Targeting the CXCR4-CD74 Heterodimer as a Therapeutic Strategy for Hidradenitis Suppurativa and Male Pattern Hair Loss

Targeted therapies that specifically modulate epithelial and hair follicle–driven inflammation in hidradenitis suppurativa and related hair disorders without broad systemic immunosuppression.

Technology

The Petukhova Lab at NYU, in collaboration with researchers at Columbia University and University of Michigan, has identified the CXCR4-CD74 heterodimer as a pharmacologically tractable target to modulate hair follicle inflammation without broad immune suppression for hidradenitis suppurativa (HS) and male pattern hair loss treatment. In recently presented work, an ancestrally diverse genome-wise associate study (GWAS) meta-analysis of 6,300 HS cases, integrated with epigenetic and transcriptomic profiling, identified 12 independent risk loci and 214 HS risk variants that converge on dysregulated epithelial gene regulatory networks and tissue remodeling pathways. These multi-omic analyses revealed a coherent epithelial gene module in HS lesional skin characterized by upregulated CXCR4, SOX9, and HLA-DQA1, mapping to an activated keratinocyte population aberrantly localized in epithelial tendrils and dermal tunnels, where these cells strongly express CXCR4 and co-express its coreceptor CD74, consistent with formation of a CXCR4–CD74 heterodimer. Functional studies demonstrated that these $CXCR4^{+}/CD74^{+}$ keratinocytes are driven by macrophage migration inhibitory factor (MIF) signaling through the MIF–CXCR4/CD74–SOX9 axis, exhibit enhanced MAPK/ERK, PI3K/AKT, and NF-κB signaling, and promote pathological inflammation and aberrant proliferation. Genetic correlation and phenome-wide association studies using HS risk variants and a multi-ancestry HS polygenic risk score further implicated this pathway in male pattern hair loss, reinforcing a central role for CXCR4–CD74–MIF signaling in hair follicle homeostasis. Ex vivo HS skin experiments using the CXCR4 antagonist Plerixafor showed that CXCR4 blockade attenuates MIF-dependent MAPK/ERK, PI3K/AKT, and NF-κB signaling, reduces WNT signaling, and upregulates apoptosis and repair-associated gene programs. Collectively, these genetic, mechanistic, and functional data support CXCR4–CD74–MIF blockade as a tractable therapeutic strategy for HS and related hair follicle disorders, including male pattern hair loss, with the potential to circumvent risks associated with systemic immune modulation.

Background

Hidradenitis suppurativa (HS) is a chronic, painful inflammatory skin disorder with an estimated prevalence of around 1%, yet treatment options are limited, with only a few FDA-approved drugs and frequent loss of response over time. Most approved and investigational therapies, including agents like adalimumab and secukinumab (Cosentyx), were originally developed for other immune-mediated diseases such as inflammatory bowel disease and rheumatoid arthritis, and act via broad systemic immunosuppression rather than HS-specific mechanisms. Clinically, HS is marked by inflammation centered on terminal hair follicles in intertriginous skin,

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infundibular hyperplasia leading to follicular occlusion and rupture, and the development of aberrant epithelial structures such as downward-growing tendrils and epithelialized dermal tunnels, culminating in chronic non-healing lesions, scarring, architectural destruction, and persistent debilitating pain. The underlying genetic contributors to these processes have only begun to be elucidated: earlier GWAS efforts identified a limited set of susceptibility loci and highlighted pathways involving γ-secretase components (e.g., NCSTN, PSENEN), and hair follicle development (e.g., SOX9, KLF5, WNT10A), underscoring the need for deeper mechanistic and genetically informed therapeutic approaches.

Applications

Treatment for hidradenitis suppurativa, male pattern hair loss, and related hair follicle disorders.

Advantages

- **Epithelial-centric mechanism:** Acts directly on the keratinocyte population enriched in epithelial tendrils and tunnels, where disease activity is concentrated.
- **Mechanism backed by human genetics and multi-omics:** Pathway is causally important and therapeutically relevant, not just a downstream marker of inflammation.
- **Potentially reduced systemic immunosuppression:** By targeting a pathway that drives epithelial tunnel formation and aberrant follicular remodeling, this approach may achieve disease control while minimizing reliance on broad immune suppression.
- **Disease-modifying approach:** CXCR4–CD74 targeting has the potential to alter structural disease drivers, not just attenuate inflammation.
- **Less stringent regulatory approval:** CXCR4 antagonists (Plerixafor) are already FDA-approved for other indications.

Intellectual Property

NYU has filed a co-owned US provisional patent application (with Columbia and University of Michigan) covering the method of targeting the CXCR4-CD74 heterodimer for treatment of HS, male pattern hair loss, and other hair follicle disorders.