Protein suppresses allergic response in mice

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A protein in mice known as RGS13 suppresses allergic reactions, including the severe, life-threatening allergic reaction known as anaphylaxis, according to scientists at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). Because RGS13 is also a protein found in humans and is expressed in only a limited number of cells—including the immune system's mast cells that are central to allergic reactions—scientists believe the protein may be an attractive target for developing new drugs to treat and prevent certain allergic reactions, including anaphylaxis.

"We still do not know what triggers the allergic or anaphylactic reaction in some people," says NIAID Director Anthony S. Fauci, M.D. "These findings open up important research avenues, such as examining the role of RGS13 protein in humans to determine if its deficiency or abnormal function triggers the mast cells to release chemicals that cause allergic diseases."

The research, led by Kirk M. Druey, M.D., senior investigator, at the Laboratory of Allergic Diseases at NIAID, is described in a report online in *Nature Immunology*.

RGS13 is one of a large group of regulator of G protein signaling (RGS) proteins that act as traffic lights for signaling networks within cells. Though the biochemical actions of most RGS proteins in laboratory tests are known, their physiological functions in the body are still a mystery. Therefore, the current findings may have broader implications for many different biological processes, such as metabolism, cancer progression,

cardiac function and others.

Mast cells serve an important role in normal immune function, but little is known about what triggers these cells to sometimes become overactive and cause allergic reactions. The severity of an allergic reaction depends on the quantity of chemicals (histamines, prostaglandins and leukotrienes) released by mast cells. Serious, quick-onset allergic reactions affecting multiple organs of the body can lead to anaphylaxis, which is characterized by a drop in blood pressure, fainting episodes, difficulty in breathing, and sometimes death.

RGS13 is known to inhibit cellular responses induced by G-protein-coupled receptors, which are the most abundant cell surface receptors in the body. It is also known that these receptors are the targets of approximately 60 percent of therapeutic drugs for various diseases. Since RGS13 is expressed in mast cells, Dr. Druey and his NIAID colleagues decided to explore the role of RGS13 in mouse models of anaphylaxis. Through genetic engineering, they made a group of mice deficient in the RGS13 gene. Normal mice served as the control group.

First, the NIAID team compared localized anaphylactic reactions in the two groups. They injected an allergen, IgE antibody and a blue dye under the skin of the mice, similar to the allergy skin test done by physicians. The results showed that RGS13-deficient mice had a larger and more intense blue reaction than normal mice, indicating that their blood vessels leaked more.

To test for systemic anaphylaxis, they injected the allergen, IgE antibody and a blue dye directly into the veins of the mice. The organs of RGS13-deficient mice showed an anaphylactic response that was twice as large as that of the normal mice. In both cases, the results indicate that RGS13 suppresses the anaphylactic response in mice, whereas RGS13 deficiency and abnormal RGS13 expression and function contribute to

increased mast cell activity, which occurs during an allergic response, including anaphylaxis.

According to Dr. Druey, the study is also important because for the first time, researchers have shown that RGS13 inhibits the activity of PI3 kinase, an enzyme involved in many biological processes, including those involved in cancer and diabetes. Therefore, the research has implications for numerous other diseases and medical conditions in addition to allergies.

Next, the NIAID team will analyze the expression of RGS13 in human mast cells in healthy individuals and in people with allergy or anaphylaxis, search for specific gene mutations in these populations, and determine whether abnormal expression or function of RGS13 correlates with specific allergic diseases.

Source: National Institute of Allergy and Infectious Diseases