Multi-tasking molecule holds key to allergic reactions

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As the summer approaches most of us rejoice, reach for the sunscreen and head outdoors. But an ever-growing number of people reach for tissue instead as pollen leaves eyes watering, noses running and spirits dwindling. Hay fever is just one of a host of hypersensitivity allergic diseases that cause suffering worldwide and others, such as severe reactions to bee stings or eating peanuts, can be more serious and even fatal.

Now, scientists at the Salk Institute for Biological Studies have uncovered the molecular mechanisms behind such allergies, insight they hope will lead to new therapies, both to stop the summer sneezing and treat more severe allergic responses.

"These results may allow us to develop acute inhibitors of allergic reactions that do not have the side-effects of current treatments such as drowsiness," says Inder Verma, Ph.D., a professor in the Laboratory of Genetics and senior author of the study published in the August 8 issue of *Cell.*

When our bodies encounter an allergen (such as pollen), specialized cells called mast cells undergo "de-granulation", during which they release the chemical histamine. Histamine in turn causes fluid to build up in the surrounding tissue. When this process is working normally it offers protection against the allergen but in people with allergic diseases, de-granulation can occur throughout the body, leading to severe inflammation and in the worst cases, anaphylactic shock and death.

And allergies are a growing problem the world over. "One out of three Japanese people suffer from allergies," says postdoctoral researcher Kotaro Suzuki, Ph.D., who led the current study.

During de-granulation, histamine is bundled into membrane bound sacks called vesicles, which then transport it to the cell surface. When the vesicles reach the surface they fuse with the outer membrane of the cell, spilling their contents into the extra-cellular space in a process known as exocytosis. To prevent this process from going overboard the scientists first had to understand how de-granulation is regulated.

Their hunch was that the allergic response would involve NF-?B, a protein found in the nucleus that regulates gene expression and was already known to be involved in other types of immune response. To investigate this hypothesis they focused on the role of IKK2, a protein kinase, which is essential for NF-?B activation.

To generate mast cells that were free of IKK2, the researchers transplanted mice that had no mast cells of their own with either normal mast cells or mast cells that lacked IKK2. Strikingly, mice with mast cells lacking IKK2 had reduced allergic reactions. The researchers assumed that the lowered response was due to reduced NF-?B, but to their surprise, inactivating NF-?B signaling alone did not have the same effect. "That was one of the first clues that IKK2 had other roles to play," says Verma.

"IKK2 knock out mast cells couldn't release enough histamine," added Suzuki 'but we still didn't know the molecular mechanisms." What they did know already was that de-granulation requires a collection of proteins — known as the SNARE complex — to assemble at the cell surface.

Suzuki and Verma used biochemical analysis to show that when an

allergen is present, IKK2 binds to and activates one particular SNARE component called SNAP-23. Without IKK2, SNAP-23 is missing from the SNARE complex and conversely, when SNAP-23 is permanently activated, removing IKK2 no longer impairs de-granulation. "This is the first major feather on the cap of IKK2 in addition to NF-?B," says Verma.

But IKK2's role in the allergic response does not stop there - it multi-tasks. After the rapid "early phase" de-granulation response, mast cells undergo a "late-phase" reaction during which certain genes are turned on to help fight the allergen. Suzuki and Verma showed that the late-phase response also requires IKK2, but that this time it functions by its more usual route - via NF-?B.

The Salk researchers are now testing inhibitors of IKK2 as acute treatment for allergic reactions. Unlike anti-histamines, which are currently used to combat allergies, IKK2 inhibitors would have the added benefit of reducing both the early and late phase allergic responses.

And the newly discovered role for IKK2's may not be limited to allergic reactions. Many fundamental processes in our bodies involve exocytosis, ranging from secretion of insulin in the pancreas to synaptic transmission, the process by which signals are passed from one nerve cell to another. If IKK2 is involved in these processes it may have a role in other pathologies such as diabetes and nervous system diseases.

Source: Salk Institute