Scientists Identify New Pathway That Influences Psoriasis

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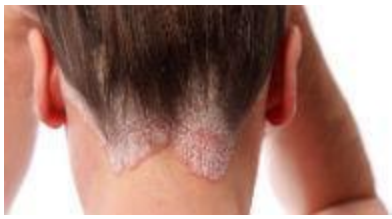
This finding could help scientists develop new treatments for psoriasis, beyond simply targeting the immune system.



Psoriasis is a noncontagious skin disease that causes itchy, red patches and silvery-white scales to appear on the skin. It occurs when the immune system mistakenly attacks the body, causing skin cells to grow and die at a very high rate, accumulating into plaques. New research published in the journal *Immunity* sheds light on the molecular pathway psoriasis uses to disrupt the skin's normal pattern of growth.

A research team at the MRC National Institute for Medical Research homed in on a molecule called the aryl hydrocarbon receptor (AhR), which is found in both skin and immune cells. AhR is a transcription factor, which means that it activates DNA, causing it to manufacture proteins. AhR reacts to environmental toxins, such as dioxin (found in Agent Orange), and plays a role in regulating how the skin responds to such toxins. Until now, its role in psoriasis—which is considered to be about 70 percent genetic and 30 percent environmental—was unclear.

"Psoriasis is largely thought of [as] being a genetic disease, with familial predisposition," said psoriasis expert Dr. Gary Goldenberg, an assistant professor of dermatology and pathology at the Icahn School of Medicine at Mount Sinai Hospital, in an interview with Healthline. "However, environmental factors contribute to psoriasis. These include cold, dry weather; stress; skin injury and trauma; and certain medications."

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Turning Genes On—and Off

The MRC team took skin samples from psoriasis patients and healthy control subjects. The researchers exposed the samples to one of two chemicals that would either stimulate AhR to act on DNA or block AhR from DNA. These chemicals caused changes in the activity levels of 41 different genes in the skin of psoriasis patients, 26 of which had already been

linked to psoriasis. Stimulating AhR in the psoriatic samples caused 70 percent of the genes to turn on, while blocking AhR caused the genes to turn off.

Meanwhile, in the healthy skin samples, the chemicals that blocked AhR instead turned these same genes on. Clearly, psoriatic skin responded differently to the same chemicals.

The next step was to test AhR response not just on skin samples but in living animals. Although mice don't get psoriasis the way humans do, they can be given psoriasis-like symptoms through exposure to a certain drug. The team gave these "psoriatic" mice the AhR-stimulating chemical, and they saw the mice's symptoms improve.

But AhR is found in both skin and immune cells, so which cells were responding? To get to the bottom of this question, the team removed AhR in some of the mice's immune cells, to no effect. Then they tested the mice's skin cells. Here, they got results: Skin cells missing AhR showed a much stronger immune response, becoming hyper-inflamed. The effect was strongest in a type of skin cell called a keratinocyte.

"Keratinocytes are cells that make up the outer layer of the skin, called the epidermis," said Goldenberg. "In psoriasis, these cells are produced at a higher than normal rate and accumulate, producing thick, scaly plaques seen in psoriasis patients. These cells may also be important in producing a pro-inflammatory environment that drives psoriasis. A recent study showed that keratinocytes deficient in AhR showed an exacerbated response to pro-inflammatory cytokines—cells that cause inflammation."

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Target the Cells, Not the Immune System

This research presents a target for scientists to develop new medications to treat psoriasis. "Most of the therapies for psoriasis target the immune system," said Goldenberg. "Topical steroids are the most commonly used treatment. Light therapy is also used and works by reducing the immune system [response] in the skin. Systemic medicines, such as biologics and oral agents, all target the immune system in the skin."

Targeting AhR inside of keratinocytes, rather than in the immune system, would be a new direction for psoriasis treatment. However, such a treatment would be difficult to fine-tune. "It is important to convey that AhR activation needs to be tightly controlled," said the study's principal investigator, Brigitta Stockinger, head of the division of molecular immunology at

the MRC National Institute for Medical Research, in an interview with Healthline. “Having no AhR signaling is probably as bad as having too prolonged signaling.”

Because of this, simply using drugs that stimulate AhR won’t do the trick. Instead, Stockinger wants to learn more about the AhR pathway itself to find out if there’s an intermediate signaling molecule that might make a better target. She added, “We need to understand more about the molecular mechanisms of how AhR influences inflammatory gene expression and how it is regulated.”