Study uncovers novel mechanisms behind food allergies

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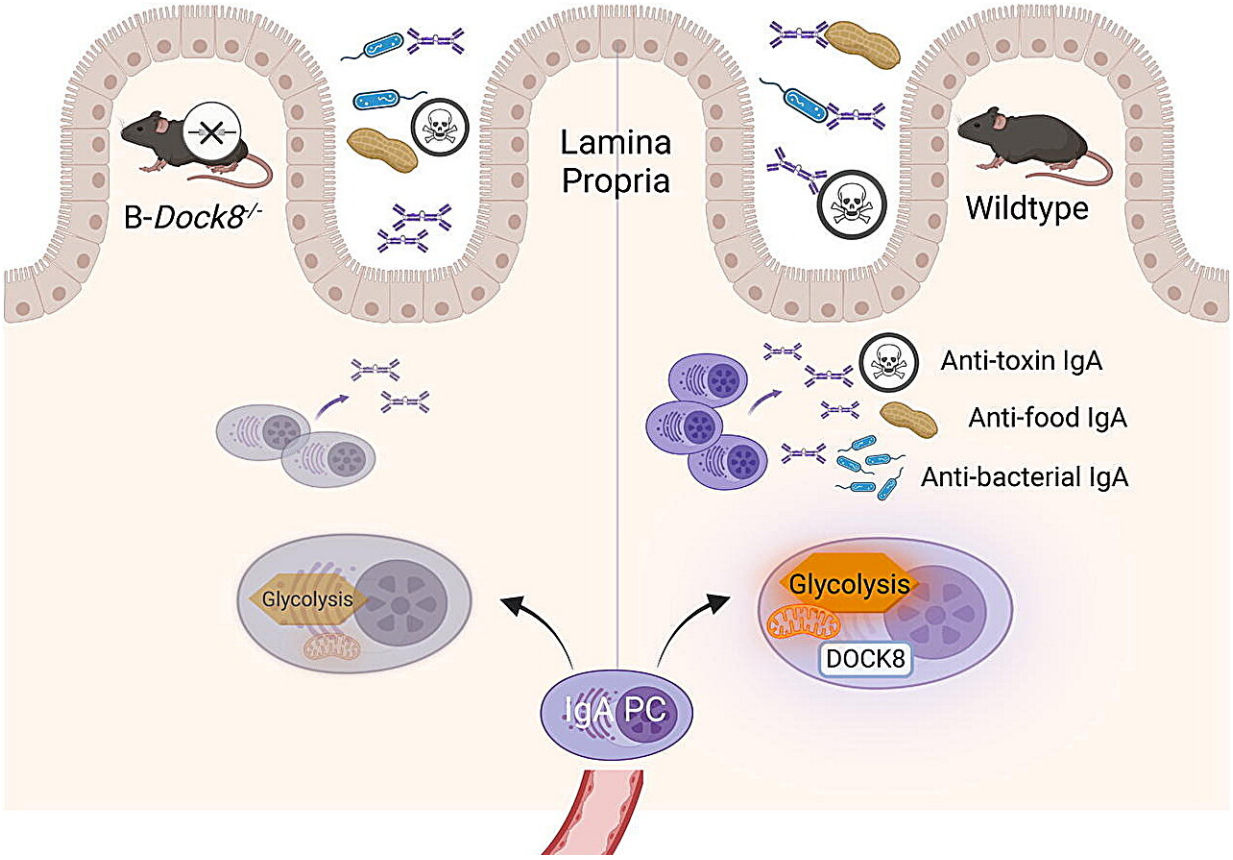

Credit: *Mucosal Immunology* (2023). DOI: 10.1016/j.mucimm.2023.12.001

A recent Northwestern Medicine study has shed light on the mechanisms of a specific protein that is necessary for the production of IgA antibodies in the gut in response to food allergens, according to findings published in the journal *Mucosal Immunology*.

Stephanie Eisenbarth, MD, Ph.D., chief of Allergy and Immunology in the Department of Medicine and the Roy and Elaine Patterson Professor of Medicine, along with Adam Williams, Ph.D., associate professor of Medicine in the Division of Allergy and Immunology, were co-senior authors of the study.

The gut maintains a regulated tolerance to food and habitual bacteria while defending against invading pathogens. However, when this balance is dysregulated, it can lead to infection, inflammation and food allergies.

The gut's mucosal tissue, which comprises the inner lining of the intestinal tract, and mucosal antibodies, specifically Immunoglobulin A, or IgA, help the gut control bacteria and neutralize toxins. Regarding allergens, however, previous work from Eisenbarth's laboratory has shown that allergen-specific IgA, which is the most common antibody found in the gut's mucosal tissue, may not be a protective factor against the development of food allergies, as was previously thought.

Patients with mutations in a protein called dedicator of cytokinesis 8 (DOCK8), which is important for immune cell migration, signaling and adhesion, as well as for maintaining antibody responses, are highly susceptible to gastrointestinal tract infections and often have severe food allergies.

This prompted a team of investigators led by Williams and Eisenbarth to investigate the precise role DOCK8 plays in IgA production in the gut's

mucosal tissue in response to toxins, bacteria and food allergens.

"Although IgA is the most abundant antibody in the body and it is produced mainly at mucosal surfaces, we still don't understand the rules that govern its production in the gut, which is still very much a black box in immunology" said Eisenbarth, who is also director of the Center for Human Immunobiology and professor of Pathology.

By deleting DOCK8 in immune cells of mice, specifically in B-cells, the investigators discovered that DOCK8 is necessary for maintaining IgA plasma cells (an antibody secreting white blood cell that develops from B-cells) in the gut's mucosal tissue.

"This finding is really an immunometabolism story about how, at a local level, IgA producing plasma cells must be able to adapt their metabolism to the cyclic nature of nutrient availability in the gut timed with food intake. In the absence of DOCK8, these cells cannot respond to nutrient fluctuations and so their lifespan is limited," Williams said.

The discovery improves the understanding of how B-cells operate within the gut and how these cells generate antibody responses to food. The findings may also help explain why patients with DOCK8 mutations are more susceptible to gastrointestinal infections and could inform new therapeutic strategies that involve maintaining IgA-secreting plasma cells in the gut, according to Eisenbarth.

More information: Biyan Zhang et al, Metabolic fitness of IgA+ plasma cells in the gut requires DOCK8, *Mucosal Immunology* (2023). DOI: 10.1016/j.mucimm.2023.12.001

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