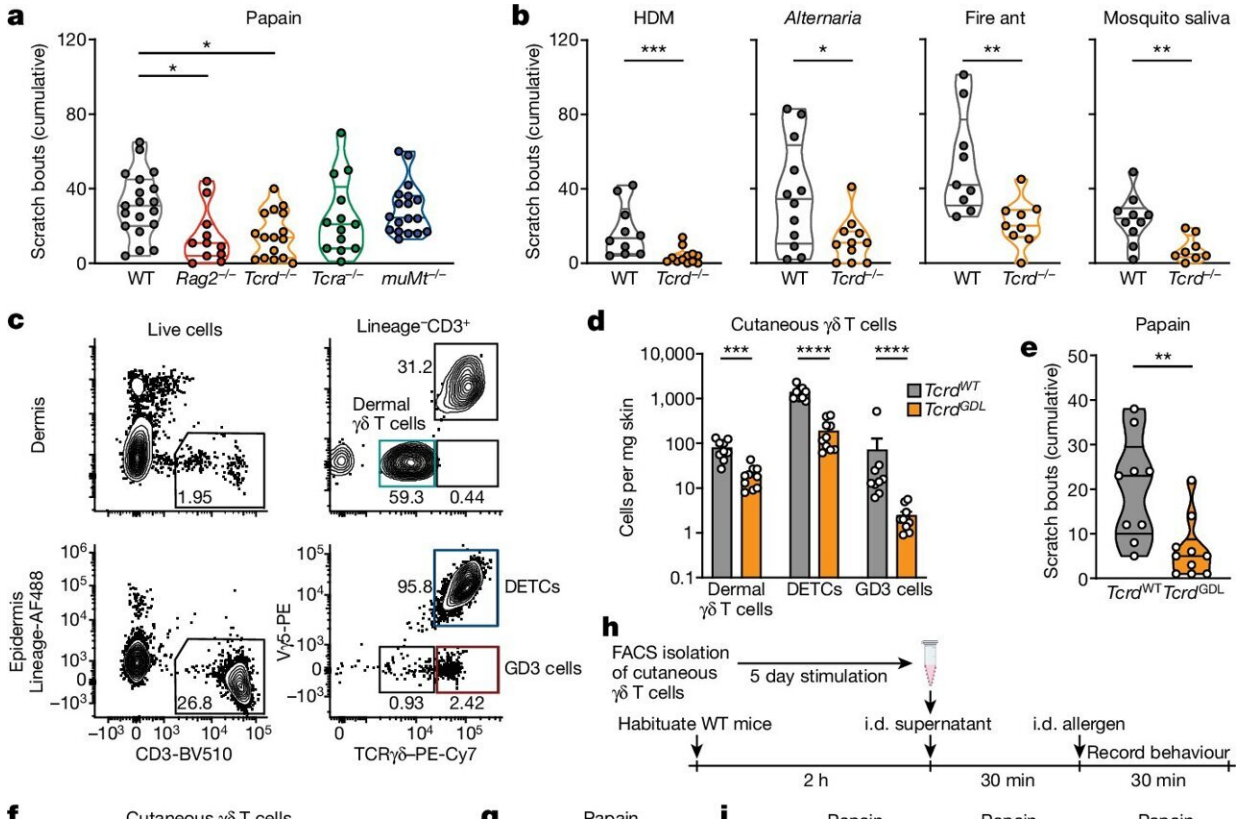
Researchers identify mechanism underlying allergic itching, and show it can be blocked

September 4 2024



γδ T cells promote allergic itch through a secreted factor. Credit: *Nature* (2024). DOI: 10.1038/s41586-024-07869-0

Why do some people feel itchy after a mosquito bite or exposure to an allergen like dust or pollen, while others do not? A new study has

pinpointed the reason for these differences, finding the pathway by which immune and nerve cells interact and lead to itching.

The researchers, led by allergy and immunology specialists at Massachusetts General Hospital, then blocked this pathway in preclinical studies, suggesting a new treatment approach for allergies. The findings are published in *Nature*.

"Our research provides one explanation for why, in a world full of allergens, one person may be more likely to develop an allergic response than another," said senior and corresponding author Caroline Sokol, MD, Ph.D., an attending physician in the Allergy and Clinical Immunology Unit at MGH, and assistant professor of medicine at Harvard Medical School.

"By establishing a pathway that controls allergen responsiveness, we have identified a new cellular and molecular circuit that can be targeted to treat and prevent allergic responses including itching. Our preclinical data suggests this may be a translatable approach for humans."

When it comes to detecting bacteria and viruses, the immune system is front and foremost at detecting pathogens and initiating long-lived immune responses against them. However, for allergens, the immune system takes a backseat to the sensory nervous system.

In people who haven't been exposed to allergens before, their sensory nerves react directly to these allergens, causing itchiness and triggering local immune cells to start an allergic reaction. In those with chronic allergies, the immune system can affect these sensory nerves, leading to persistent itchiness.

Previous research from Sokol and colleagues showed that the skin's sensory nervous system—specifically the neurons that lead to

itch—directly detect allergens with protease activity, an enzyme-driven process shared by many allergens. When thinking about why some people are more likely to develop allergies and chronic itch symptoms than others, the researchers hypothesized that innate immune cells might be able to establish a "threshold" in sensory neurons for allergen reactivity, and that the activity of these cells might define which people are more likely to develop allergies.

The researchers performed different cellular analyses and genetic sequencing to try and identify the involved mechanisms. They found that a poorly understood specific immune cell type in the skin, that they called GD3 cells, produces a molecule called IL-3 in response to environmental triggers that include the microbes that normally live on the skin.

IL-3 acts directly on a subset of itch-inducing sensory neurons to prime their responsiveness to even low levels of protease allergens from common sources like house dust mites, environmental molds and mosquitos. IL-3 makes sensory nerves more reactive to allergens by priming them without directly causing itchiness. The researchers found that this process involves a signaling pathway that boosts the production of certain molecules, leading to the start of an allergic reaction.

Then, they performed additional experiments in mouse models and found removal of IL-3 or GD3 cells, as well as blocking its downstream signaling pathways, made the mice resistant to the itch and immune-activating ability of allergens.

Since the type of immune cells in the mouse model is similar to that of humans, the authors conclude these findings may explain the pathway's role in human allergies.

"Our data suggest that this pathway is also present in humans, which

raises the possibility that by targeting the IL-3-mediated signaling pathway, we can generate novel therapeutics for preventing an allergy," said Sokol.

"Even more importantly, if we can determine the specific factors that activate GD3 cells and create this IL-3-mediated circuit, we might be able to intervene in those factors and not only understand allergic sensitization but prevent it."

More information: Caroline Sokol, A γδ T cell–IL-3 axis controls allergic responses through sensory neurons, *Nature* (2024). DOI: 10.1038/s41586-024-07869-0.
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Provided by Mass General Brigham