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Abnormal immune cells may cause unprovoked anaphylaxis

Two new clinical reports shed light on why some people suffer from recurrent episodes of idiopathic anaphylaxis--a potentially life-threatening condition of unknown cause characterized by a drop in blood pressure, fainting episodes, difficulty in breathing, and wheezing.

In some of these individuals, researchers have found mast cells (a type of immune cell involved in allergic reactions) that have a mutated cell surface receptor that disturbs normal processes within the cell. Scientists supported by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), say the association of this mutation with unprovoked anaphylaxis is striking. The hope is that these individuals may respond to inhibitors targeting the mutated cell surface receptor.

While some people suffer anaphylaxis as part of a serious allergic reaction, in two out of three people, anaphylaxis has no known cause and thus the anaphylactic reaction is called idiopathic.

Anaphylaxis occurs when mast cells release large quantities of chemicals (histamines, prostaglandins and leukotrienes) that cause blood vessels to leak, bronchial tissues to swell and blood pressure to drop. Resulting conditions such as shock and unconsciousness usually resolve in most people treated with epinephrine (adrenaline) and first aid measures. In rare cases, however, death may occur.

Abnormally low blood pressure and fainting episodes are also features of mastocytosis--a disease in which people have an excessive number of mast cells. Several years ago, Dean Metcalfe, M.D., chief of the Laboratory of Allergic Diseases at NIAID, Cem Akin, M.D., Ph.D., and their NIAID colleagues decided to find out whether idiopathic anaphylaxis might have a genetic trigger related to that seen in mastocytosis. It is known that systemic mastocytosis in adults often results from a mutation in the Kit receptor found on the surface of mast cells, a discovery first made by Dr. Metcalfe's team in 1995.

The mutation causes an abnormal growth of mast cells, as is observed in bone marrow biopsies of patients with mastocytosis. So the NIAID team asked, if the Kit mutation could make mast cells grow and cause mastocytosis, and this was associated with anaphylactic reactions, could the same mutation predispose mast cells to release chemicals responsible for idiopathic anaphylaxis?

In a two-year study conducted at the NIH Clinical Center, the researchers examined 48 patients diagnosed with mastocytosis with or without associated anaphylaxis, 12 patients with idiopathic anaphylaxis, and 12 patients with neither disease. Within the group of 12 patients who had idiopathic anaphylaxis, five were found with evidence of a disorder in a line of mast cells (clonal mast cell disorder). The researchers looked for evidence of a Kit mutation in three patients by analyzing bone marrow samples, and all three samples yielded a positive result. The findings demonstrate that some patients with idiopathic anaphylaxis have an aberrant population of mast cells with mutated Kit.

"We believe the mutation may be predisposing people to idiopathic anaphylaxis," says Dr. Metcalfe. "Our findings suggest that in patients with idiopathic anaphylaxis as well as in people with severe allergies, we should look for critical genetic mutations that may change the way a mast cell reacts."

Dr. Metcalfe and his NIAID colleagues report their findings in two journals. The study that appears in an early online edition in Blood describes the presence of an abnormal mast cell population in a subset of patients with idiopathic anaphylaxis. The findings about the mechanism leading to mass cell activation by Kit and the IgE receptor responsible for allergic reactions appear online in Cellular Signalling.

According to the NIAID team, both Kit and the IgE receptor responsible for allergic reactions activate mast cells via a common interior protein of mast cells. They also found that the mutated Kit markedly elevates the activity of that protein, which results in increased cell signaling.

The scientists are now looking to see if artificial mast cells with mutated Kit behave or release chemicals in a manner different from normal mast cells, and also if they respond to inhibitors targeting Kit.

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