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WHAT'S NEW

IL-9 and IL-18 — A new axis in atopic dermatitis inflammation

This section is a contribution from the SKINTEGRITY.CH interdisciplinary research consortium. The collaborative work was performed by Stefanie Schärli and colleagues, led by SKINTEGRITY.CH Principal Investigator Prof. Christoph Schlapbach, with colleagues in Australia, Denmark, Germany, Switzerland and The Netherlands.

Maarten Schledorn

A New Perspective on AD Inflammation

Atopic dermatitis (AD) is a chronic inflammatory skin disease that affects millions worldwide, characterized by skin barrier dysfunction, intense itching and reduced quality of life. While advances in biologics have improved treatment, a subset of patients still experience inadequate disease control. Hence, research has focused on identifying novel upstream regulators of T_H2-driven inflammation that could be targeted for more effective interventions.

A study by Schärli et al., published in the *Journal of Allergy and Clinical Immunology*, has identified IL-18 as a previously unknown upstream regulator that exacerbates AD inflammation. These insights offer a new perspective on the disease and pave the way for novel therapeutic approaches.

IL-18 – An Emerging Player in AD Pathogenesis

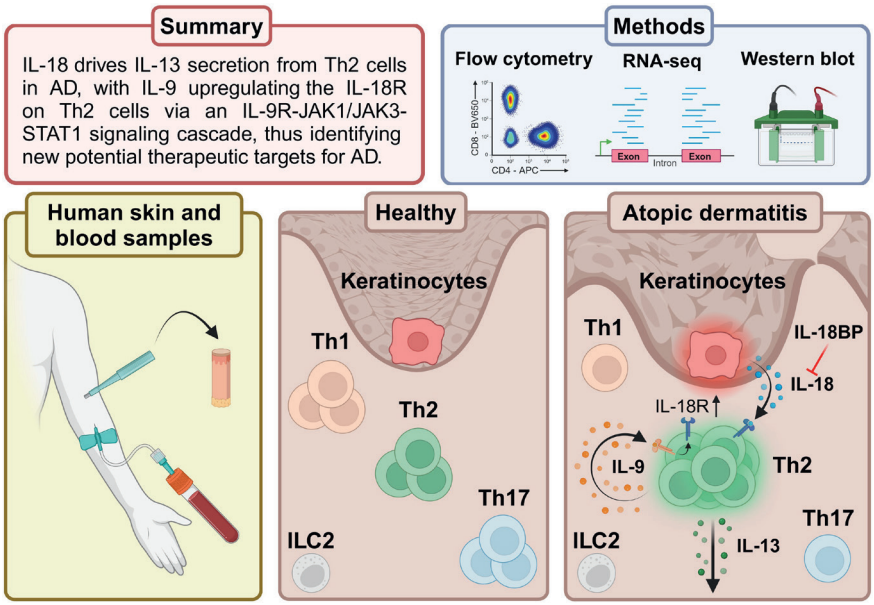
IL-18, a member of the IL-1 cytokine family, is known for its proinflammatory role in type 1 immune responses. Although it has been implicated in various inflammatory skin conditions, its precise function in AD was unclear. Schärli et al. found that IL-18R expression is significantly upregulated on T_H2 cells in both blood and lesional skin of AD patients.

This discovery is particularly noteworthy because T_H2 cells are central to AD pathogenesis, producing IL-13 and IL-22 that drive inflammation and impair skin barrier function. The study demonstrated that IL-18 directly stimulates these cells, leading to increased secretion of these key cytokines. However, the effect of IL-18 alone was moderate - until the researchers uncovered the role of IL-9.

IL-9 – The Sensitizing Factor

IL-9, traditionally linked to allergic inflammation, was not previously considered a major player in AD. However, Schärli et al. found that IL-9 upregulates IL-18R expression on T_H2 cells, effectively «priming» them to respond stronger to IL-18 signals.

This is a significant discovery, as it highlights IL-9 as a key amplifier of AD inflammation rather than just a secondary cytokine.



IL-9 sensitizes human T_H2 cells to pro-inflammatory IL-18 signals in atopic dermatitis (AD). *Top left: Summary of findings. Top right: Methods used in the study included flow cytometry, RNA sequencing (RNA-seq), and Western blot analysis. Bottom left: Human skin and blood samples were collected to analyze immune cell responses in AD. Bottom center: In healthy skin, T_H2 cells express minimal IL-18R, leading to limited IL-18-mediated cytokine production. Bottom right: In AD skin, activated T_H2 cells produce IL-9, which enhances IL-18R expression on T_H2 cells, making them more responsive to IL-18. This leads to increased IL-13 secretion, driving inflammation and skin barrier dysfunction. IL-18 binding protein (IL-18BP) neutralizes IL-18 by preventing it from binding to the IL-18R, thereby downregulating IL-13 secretion and modulating inflammation. These findings highlight the IL-9/IL-18 axis as a key driver of AD pathogenesis and a promising therapeutic target. (Abbreviations:* ***AD:*** *atopic dermatitis;* ***IL-18BP:*** *interleukin 18 binding protein;* ***IL-18R:*** *interleukin 18 receptor;* ***ILC:*** *innate immune cell;* ***JAK:*** *janus kinase;* ***STAT:*** *signal transducer and activator of transcription;* ***Th:*** *T helper cell.)*

The IL-9/IL-18 Axis - A Driver of IL-13 and IL-22 Production

The study demonstrated that when T_H2 cells were stimulated with IL-18 alone, they secreted moderate levels of IL-13 and IL-22. However, when IL-18 was combined with IL-9, cytokine production increased dramatically.

