Topical Inhibition of HIF-1a as a Novel Therapeutic Strategy for Inflammatory Skin Diseases

An effective, differentiated, and targeted therapeutic strategy for the treatment of inflammatory skin diseases such as psoriasis, atopic dermatitis, and hidradenitis suppurativa.

Technology ID
NAI02-03

Category
Life Sciences/Therapeutics/Inflammat Disease

Authors
Shruti Naik, PhD

View online page

Technology

The Naik research group has identified and characterized a novel therapeutic target driving inflammatory skin disease and is currently developing a topical genetic medicine treatment. As described in a comprehensive spatial transcriptomics study of primary patient biopsies (*Castillo et al, Sci Immnol 2023*), the Naik group identified the transcription factor HIF-1alpha (HIF-1a) as a key regulator of the suprabasal epidermal inflammation which underpins psoriasis, atopic dermatitis, and hidradenitis suppurativa. In unpublished work, using well-established *in vivo* models of psoriasis, the group found that both pharmacological inhibition (using a commercially-available tool compound) and epidermal-specific genetic ablation of HIF-1a (using a topically-administered siRNA) protected animals from disease and outperformed standard of care (SOC) anti-TNFa (Etanercept) or anti-IL17A (Secukinumab) therapeutics. Subsequent mechanistic studies using epithelial HIF-1a knock-out mice showed HIF-1a to broadly modulate metabolic activity, cell differentiation, and immune response in the epithelium. In addition to the therapeutic potential of HIF-1a targeting, the gene signatures associated with HIF-1a repression could be leveraged to stratify responders and non-responders to SOC therapies for inflammatory skin diseases, such as Secukinumab. In all, these findings establish the clinical potential of localized HIF-1a repression using genetic medicine approaches to treat inflammatory skin diseases.

Background

Inflammatory skin diseases such as psoriasis, atopic dermatitis, and hidradenitis suppurativa are serious public health concerns and cause considerable economic burden, with limited effective treatment options available. Psoriasis alone is estimated to affect 2-3% of the global population. In the U.S., the financial burden of psoriasis and its comorbidities to the healthcare system is in the range of $112 billion. Current treatments of inflammatory skin diseases center around the use of corticosteroids, phototherapies, or systemic biologics that suppress global immune responses, which can have adverse side effects. Therefore, there is an unmet clinical need to develop therapeutics that selectively target key drivers of epithelial inflammation, such as HIF-1a, that cause inflammatory skin diseases.

Development Status

The Naik research group, in collaboration with NYU TOV's Therapeutics Alliances accelerator, is currently developing and testing a topically-administered siRNA therapeutic candidate delivered

in liposomes to selectively abrogate HIF-1a expression in the epidermis.

Application

Topical treatment of inflammatory skin diseases, such as psoriasis, atopic dermatitis, and hidradenitis suppurativa.

Advantages

- **Expedited FDA review and approval**: Topical administration qualifies for less stringent regulation.
- **Novel, differentiated, and targeted approach:** Locally targets HIF-1a in the epidermis, thereby avoiding possible off-target effects
- **Superior efficacy:** HIF-1a inhibition is more protective against skin inflammation than the SOC.
- **Predictive biomarker:** Gene signatures associated with HIF-1a repression could stratify patient response to SOC therapies.
- **Well-characterized target:** HIF-1a has been extensively studied across many disparate indications

Intellectual Property

NYU has filed two U.S. provisional patent applications covering the general method of HIF-1a inhibition for the treatment of inflammatory skin diseases, as well as specific topical genetic medicine formulations related to the same.

References

1. Castillo et al , https://ncbi.nlm.nih.gov/pmc/articles/PMC10502701/
2. Konieczny et al , https://ncbi.nlm.nih.gov/pmc/articles/PMC9753231/
3. Subudhi, Ipsita et al. , https://pubmed.ncbi.nlm.nih.gov/38772365/