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【Overview presentation】

An unbiased tissue transcriptome analysis identifies potential markers for skin phenotypes and therapeutic responses in atopic dermatitis

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Overview presentation	**Objectives** Atopic dermatitis (AD) is a disease with significant interindividual variability in symptoms and severity, making personalized medicine highly necessary. While previous studies have suggested that skin inflammation is mainly driven by type 2 inflammation , recent findings indicate the involvement of other immune pathways, highlighting the complexity of its molecular mechanisms. Moreover, the effectiveness of molecular targeted therapies varies among individuals, and the mechanisms for this variability remain unclear. **Methods** The research team collected 951 full-thickness 1-mm skin biopsy samples from 156 patients with atopic dermatitis (AD) and performed comprehensive gene expression analysis using RNA sequencing. An unsupervised machine learning technique, non-negative matrix factorization (NMF), was applied to identify 29 gene co-expression patterns without relying on prior hypotheses. In addition, cross-sectional analyses of skin symptoms and blood biomarkers measured using the HISCL-5000™ system were conducted, along with longitudinal assessments of the therapeutic response to the molecular targeted drug Dupilumab over a six-month period.

	Results **Gene Pattern Extraction via NMF** Application of NMF to the gene expression data from skin samples identified 29 gene clusters, referred to as "SKIn-Tissue derived Metagenes (SKITm)". **Cross-sectional Study: Associations with Local Skin Symptoms** Analysis of the relationship between specific SKITm and clinical features such as erythema (redness), infiltration (raised skin), lichenification (thickened skin), and excoriation (scratch marks), as well as overall disease severity, revealed that certain gene clusters are associated with specific clinical findings. For example, erythema was linked to SKITm17 (type 2 inflammation) and SKITm10 (type 17 inflammation), while amyloid lichenification was associated with SKITm11 (type 1 inflammation). In addition, blood levels of EDN (eosinophil-derived neurotoxin) correlated with skin SKITm17 (type 2 inflammation), and CCL20 (type 17 inflammation-related cytokine) with SKITm10 (type 17 inflammation). The widely used clinical disease severity marker CCL17 (TARC) was associated with both SKITm17 and SKITm10. **Longitudinal Study: Association between Therapeutic Response to Dupilumab and Molecular Profiles** Dupilumab, a molecular targeted drug against type 2 inflammation, was administered to 24 patients for six months. Patients were classified into early responders, intermediate responders, and poor responders based on treatment outcomes, and their skin gene expression and blood biomarkers were analyzed. In poor responders, elevated expression of SKITm10, a newly identified extracellular matrix-related gene cluster (SKITm16), and a transcription factor-related cluster (SKITm5) was observed prior to treatment, along with high levels of blood biomarkers such as IL-22, IL-18, and CCL20. During treatment, SKITm17 was rapidly suppressed in all groups, while SKITm10 remained persistently elevated in the poor

	responder group. These findings suggest that in patients where Dupilumab shows limited efficacy, residual inflammatory pathways and tissue-specific gene abnormalities may serve as potential therapeutic targets. **Conclusion** This study revealed part of the molecular pathophysiology underlying the heterogeneity of symptoms and individual differences in treatment response in AD through an unbiased, comprehensive analysis. The identification of gene clusters associated with specific symptoms and predictive biomarkers for treatment response represents a significant step toward personalized medicine. These insights may contribute to diagnostic support, the development of new therapeutic targets, and the application of this method to other skin diseases.
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