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One of life's most common compounds causes allergic inflammation

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The beetle's back and the crab's shell owe their toughness to a common compound called chitin that now appears to trigger airway inflammation and possibly asthma, UCSF scientists have found.

Insects, molds and parasitic worms – all common sources of allergies or inflammation -- produce billions of tons of chitin a year. Humans and other mammals lack chitin, but we do have specialized enzymes to break it down. The scientists wondered why.

They discovered that chitin triggers an allergic inflammatory response in the lungs of mice, as well as increased production of the chitin-destroying enzyme made by cells lining the lung airways. This and other results support their hypothesis, still under study, that chitin causes inflammation and allergy, and that the chitin-destroying enzyme in the lung could play an important role in regulating the body's response.

The results of their studies on inflammation in mice were reported April 22 in an early online publication by the journal "Nature." The journal will also publish the finding in an upcoming print edition.

"Now that we've demonstrated that chitin can trigger this kind of allergic inflammation in mice, we want to determine whether chitin naturally present in the environment can contribute to allergic or inflammatory responses," said Richard Locksley, MD, the Sandler Distinguished Professor of Medicine and Microbiology and Immunology at UCSF and senior author of the paper. Locksley is also a Howard Hughes Medical

Institute investigator.

In people, the anti-chitin enzyme is known to have several variants due to small mutations in the gene. Locksley and colleagues at UCSF are trying to determine if some of the variants are less effective at breaking down chitin, and if people with those variants are more prone to asthma because they are less able to control their exposure to inhaled chitin.

The researchers knew that the mouth and eggshells of parasitic worms are chitin-rich and that infection by the worms triggers an inflammatory response very similar to the kind that occurs in asthma and allergic disease. Using a gene chip containing most mouse genes and employing antibodies raised in the lab, the scientists confirmed an earlier finding that the gene and the protein for the anti-chitin enzyme were dramatically activated in mice during infection by the parasitic worms.

"Chitinase – the enzyme that breaks up chitin – really lit up," Locksley recalls. "It popped up as one of the most highly activated genes in response to the parasites." As the enzyme is only known to break down chitin, which is not present in mice, the scientists next exposed the animals to chitin alone, which induced tissue inflammation similar to that seen in mice after infection with worms and in humans with asthma.

Locksley thinks that the presence of chitin in molds, worms and insects, which can all invade humans by penetrating skin or mucus membranes, may have pressured vertebrates to maintain "chitin-recognition molecules," akin to those that evolved in plants and primitive animals to trigger recognition of invading bacteria and fungi.

He speculates that people normally mount an immune attack against an allergen or parasite in response to chitin, among other signals. This kind of inflammation is important in repelling the foreign allergen or parasite. In turn, the inflammatory cells themselves trigger cells in the invaded

tissue to ramp up production of the chitin-disabling enzyme.

The two actions together make a feedback system, both promoting recognition of the invading chitin-rich organisms, and preventing an out-of-control immune response to chitin by degrading the "signal" when enough inflammatory cells have accumulated to prompt increased production of the chitin-degrading enzyme.

Locksley notes that the shellfish processing industry has been plagued with "crab asthma" among its employees, an industrial hazard that has attracted the attention of the Centers for Disease Control and Prevention.

"Chitin exposure may be particularly high among industry workers, who need to remove and destroy the hard chitin shells of crabs and other crustaceans," he says. "It is also possible that afflicted workers have forms of the chitin-degrading protein that function less well than the other common genetic variants. These are areas we are interested in following up." He suggests that it might be worth confirming the chitin levels in shellfish processing plants, and, if high, considering ways to reduce exposure to chitin among workers.

His lab is now carrying out studies in collaboration with Esteban Burchard, MD, a UCSF assistant professor of biopharmaceutical sciences and of medicine, to determine whether patients with asthma will be more likely to have a less-active version of the gene for the anti-chitin enzyme.

In the last 10 years, the "hygiene hypothesis" has been proposed and explored to explain why asthma and other allergies have greatly increased in many industrial nations, Locksley explains. The hypothesis holds that modern societies have largely cleaned up living conditions so that people are exposed to far less dirt and all of its organic constituents.

At the same time, antibiotics and microbicides have reduced the numbers of microbes in the environment. Bacteria are known to degrade chitin, and Locksley suggests that the reduction in bacteria may lead to an increase of chitin in the environment – largely from molds and insects -- perhaps explaining the findings from several studies that the highest childhood asthma risk tends to be associated with the lowest exposure to bacteria.

Locksley is director of the Sandler Asthma Basic Research Center, or SABRE Center, at UCSF, a seven-year-old research organization devoted to the study of basic asthma pathogenesis with the intention of uncovering new directions for therapy in controlling the disease. The SABRE Center consists of a core basic science faculty, some of whom are still being recruited to UCSF, a larger group of interactive scientists from both basic science and clinical disciplines and core facilities in genetics, genomics, imaging, small animal physiology, flow cytometry and techniques for gene-inactivation that enable scientists to move new findings forward quickly.

"Asthma is increasing in all industrialized societies," he says, "not only in some of the less-served areas of large cities, but even in the suburbs. This is a huge health problem that impacts enormous numbers of children everywhere."

Like many modern afflictions, such as diabetes, autoimmune diseases and obesity, the causes are many, and reflect the interactions of many different genes. Understanding the environmental exposures, such as chitin, that may influence the development of asthma could lead to treatments or new public health practices to reduce the disease or the severity of its symptoms for many people.

Source: University of California - San Francisco