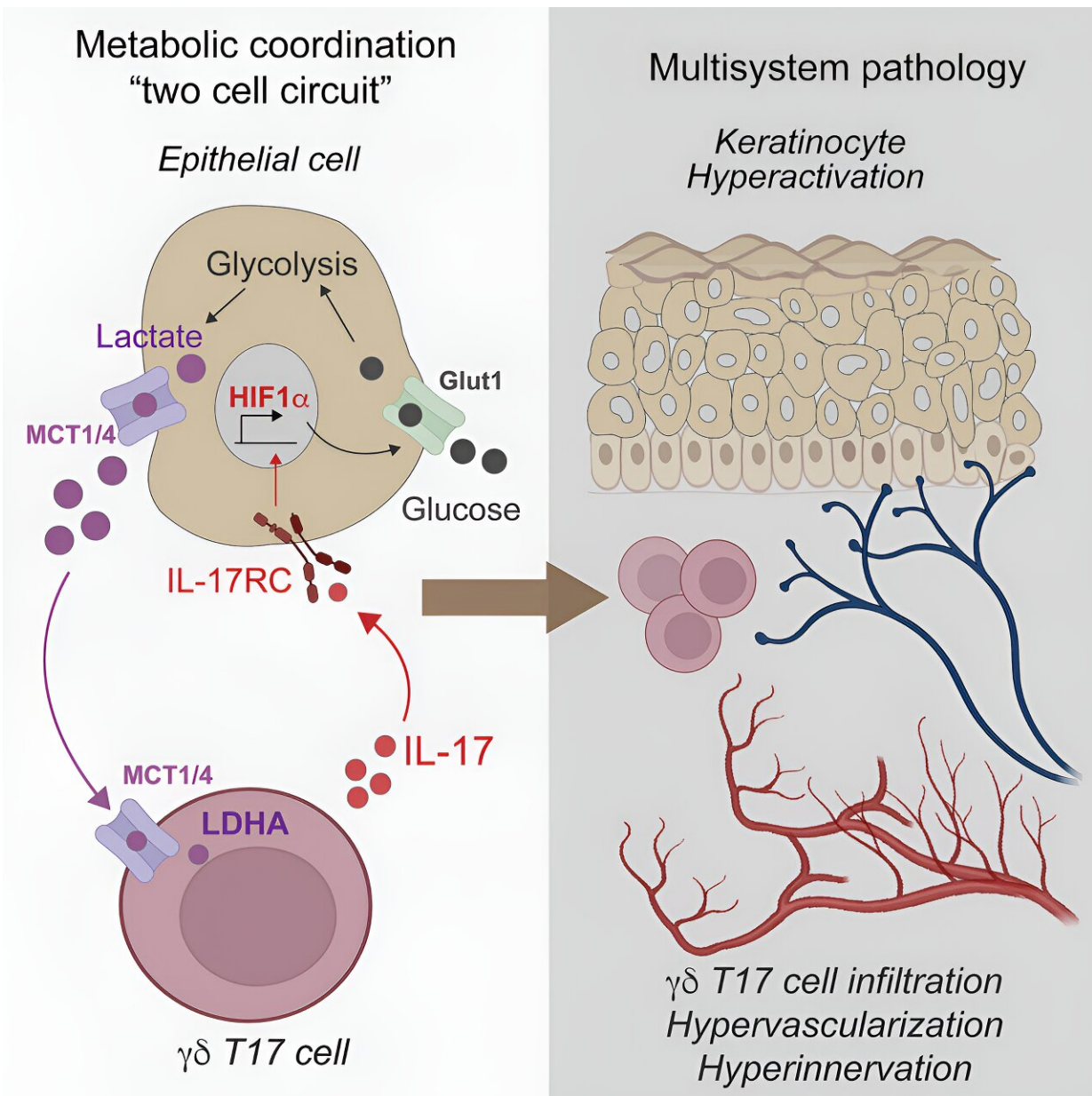


Research shows linked biological pathways driving skin inflammation

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Credit: *Immunity* (2024). DOI: 10.1016/j.immuni.2024.04.022

A certain biological pathway—a set of linked reactions in the body—drives the inflammation seen in the skin disease psoriasis, a new study finds. The work could lead to improved therapies for all inflammatory skin diseases, including atopic and allergic dermatitis and a type of boil called hidradenitis suppurativa, say the study authors.

The findings are [published](#) in the journal *Immunity*.

Inflammation is the body's natural response to irritation and infection, but when out of control, it can lead to the reddish, flaky, itchy lesions that come with these skin diseases.

Led by researchers at NYU Langone Health, the new study found that the interleukin-17 (IL-17) pathway, whose activity is blocked by existing [anti-inflammatory drugs](#), activates a protein called hypoxia inducible factor 1-alpha (HIF-1-alpha) in psoriasis. Researchers say that IL-17 has long been known to be active in inflammation, but the role of HIF-1-alpha has until now been unclear.

