A new study finds that a certain biological pathway, a set of linked reactions in the body, drives the inflammation seen in psoriasis.

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. 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 conditions.

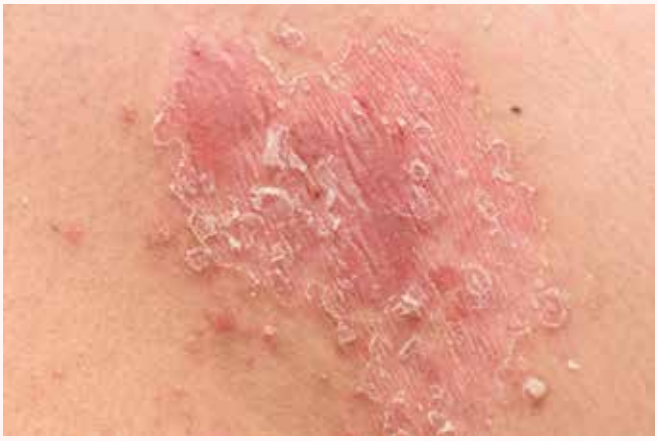
Led by researchers at NYU Langone Health*, the new study found that the interleukin-17 (IL-17) pathway, whose activity is blocked by existing anti-inflammatory drugs, activates a protein called hypoxia-inducible factor 1-alpha (HIF-1-alpha) in psoriasis. Researchers say that IL-17 has long been known 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 lets 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 the production of IL-17, fuelling even more inflammation.

Publishing in the journal *Immunity* online in May, 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-signalling molecule," said corresponding study author Shruti Naik, PhD, 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.

"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 Centre for Autoimmunity.

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, concerning HIA-1-alpha inhibition, before clinical trials could start.

About:

*NYU Langone Health is an American academic medical centre that states it is devoted to excellence in patient care, education, and research.

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