epidermal junction, confirming functional cellular proximity between alarmin source and innate immune target. Dermal type 2 innate lymphoid cell density quantified by flow cytometry of skin digests correlated significantly with both lesional thymic stromal lymphopoietin concentration and serum interleukin-13 levels, establishing the alarmin-innate lymphoid cell-Th2 cytokine cascade as a quantitatively coherent and clinically relevant mechanistic pathway. Children with the highest tertile of thymic stromal lymphopoietin expression demonstrated significantly faster progression to respiratory atopic disease at the 24-month follow-up assessment, underscoring the predictive value of alarmin quantification for atopic march risk stratification.

Epithelial alarmin cytokines, principally thymic stromal lymphopoietin and interleukin-33, constitute the mechanistically upstream mediators linking epidermal barrier dysfunction to innate and adaptive Th2 immune amplification in pediatric atopic dermatitis, identifying alarmin pathway blockade as a scientifically compelling preventive and therapeutic target for early intervention and atopic march interruption.

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