MedicalXpress

Key immune substance linked to asthma, study finds

July 1 2011

Stanford University School of Medicine investigators have linked a master molecule of the immune system, gamma-interferon, to the pathology of asthma, in a study of mice. This somewhat surprising finding — the key immune molecule has often been assumed to steer the immune system in a different direction from the cluster of allergic disorders to which asthma belongs — could lead to new treatments for the disease.

Gamma interferon's role in asthma has been fuzzy. High levels of this substance in children's blood seem to be protective against the development of asthma. Yet high gamma-interferon concentrations are often found in severe asthmatics' lungs. The new study, which will be published online July 1 in the *Journal of Clinical Investigation*, amasses several lines of evidence indicating that gamma-interferon may be contributing to the severity of asthma.

"People thought gamma-interferon might have something to do with driving asthma's pathology, but there wasn't a whole lot of corroborating evidence," said the study's senior author, Stephen Galli, MD, professor and chair of the Department of Pathology at Stanford medical school.

As many as 28 million people in the United States have asthma, whose prevalence has increased a great deal in the past few decades in developed countries. Asthma's signature symptom, extreme difficulty in breathing, is accompanied by transient narrowing and long-term inflammation of the air passages and, with time, lasting and detrimental

structural changes in the architecture of the lungs.

Gamma-interferon, a signaling molecule secreted by certain immune cells, mobilizes the immune system to fight infectious pathogens — or, inappropriately, to attack healthy tissues, resulting in autoimmune disease. Asthma has been thought to result from a quite different mode of immune-system response that battles multi-celled parasites such as intestinal worms, but can unfortunately also trigger allergic reactions.

Another prominent feature of asthma is local abundance and activation, in lung tissue, of immune cells called mast cells, along with increased numbers of other kinds of inflammatory cells. But mast cells appear to be particularly critical in the development of asthma. These cells carry, on their surfaces, outward-facing antibodies that, in some cases, bind to allergens such as cat dander, pollen or cockroach droppings. This spurs the mast cells to secrete substances that trigger an asthma attack.

Curiously, mast cells have receptors for gamma-interferon.

The researchers used a mouse model of asthma to pin down gamma-interferon's role in that disease. Galli credits the study's first author, Mang Yu, MD, PhD, a senior research scientist who works closely with Galli, with producing the animal model of asthma that was used in the study. Five years ago, Yu, Galli and their associates had reported on Yu's then-new method for inducing asthma-like symptoms in ordinary, otherwise healthy mice in a study published in the same journal. The method involves repeatedly exposing the mice to a foreign substance over a period of 12 weeks.

In that 2006 study, the Stanford team employed both Yu's asthma-inducing protocol and mast-cell-lacking mice — pioneered by Galli, a specialist in mast-cell biology, in the 1980s — to show that, as good as Yu's protocol may be at producing asthma-like features in normal mice,

it loses its ability to do so in mast-cell-free mice, even after those mice are supplied with mast cells that have been genetically altered so that all of their antibody-like surface receptors are defective. Providing those same mast-cell-lacking mice with healthy mast cells completely restored the protocol's capacity to induce asthma-like features.

In the new study, a similar approach — providing mast-cell-deficient mice with mast cells whose surface receptors for gamma interferon had been knocked out — showed a roughly equivalent ability to negate Yu's protocol's induction of asthma in the mice. Alternatively, giving fully functioning mast cells to such mice restored the protocol's power to trigger the asthma-associated symptoms and gene-activity level changes that normal mice develop under the regimen.

"This is potential important news, because it suggests that gamma-interferon might represent a therapeutic target," said Galli, who is also a professor of microbiology and immunology and the Mary Hewitt Loveless, MD Professor in the School of Medicine.

In addition to its discovery about gamma-interferon, the new study also further validated Yu's mouse model. Working with PhD student Alexander Morgan under the direction of his adviser, associate professor of pediatrics and of computer science Atul Butte, MD, PhD, the researchers were able to reproduce in such mice not only the gross symptoms of asthma but also the overall patterns of changes in the activity of genes in lung tissue that typify people with asthma.

Still, Galli said, "My MD doesn't stand for 'mouse doctor.' It stands for 'medical doctor.' And I recognize that human asthma is not necessarily the same as a mouse model of asthma, even a very good one like the one we're using. In implicating gamma-interferon as one of the drivers of pathology in this mouse model of asthma, we've raised just one question, which is: 'Could this also be true in humans and, if so, might interfering

with gamma-interferon be helpful in treating them?' Mang and I can work on mice until the cows come home, and we couldn't answer that question."

Galli added a further caveat. "Even if levels of gamma-interferon are high in patients with severe asthma, that doesn't necessarily mean that if you block gamma-interferon they're going to get better. That would have to be established in clinical tests of human patients" — a prospect that may not be all that remote.

"The reason severe asthma exists is that some people don't respond well to typical therapies," said Sally Wenzel, MD, director of the University of Pittsburgh Asthma Institute and a professor of medicine at that university, who has identified increased levels of gamma-interferon in the lungs of severe asthma patients. Wenzel, who is familiar with Galli's new study but did not participate in it, said that she and Galli intend to collaborate in further research "to see whether the findings he's observed in the mouse model actually apply to living, breathing, asthmatic human beings."

Provided by Stanford University Medical Center