New therapeutic targets for virally-induced asthma attacks suggested

May 29 2011

When children with asthma get the flu, they often land in the hospital gasping for air. Researchers at Children's Hospital Boston have found a previously unknown biological pathway explaining why influenza induces asthma attacks. Studies in a mouse model, published online May 29 by the journal *Nature Immunology*, reveal that influenza activates a newly recognized group of immune cells called natural helper cells – presenting a completely new set of drug targets for asthma.

If activation of these cells, or their asthma-inducing secretions, could be blocked, asthmatic children could be more effectively protected when they get the flu and possibly other viral infections, says senior investigator Dale Umetsu, MD, PhD, of Children's Division of Immunology.

Although most asthma is allergic in nature, attacks triggered by viral infection tend to be what put children in the hospital, reflecting the fact that this type of asthma isn't well controlled by existing drugs.

"Virtually 100 percent of asthmatics get worse with a viral infection," says Umetsu. "We really didn't know how that happened, but now we have an explanation, at least for influenza."

Natural helper cells were first, very recently, discovered in the intestines and are recognized to play a role in fighting parasitic worm infections as part of the innate immune system (our first line of immune defense).

"Since the lung is related to the gut – both are exposed to the environment – we asked if natural helper cells might also be in the lung and be important in asthma," Umetsu says.

Subsequent experiments, led by first authors Ya-Jen Chang, PhD, and Hye Young Kim, PhD, in Umetsu's lab, showed that the cells are indeed in the lung in a mouse model of influenza-induced asthma, but not in allergic asthma. The model showed that influenza A infection stimulates production of a compound called IL-33 that activates natural helper cells, which then secrete asthma-inducing compounds.

"Without these cells being activated, infection did not cause airway hyperreactivity, the cardinal feature of asthma," Umetsu says. "Now we can start to think of this pathway as a target – IL-33, the natural helper cell itself or the factors it produces."

Personalized medicine in asthma?

The study adds to a growing understanding of asthma as a collection of different processes, all causing airways to become twitchy and constricted. "In mouse models we're finding very distinct pathways," Umetsu says.

Most asthma-control drugs, such as inhaled corticosteroids, act on the best-known pathway, which involves immune cells known as TH2 cells, and which is important in allergic asthma. However, