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# Gene's role in immunological response is new lead for allergy treatment

*Research points the way to new relief strategies targeting a range of human allergies*

Medical researchers have known for decades what in general underlies a range of immune reactions in humans, from slight localized swelling in the case of insect bites, to hives and worse for people with hypersensitivity to certain foods and chemicals. Researchers at RIKEN are reporting they have isolated what they believe is the specific factor in such allergic responses: a calcium-linked protein activated by a gene in mammalian mast cells.

The discovery may lead to new gene-based approaches on how to treat certain allergies and even prevent anaphylactic shock, which can be fatal in the worst cases of food and chemical allergies.

Mast cells are resident cells of several types of human tissues, including the skin, and contain granules rich in histamine and heparin that play a key part in the body's immunological protection. When activated, the mast cell rapidly releases its granules and various hormonal mediators. Mast cells can be stimulated to 'degranulate' by direct injury, cross-linking of immune receptors, or - in the case of a mosquito bite - as a response to previous exposure to proteins resident in mosquito saliva.

What induces the cells to do this has been the focus of several earlier immunological studies that explored a chain reaction in which calcium ($Ca^{2+}$) is released as part of a two-stage process in the body's immune response. In the first stage, stores of $Ca^{2+}$ within the tissue cells are released at or near the site of the invasion or injury. In the second stage, a sustained influx of extracellular $Ca^{2+}$ occurs across the plasma membrane of the cells. Initiation of this second step had been thought to result directly from the emptying of the $Ca^{2+}$ stores, thus activating $Ca^{2+}$ channels within the plasma membrane. But the earlier research has not been conclusive on this point.

Until now, just how this calcium influx is specifically triggered has not been understood. To gain greater insight, the RIKEN researchers used a genome screen of mouse RNA

and subsequently identified a gene, *Stim1*, which acts as a sensor to alert when there is a depletion of the calcium stores. Working backwards, they removed the STIM1 protein from the tissues of lab mice. Through a series of tests they showed that the absence of the STIM1 protein either substantially or completely abolished $Ca^{2+}$ influx in the mouse tissues when they were subjected to test allergens.

The researchers also noted that the failure of some people to exhibit normal immunity may be another consequence of deficiencies in STIM1-dependent immune response caused by defective intracellular signaling activity in mast cells. If so, among other possible applications, a 'genetic fix' might be useful in boosting the body's sagging natural defenses by raising the expression level of *Stim1*.

The RIKEN study showed as well that STIM1 figures in the body's anaphylactic response to tissue damage or biological or chemical invasions, including miniscule amounts that can kill hypersensitive individuals. These include bee stings, peanut ingestion and exposure to trace chemicals in the workplace. The researchers noted that the role STIM1 plays in such dangerous hypersensitivity warrants further investigation.

The findings were reported by a research team headed by Tomohiro Kurosaki at RIKEN Research Center for Allergy and Immunology in Yokohama.

**Original work:**

Baba, Y., Nishida, K., Fujii, Y., Hirano, T., Hikida, M. and Kurosaki, T.
Essential role for STIM1 in mast cell activation and anaphylactic responses
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