

Blood endotypic signature in atopic dermatitis: The challenge in personalized medicine

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Atopic dermatitis (AD) is the most common chronic inflammatory skin disease, and it is challenging to manage. The current understanding of AD pathogenesis is based primarily on the outcomes of immunopathologic and translational studies, which show that AD is characterized by dense cutaneous dendritic cell and T-cell infiltrates, increased detection of inflammatory mediators in affected tissues, and barrier defects that develop primarily or secondary to the downregulation of differentiation proteins and lipids.^{1,2} According to molecular profiling performed in affected skin, AD is associated with a polarized type 2 immune axis. However, studies have increasingly demonstrated that AD is not a homogenous disease. AD presentations are diverse across different populations, and AD may be categorized into multiple clinical phenotypes depending on the underlying molecular signature (endotype).^{3,4}

Precision medicine requires the precise identification of potential targets, and translational research indicates that different populations may be associated with different targets. The development of robust treatment approaches designed for unique populations requires accurate prediction of phenotype-specific responses and may lead to better treatment outcomes. Therefore, careful dissection of the molecular mechanisms underlying AD development and their phenotypic correlations with specific AD presentations are critical for establishing optimal treatment strategies.

Conventional skin transcriptomics or proteomics profiling using skin biopsy samples have been applied for identification of robust biomarkers that can be used to stratify endotypes or as therapeutic indicators⁵; however, skin biopsies are invasive and may not be practical to perform in real-world clinical practice. In contrast, omics-based approaches that can be performed on samples of

peripheral blood may be useful for identifying practical indicators of endotypes or monitoring therapeutic effects.⁶

In this issue of the *Journal of Allergy and Clinical Immunology*, Möbus et al reported a global molecular profiling study conducted on patients with moderate-to-severe AD and healthy controls.⁷ Möbus et al⁷ also compared findings before and after treatment with dupilumab, an IL-4 receptor alpha antagonist. All study subjects were evaluated, and clinical severity was correlated with the findings of whole-blood transcriptomic profiling. Unsurprisingly, the global transcriptome of blood samples from patients with AD presented with highly expressed inflammatory signatures. Moderate-to-severe AD lesions are often widespread, and AD is associated with other nonatopic comorbidities, such as cardiovascular disease or metabolic disorder,^{8,9} leading to characterization of AD as a systemic disease producing inflammatory mediators that can be distantly transported via systemic circulation, thus contributing to end-organ pathologies. Therefore, specific immunologic signatures identified in the peripheral blood might serve as practical indicators that reflect disease severity and treatment response. The heuristic elevated circulation of proinflammatory cytokines that originate in the pronounced cutaneous inflammatory environment of AD lesions has not been fully supported by existing evidence owing to the inconsistent expression of key cytokines reported in both skin and blood samples.⁷

Möbus et al⁷ identified increased levels of circulating myeloid and IL-5–related markers as a hallmark signature in the blood transcriptome of patients with AD. However, the characteristic cutaneous signals associated with type 2 inflammation, including *IL4*, *IL4RA*, *IL13RA1*, *IL31*, *IL31RA1*, and *TSLP*, were not found to differ significantly in the blood transcriptome between patients with AD and healthy controls. Some immune-related molecules demonstrated opposite patterns between blood and skin transcriptomes.⁷ These findings remind us that the circulating biomarkers for use in the monitoring of disease severity or the prediction of treatment response should be selected carefully, as circulating factors do not always parallel those that contribute to cutaneous inflammation.

Blood transcriptomic changes were also evaluated following treatment with dupilumab, which was associated with the downregulation of innate immune responses, including genes involved in neutrophil activation and macrophage differentiation (*LILRA2*, *IL1RN*, *MMP9*, *PRTN3*, *OSM*, *BCL3*, *ORM1*, and *S100A11*) and the upregulation of IgE and natural killer cell signatures (*IGHE*, *KLRF1*, and *KLRC2*).⁷ Although significant relative to pretreatment transcriptome profiles, these changes did not correlate well with clinical severity or posttreatment outcomes. No observable changes in T_H2 cell–related factors were identified despite dupilumab treatment having been reported to reduce T_H2 cell signals. These findings suggest that the blood endotypic signature profiled in patients with AD might provide more information relevant to AD pathogenesis than to predicted treatment outcomes.

