Study helps explain how allergic reactions are triggered

January 14 2008

In demonstrating that a group of calcium ion channels play a crucial role in triggering inflammatory responses, researchers at Beth Israel Deaconess Medical Center (BIDMC) have not only solved a longstanding molecular mystery regarding the onset of asthma and allergy symptoms, but have also provided a fundamental discovery regarding the functioning of mast cells. Their findings appear in the January 2008 issue of *Nature Immunology*.

A group of immune cells found in tissues throughout the body, mast cells were once exclusively known for their role in allergic reactions, according to the study's lead author Monika Vig, PhD, an investigator in the Department of Pathology at BIDMC and Instructor of Medicine at Harvard Medical School. "Mast cells store inflammatory cytokines and compounds [including histamine and heparin] in sacs called granules," she explains. "When the mast cells encounter an allergen – pollen, for example – they 'degranuate,' releasing their contents and triggering allergic reactions."

But, she adds, in recent years, scientists have uncovered numerous other roles for mast cells, suggesting they are key to a number of biological processes and are involved in diseases ranging from multiple sclerosis and rheumatoid arthritis to cancer and atherosclerosis.

In order for mast cells to function, they require a biological signal – specifically, calcium. Calcium moves in and out of the cells by way of ion channels known as CRAC (calcium-release-activated calcium)

currents. Last year, several research groups, including Vig's, identified CRACM1 as being the exact gene that was encoding for this calcium channel.

"With the identification of this long-elusive gene, we were able to create a knockout mouse that lacked CRACM1, and [as predicted] these animals proved to be resistant to various stimuli that usually cause severe allergic reactions," she explains. Further experiments demonstrated that mast cells removed from the CRACM1 knockouts were not able to take in calcium, and therefore, were unable to provoke allergic responses when they were exposed to allergens.

"These findings provide the genetic demonstration that CRAC channels are essential in mast-cell activation," notes senior author Jean-Pierre Kinet, MD, BIDMC Professor of Pathology at Harvard Medical School. "This provides the proof of concept that an inhibitor of the CRAC channel should be able to impact mast-cell related diseases, including asthma and allergic diseases."

Adds Vig, "Since mast cells are also known to contribute to the progression of several other debilitating diseases, including multiple sclerosis, rheumatoid arthritis and cancer, an inhibitor of the CRAC channel could, in the future, help in slowing the progression of these diseases as well as alleviate disease symptoms."

Source: Beth Israel Deaconess Medical Center