Superficial relationship: Enzymes protect the skin by ignoring microbes and viruses

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The human body is constantly exposed to various environmental actors, from viruses to bacteria to fungi, but most of these microbial organisms provoke little or no response from our skin, which is charged with

monitoring and protecting from external dangers.

Until now, researchers weren't quite sure how that happened—and why our skin wasn't constantly alarmed and inflamed.

In a study published May 21, 2021 in *Science Immunology*, scientists at University of California San Diego School of Medicine identify and describe two enzymes responsible for protecting our skin and body's overall health from countless potential microbial intruders. These enzymes, called histone deacetylases (HDACs), inhibit the body's inflammatory response in the skin.

"We have figured out why we tolerate certain microbes living on our skin, while the same bacteria would make us very sick if exposed elsewhere in the body," said Richard Gallo, MD, Ph.D., Ima Gigli Distinguished Professor of Dermatology and chair of the Department of Dermatology at UC San Diego School of Medicine. "In our research, we identified enzymes that act on the chromosome of specific skin cells that provide immune tolerance by the skin.

"Without these enzymes telling our cells to ignore certain bacteria, we'd have a constant rash on our skin."

Gallo and colleagues say the potential mechanism for how the environment can interact and alter cell function is through epigenetic control of gene expression. Within the skin cells, proteins called toll-like receptors (TLRs) allow the cells to sense their surroundings and potential dangers.

In most organs, TLRs act as a warning system that triggers an inflammatory response to threats. But in skin cells, the two identified HDAC enzymes, HDAC8 and HDAC9, inhibit the inflammatory response.

"This is one of the first demonstrations of how the microbiome can interact with epigenetic factors in the skin and modulate the skin's behavior through the inflammatory response," said George Sen, Ph.D., associate professor of dermatology and cellular and molecular medicine at UC San Diego School of Medicine. "Whatever environment we're facing can change a person's specific response to it. Since this epigenetic change is reversible, unlike alterations to our DNA, we can potentially control our skin inflammatory response through targeting of these enzymes."

The research was initially conducted in mouse models in which HDAC8 and HDAC9 had been genetically knocked out. As a result, the mice's skin could not tolerate microbial or viral exposures, resulting in a heightened immune reaction. The team then reproduced the findings with human cells in a culture dish.

Gallo said the work could change how doctors treat certain types of skin inflammation or other dermatologic conditions.

"This is a completely new way to think about skin immune regulation," said Gallo. "Through alterations in HDAC activity, we've provided a possible way to explore and quiet down unnecessary inflammation by working with skin cells themselves. In the future, drugs designed to turn these enzymes on or off could help treat skin disease as an alternative to antibiotics."

More information: Yu Sawada et al, Cutaneous innate immune tolerance is mediated by epigenetic control of MAP2K3 by HDAC8/9, *Science Immunology* (2021). DOI: 10.1126/sciimmunol.abe1935

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