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Molecular Insights: Immune and Barrier Dysregulation in Seborrheic Dermatitis

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INTRODUCTION

Seborrheic dermatitis (SD) is a chronic inflammatory skin disease that affects sebaceous areas, typically the face and scalp, with an estimated prevalence of 2% to 5%. It is thought to result from a combination of immune dysregulation, barrier dysfunction, and colonization with *Malassezia* species.[1,2] However, its underlying molecular mechanisms have been incompletely defined, limiting the development of new therapies. As a result, treatment options largely include nonspecific topical antifungals and corticosteroids, with roflumilast 0.3% foam as the only US Food and Drug Administration (FDA)-approved treatment in recent years.[2] In a 2025 study published in *JAAD*, Ungar et al performed non-invasive transcriptomic profiling to characterize gene expression in facial SD.[3] This review summarizes their findings, which provide new insight into SD pathogenesis and support the rationale for emerging immunomodulatory treatments.

Study Overview

The study included 26 adults with mild to severe facial SD and 18 matched healthy controls. Lesional and matched control skin were sampled using sequential tape strips (a non-invasive method for collecting the outer layers of the epidermis, including the stratum corneum and upper granulosum) and analyzed by RNA sequencing. Differentially expressed genes (DEGs) that were significantly up- or downregulated in SD vs controls were identified and grouped by functional gene families and known biological pathways. These were then analyzed using established biological pathway databases and published gene sets to identify enriched pathways among DEGs and assess broader pathway-level activity across all samples. Results were further compared with existing transcriptomic datasets from atopic dermatitis (AD) and psoriasis to contextualize SD within the spectrum of better-characterized inflammatory skin diseases.

Key Findings

1. *Unique Immune Signature:* 1,037 DEGs were identified in SD lesional skin vs controls, demonstrating strong upregulation of genes in the interleukin (IL)23/T-helper (Th)17 and Th22 pathways, including IL-17, IL-23A, IL-22, and IL-36 family members, as well as Th1-related genes (IL1B, OASL), with minimal Th2 involvement. Pathway enrichment analyses further showed significant upregulation of IL-17 signaling, innate immunity (IL-1 signaling, interferon-α/β, neutrophils), and general inflammatory pathways.

2. *Epidermal Barrier Dysfunction:* SD was associated with a broad downregulation of barrier-related genes, including those involved in lipid metabolism (eg, FA2H, ELOVL3, GAL) and tight junction/cell adhesion (eg, CLDN1, GJB3/GJB5). Enrichment analyses further supported the attenuation of lipid metabolism pathways.

3. *SD Disease Severity Correlates with Immune/Barrier Dysregulation:* Higher SD disease severity, as measured by Investigator's Global Assessment (IGA) scores, correlated significantly with increased expression of Th17/Th22 cytokines, T-cell markers (CD3D, CD3G), and general inflammatory genes (PDE10A), and negatively with lipid metabolism genes.

4. *SD Exhibits a Distinct Molecular Profile:* Transcriptomic comparisons revealed a partial overlap between SD, AD, and psoriasis, with SD more closely resembling psoriasis due to shared IL-17 and TNF signaling, while lacking the Th2 polarization characteristic of AD. Barrier-related pathways were attenuated in all three, yet SD showed a distinct overall pattern of immune and barrier dysregulation.

Clinical Implications

This study represents the first and largest transcriptomic analysis of SD, offering key insights into its molecular underpinnings and highlighting the central role of immune dysregulation accompanied by barrier dysfunction. While topical antifungals remain a common treatment, the link between *Malassezia* dysbiosis and disease activity remains incompletely defined. In susceptible individuals, immune reactivity to commensal microbes may exacerbate inflammation.[2,4] This may be analogous to improvement in *S. aureus* colonization after anti-inflammatory treatment with dupilumab in AD.[5] Prior studies suggest that sebocytes in sebaceous glands respond to microbial metabolites by producing proinflammatory cytokines that promote Th17 and Th1 signaling, while microbial enzymes, together with this immune activation, may contribute to lipid metabolism and barrier disruption.[2,4,6] The Th17/Th22-skewed signature identified in this study highlights specific

inflammatory pathways that may confer susceptibility to SD and guide therapeutic intervention.

Targeting these dysregulated immune pathways can offer more effective treatment options than traditional approaches, while avoiding safety concerns associated with topical steroids and improving stewardship of antifungal use in an era of increasing treatment-resistant fungal infections.[7] The upregulation of IL-17, IL-22, and IL-1β aligns with the mechanism of action of topical roflumilast, a phosphodiesterase 4 (PDE4) inhibitor recently FDA-approved for SD, which has demonstrated clinical efficacy and safety, while also offering other potential treatment targets involving specific cytokine inhibition.[8-10] This context illustrates how improved molecular characterization of SD may guide the development of more precise and effective treatment strategies. Finally, this study establishes tape-strip transcriptomics as a feasible, non-invasive platform for molecular profiling in SD.

DISCLOSURES

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