Möbus et al⁷ also found differences in eosinophil signaling, which they successfully used to categorize patients with AD

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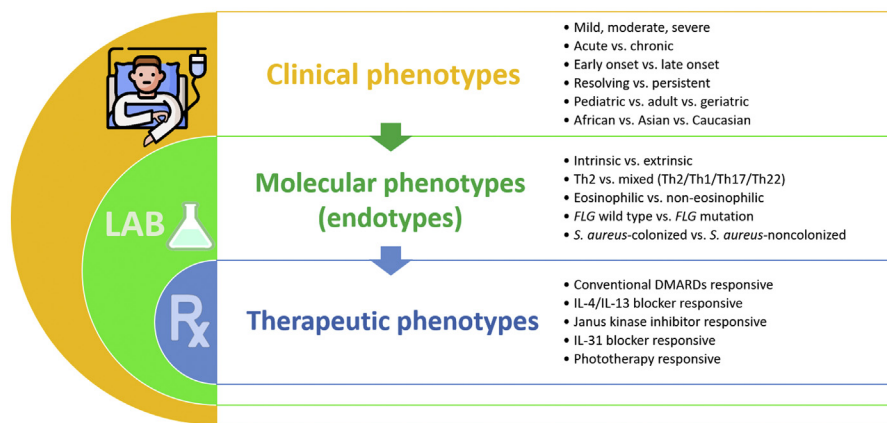


FIG 1. Evolution of AD subtypes. AD is a heterogeneous disease that is clinically characterized by various subtypes based on different population groups. With further understanding of cutaneous pathomechanisms via translational medicine, there is advanced classification of AD by tissue's molecular features (so-called endotypes or molecular phenotypes). However, the assumable correlation of molecular phenotypes with therapeutic responses has not been established. We proposed a hypothetical classification of therapeutic phenotypes that represents a more finely tailored, endotype-driven definition of the disease's variability based on integrated blood and skin transcriptomes. Personalized and precision medicine should therefore stress the need for specific targets with the best value for prediction of treatment outcomes according to their therapeutic phenotypes. *DMARDs*, Disease-modifying anti-rheumatic drugs; *FLG*, filaggrin gene.

into the novel eosinophil-high (EoH) and eosinophil-low (EoL) endotypes.⁷ The EoH endotype was associated with increased immune dysregulation, and a positive correlation between disease activity and IL-5 signals was identified for these patients. The EoL endotype, in contrast, demonstrated little transcriptomic dysregulation, with no association between disease activity and gene expression. In this AD cohort, the endotypic signatures (EoH and EoL subtypes) remained largely unchanged, even following successful treatment with dupilumab, indicating that circulating endotypic signatures reflect pathologic pathways rather than treatment responses. Although the unique molecular features of specific AD endotypes likely have therapeutic implications, they do not guarantee clinical efficacy when targeting designated molecules. This fundamental heterogeneity of AD highlights the importance of recognizing that the response to targeted therapeutics could hypothetically result in classification of patients with AD into distinct therapeutic phenotypes that may not necessarily parallel their underlying molecular endotypes (Fig 1).^{6,10} More finely tailored and more reliable molecular endotypes or laboratory biomarkers are yet to be investigated to guarantee their usefulness toward identification of the effects of specific treatments for AD, which we refer to as practical classification of "therapeutic phenotypes."

Overall, the large-scale study by Möbus et al⁷ evaluating the transcriptomic profiles of blood samples from patients with moderate-to-severe AD demonstrates inconsistencies associated with the leading immunologic biomarkers that can be detected in the blood and skin. Although TH2 cell-related molecules are not significantly expressed in blood samples, a novel eosinophilic subtype could be identified by the blood transcriptome, including the IL-5-related signature, which could serve as an indicator of disease severity. A limitation of this study is the lack of corresponding transcriptomic analyses from matched blood and skin samples obtained from the same individuals. In addition, although effector end products (proteins) are the most representative of the biologic impacts, the valuable correlation between transcriptome and proteome due to posttranscriptional and posttranslational regulation was not

included in the study by Möbus et al.⁷ Another limitation comes from the perception that only a minority of cellular subpopulations mediating AD pathophysiology in the skin recirculate in the blood, reflecting a systemic inflammatory response that is profoundly diluted by the overwhelming majority of the principal circulating blood cells. The simultaneous analysis of transcriptomes and proteomes of the blood and skin from the same individuals would allow us to make more consistent and promising conclusions.

Although the findings of the study by Möbus et al⁷ are not readily applicable to the monitoring of AD disease activity or therapeutic effectiveness, they offer important insights for assessing changes in circulating biomarkers over time and with specific treatments, including for evaluation of how well these changes echo changes in disease severity and treatment response. Similar systemic and cutaneous biomarker studies should be expanded to larger cohorts that include all ethnic and age groups, providing a more comprehensive and universal understanding of AD.

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