IL-13 is a well-known driver of AD, contributing to epidermal thickening, reduced skin barrier function, and itch signaling. IL-22, on the other hand, promotes keratinocyte proliferation and hyperplasia, leading to the characteristic thickened plaques seen in chronic AD. By increasing the secretion of these cytokines, the IL-9/IL-18 axis appears to play a pivotal role in sustaining inflammation in AD lesions.

Potential Therapeutic Implications

Current biologics for AD primarily target IL-4 and IL-13 (such as dupilumab and lebrikizumab) or JAK signaling. However, some patients remain refractory to these treatments, indicating alternative pathways are involved. Targeting the IL-9/IL-18 axis provides a promising new strategy. The study found that neutralizing IL-18 signaling in lesional skin explants from AD patients significantly reduced IL-13 and IL-22 production. Likewise, modulating IL-9 could dampen T_H2 cell sensitization to IL-18, reducing inflammation.

A phase 1b clinical trial of an IL-18-blocking antibody (NCT04 975 438) has shown promising results in moderate-to-severe AD. Meanwhile, IRAK4 inhibitors, blocking IL-18R signaling, are also under investigation.

A Paradigm Shift in AD Research

The identification of IL-9 as a sensitizing factor for IL-18-driven inflammation in AD marks a major advancement in our understanding of the disease. By enhancing IL-18R expression on T_H2 cells, IL-9 helps sustain chronic inflammation in AD. Crucially, these findings highlight IL-18 as a viable therapeutic target, offering new hope for patients unresponsive to current treatments. Shifting the focus on upstream regulators of T_H2 inflammation could lead to more effective and lasting solutions for AD patients.

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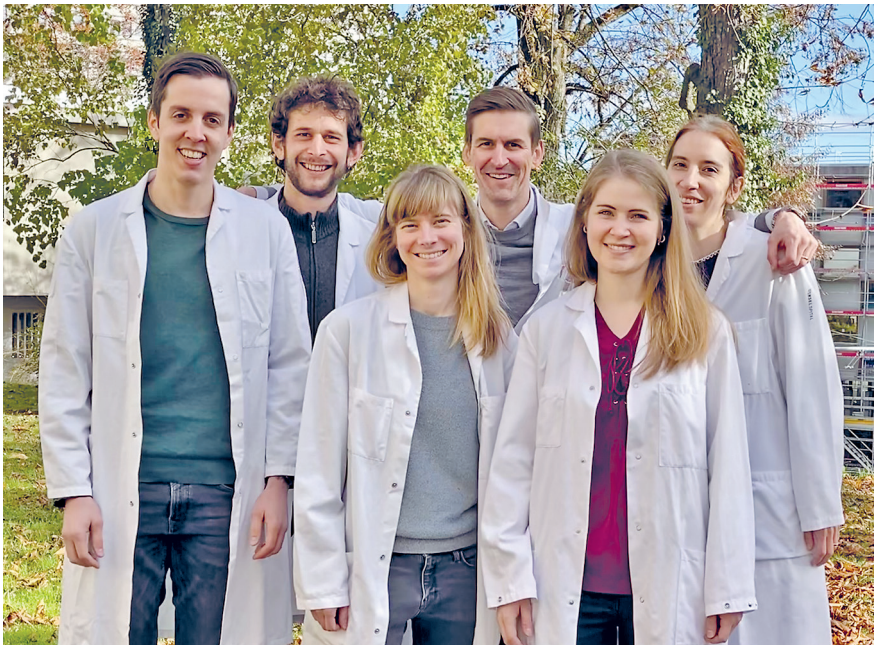

The Schlapbach lab with (from left to right) Fabian Luther, Oliver Steck, Nicole L. Bertschi, Christoph Schlapbach, Stefanie Schärli, Angela Vallone.

Reference

Schärli S, Luther F, Di Domizio J, Hillig C, Radonjic-Hoesli S, Thormann K, Simon D, Rønnstad ATM, Ruge IF, Fritz BG, Bjarnsholt T, Vallone A, Kezic S, Menden MP, Roesner LM, Werfel T, Thyssen JP, Eyerich S, Gilliet M, Bertschi NL & Schlapbach C (2025). IL-9 sensitizes human T_H2 cells to proinflammatory IL-18 signals in atopic dermatitis. J Allergy Clin Immunol, 155(2), 491-504.