Presence of staph bacteria in skin microbiome promotes Netherton syndrome inflammation

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Netherton syndrome, a rare skin disease caused by a single genetic mutation, is exacerbated by the presence of two common *Staphylococcal*

bacteria living on human skin, one of which was previously thought to only offer protective properties, report University of California San Diego School of Medicine researchers.

"Our study shows how closely tied the human genome is to the genetic information in our skin microbiome. This rare disease is due to a mutation in a human gene. But, in adults, the symptoms of the disease are driven by the skin microbiome," said senior author Richard Gallo, MD, Ph.D., Irma Gigli Distinguished Professor and chair of the Department of Dermatology at UC San Diego School of Medicine.

"The two genomes work closely together. When one is off, even by a single gene, the other genome reacts."

In a multi-institutional study published online in *Cell Reports* on March 3, 2020, Gallo and collaborators identified how *Staphylococcus aureus* and *Staphylococcus epidermidis* can act as a catalyst for skin inflammation and barrier damage in mouse models.

S. aureus is a pathogenic bacteria known to aggravate skin conditions, such as atopic dermatitis. When it becomes resistant to antibiotics, it is known as methicillin-resistant *Staphylococcus aureus* or MRSA. It is a leading cause of death resulting from infection in the United States.

Conversely, *S. epidermidis* is common on healthy human skin and presumed benign. In a previous study, Gallo reported that a specific strain of this bacterium seemed to hold a protective property by secreting a chemical that kills several types of cancer cells but does not appear to be toxic to normal cells. *S. epidermidis* was also known to promote wound repair, skin immunity and limit pathogen infections. It was not known that, in some cases, *S. epidermidis* can have pathogenic effects.

Netherton syndrome is a result of a mutation in the SPINK5 gene, which normally provides instructions for making a protein called LEKT1. This protein is a type of protease inhibitor.

With the loss of LEKT1, excess proteases are stimulated by *Staphylococcal* bacteria on people with Netherton syndrome. This protease activity leads to a breakdown of proteins and skin inflammation.

"This is a major breakthrough for these patients as it describes how we can treat a human genetic mutation by targeting the microbiome," said Gallo, who is also a faculty member in the Center for Microbiome Innovation at UC San Diego. "Altering bacterial gene expression is much easier than trying to fix a mutation in humans."

Researchers swabbed the skin of 10 people with Netherton syndrome and found that their skin microbiome had an abundance of certain strains of *S. aureus* and *S. epidermidis*. However, unlike the skin of normal subjects, the excess bacteria produced genes that could not be controlled due to the gene mutation in Netherton syndrome.

According to the National Institutes of Health, most people with this recessive inherited genetic disorder have immune system-related problems, such as food allergies, hay fever, asthma, or an inflammatory skin disorder called eczema. It is estimated that 1 in 200,000 newborns are affected.

"In addition to demonstrating how an abnormal skin microbiome promotes inflammation in Netherton syndrome, this study provides one of the most detailed genomic descriptions to date of the skin microbiome," said Gallo.

More information: Michael R. Williams et al. Interplay of

Staphylococcal and Host Proteases Promotes Skin Barrier Disruption in Netherton Syndrome, *Cell Reports* (2020). DOI: 10.1016/j.celrep.2020.02.021