Researchers identify mechanisms that make skin a protective barrier

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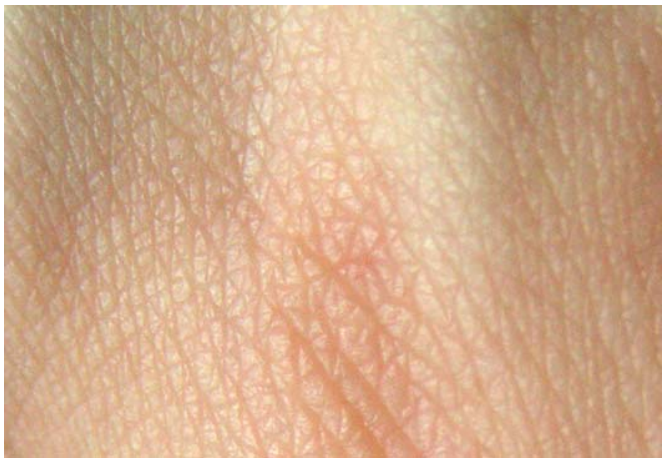

Human skin structure. Credit: Wikipedia

A Mount Sinai research team has identified one of the mechanisms that establish the skin as a protective barrier, a breakthrough that is critical to understanding and treating common skin conditions including eczema and psoriasis, according to a study published Thursday, May 28, in the scientific journal *Genes & Development*.

One of the most important roles of the skin is to act as a barrier that prevents water loss and protects the skin from pathogens. Failure of this protective function contributes to dermatological diseases. The research team led by Sarah E. Millar, Ph.D., Director of the Black Family Stem Cell Institute at the Icahn School of Medicine at Mount Sinai, found that the scaffolding protein, histone deacetylase 3 (HDAC3), is essential for proper skin development and barrier formation.

The group found that mice lacking HDAC3 specifically in the epidermis—the outermost layer of the skin—fail to develop a functional skin barrier and die shortly after birth due to dehydration. The team's extensive research describes a complex process in which HDAC3 regulates expression of its target genes in the epidermis by interacting with multiple DNA-binding proteins.

"HDAC3 is particularly interesting to us, as it associates with different proteins in different tissue types to regulate its target genes," says Katherine Szigety, an MD/Ph.D. student in the Millar Lab and first author of the study. "While HDAC3 has been studied in diverse contexts, its role and transcriptional partners in the developing epidermis had not been identified until now."

HDAC3 is a member of a family of epigenetic regulators, known as histone deacetylases (HDACs), which control gene expression by changing the structure of genetic material. Understanding the biology of epigenetic regulation is an area of active scientific investigation, as many new therapeutics are designed to modify this process. With a focus on skin biology, Dr. Millar's lab is studying HDACs because a group of drugs called HDAC inhibitors are used to treat cutaneous T-cell lymphoma, a rare cancer that affects the skin.

The lab's research on HDAC3 builds on their previous studies of the related proteins HDAC1 and HDAC2 in skin development. The team discovered that the mechanisms by which HDAC3 regulates target gene expression are distinctly different from those involving HDAC1 and HDAC2.

"Unlike HDACs 1 and 2, HDAC3's functions in regulating epidermal development appear to be independent of its enzyme activity. Because clinically available HDAC inhibitors specifically block enzyme function, our findings suggest that the effects of treatment with an HDAC inhibitor might resemble loss of HDACs 1 and 2 in the skin, but perhaps not HDAC3," said Dr. Millar. "This may have important implications for the use of HDAC inhibitors in managing CTCL and other skin conditions. An exciting next step for our group will

be to characterize the role of HDAC3 in skin disease."

Provided by The Mount Sinai Hospital