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Immune system, skin microbiome 'complement' one another, study finds

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Researchers from the Perelman School of Medicine at the University of Pennsylvania demonstrate for the first time that the immune system influences the skin microbiome. A new study found that the skin microbiome – a collection of microorganisms inhabiting the human body – is governed, at least in part, by an ancient branch of the immune system called complement. In turn, it appears microbes on the skin tweak the complement system, as well as immune surveillance of the skin. They found that complement may, in part, be responsible for maintaining a diverse set of microbes on our skin and keeping our skin healthy, which could play a role in a host of skin diseases.

Penn researchers Elizabeth Grice, PhD, assistant professor of Dermatology, and John Lambris, PhD, the Dr. Ralph and Sallie Weaver Professor of Research Medicine in the Department of Pathology and Laboratory Medicine, published findings in the August 26 issue of the *Proceedings of the National Academy of Sciences*.

Commensal, non-pathogenic bacteria that live on the skin provide an important service to their host, blocking pathogenic microbes from gaining a foothold, among other functions. In previous research, Grice and colleagues illuminated the great diversity of bacteria living on the skin using DNA-based sequence analysis of bacterial genes. However, until this study, very little was known about how the immune system influences those populations of bacteria living on the skin.

The complement system is like a molecular alarm system and first

responder, Grice explains. "It leads the counterattack against microbial insult." The system is an evolutionarily ancient branch of the immune response and a key function is marking microbial and dying host cells for elimination.

Complement also has inflammatory functions, and the team explored the relationship between the signaling of one particular inflammatory protein of the complement cascade, C5aR (the C5a receptor), and the skin microbiome. Their findings highlight a previously unrecognized role for complement on the skin.

The team treated one group of mice with an inhibitor of C5aR, and another with an inactive analog and compared the animals' skin microbiome before and after treatment, based on DNA sequence analysis. They found that while the absolute number of microbes on the skin remained unchanged, the population diversity shifts in animals treated with a C5aR inhibitor compared to those who were not, with some groups of organisms increasing in abundance and others petering out.

The team also looked at the impact of C5aR inhibitor treatment on the immune system itself. They found that genes associated with immune surveillance were downregulated in the skin in inhibitor-treated animals, as was the number of immune cells overall.

Those results suggest that the complement system somehow influences the microbiome. To see if the effect also works in reverse, the team asked whether mice grown in a germ-free environment would express genes encoding complement components differently than mice grown under normal conditions. The microbiome did modulate the immune system: the animals grown in germ-free conditions expressed complement genes at lower levels in the skin than control animals.

"There's a balance between the microbiome and the immune system," Grice concludes. "Decreased microbial diversity has been associated with skin diseases such as atopic dermatitis, a type of eczema. Complement may in part be responsible for maintaining that diversity and keeping our skin healthy."

And that's important, she says, because it is becoming increasingly evident that many diseases are caused (or at least exacerbated) not by pathogens per se, but by "dysbiosis," an imbalance in the microbial community.

"That balance is probably highly evolved so our optimal skin health is maintained when these two factors are in balance and communicating. And it's when you disrupt one of those components that you can trigger or exacerbate a skin disorder or infection."

Such a symbiotic relationship has already been documented in the gut.

While this study did not address the cause and effect between host and microbe, this interaction ultimately represents a potential therapeutic target, Grice says. If researchers can work out the skin microbiome and its relationship with complement, they might be able to tweak the microbial population one way or another to, for instance, modulate complement activation in patients with diseases that are in part caused by dysregulated or dysfunctional signaling, for example, psoriasis.

On the other hand, complement inhibitors, such as those being developed by Lambris' lab and some of which are in clinical trials, may be used to therapeutically manipulate the skin microbiome back to a "healthy," less dysbiotic state.

Now, Grice says, her team is working to better understand the mechanism of the complement-microbiome interaction, as well as its

relationship to normal skin health and pathogenesis.

"I think our definition and labeling of 'bad microbes' needs to change," Grice says. "We need to think about how we nurture our microbes rather than eradicate them. They evolved with us for a reason."

More information: Complement modulates the cutaneous microbiome and inflammatory milieu , www.pnas.org/cgi/doi/10.1073/pnas.1307855110

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