The research team also found that HIF-1-alpha let inflamed [skin cells](#) more actively break down sugar for energy, supporting their metabolism and leading to the production of a waste product called lactate. When consumed by inflammatory T cells, lactate triggered production of IL-17, fueling even more inflammation.

The findings show that in human skin tissue samples from people with psoriasis, measures of gene activity around IL-17 and HIF-1-alpha were similar, suggesting that these factors are interconnected. Experiments in mice treated to develop psoriasis found that subsequent treatment with

an experimental drug that blocks the action of HIF-1-alpha, called BAY-87-2243, resolved inflammatory skin lesions.

Further, skin samples from 10 patients successfully treated with anti-inflammatory drug etanercept showed diminished activity for both IL-17 and HIF-1-alpha, suggesting to researchers that when IL-17 is blocked, so is HIF-1-alpha.

"Our study results broadly show that activation of HIF-1-alpha is at the crux of metabolic dysfunction observed in psoriasis and that its action is triggered by IL-17, another key inflammatory-signaling molecule," said corresponding study author Shruti Naik, Ph.D., associate professor at NYU Grossman School of Medicine in the Departments of Pathology and Medicine, and the Ronald O. Perelman Department of Dermatology.

Further experiments were performed on skin samples from five patients with psoriasis whose healthy and inflamed skin was separately treated with either BAY-87-2243 or an existing combination of topical drugs (calcipotriene and betamethasone dipropionate).

Researchers then compared differences in inflammatory gene activity as a measure of impact and found that the HIF-1-alpha inhibitor had a greater effect than existing topical drugs. Specifically, skin samples that responded to HIF-1-alpha therapy had 2,698 genes that were expressed differently, while standard-of-care-treated samples had 147 differently expressed genes.

Genetic analysis of skin samples from another 24 psoriatic patients treated with the IL-17A-blocking drug secukinumab showed only decreased, not heightened, gene activity connected to HIF-1-alpha when compared to HIF-1-alpha gene activity in nine healthy patients with no psoriatic disease. Researchers say this indicates HIF-1-alpha's blocked action was codependent on blockage of IL-17.

Additional experiments in mice showed that blocking sugar (glucose) uptake in the skin slowed psoriatic disease growth by limiting glucose metabolism, or glycolysis. Both the number of immune T cells tied to inflammation and the cell levels of IL-17 also decreased. The researchers found further that levels of lactate, the main byproduct of glycolysis, in psoriatic skin cell cultures dropped once exposed to the glycolysis-inhibiting drug 2-DG.

Directly targeting lactate production in psoriatic mice using a topical skin cream containing lactate dehydrogenase, which breaks down lactate, also slowed disease progression in the skin, with reduced numbers of inflammatory gamma-delta T cells and reduced IL-17 activity. Gamma-delta T cells were shown to take up lactate and use it to produce IL-17.

"Our findings suggest that blocking either HIF-1-alpha's action or its glycolytic metabolic support mechanisms could be effective therapies for curbing the inflammation," added Naik, who is also the associate director for NYU Langone's Judith and Stewart Colton Center for Autoimmunity.

"Evidence of HIF-1-alpha's depressed action, or downregulation, could also serve as a biomarker, or molecular sign, that other anti-inflammatory therapies are working," said study co-senior investigator Jose U. Scher, MD, the Steere Abramson Associate Professor of Medicine in the Department of Medicine at NYU Grossman School of Medicine.

Scher, who also serves as director of NYU Langone's Psoriatic Arthritis Center and the Judith and Stewart Colton Center for Autoimmunity, says the team plans to develop experimental drugs that can block HIF-1-alpha and lactate action in the skin "to end the underlying vicious cycle of IL-17-driven inflammation in skin disease. Our research fundamentally expands the scope of feasible therapeutic options."

Naik points out that while many available therapies for psoriasis, including steroids and immunosuppressive drugs, reduce inflammation and symptoms, they do not cure the disease. She said further experiments are needed to refine which [experimental drug](#) works best, with respect to HIA-1-alpha inhibition, before clinical trials can start. Naik and study co-lead investigators Ipsita Subudhi and Piotr Konieczny have a [patent application](#) pending (U.S. application number 63/540,794) for inflammatory skin disease therapies derived from their work on HIA-1-alpha inhibition.

More than 8 million Americans and 125 million worldwide are estimated to have psoriatic disease. The condition affects men and women equally.

More information: Ipsita Subudhi et al, Metabolic coordination between skin epithelium and type 17 immunity sustains chronic skin inflammation, *Immunity* (2024). [DOI: 10.1016/j.immuni.2024.04.022](https://doi.org/10.1016/j.immuni.2024.04.022)

Provided by NYU Langone Health

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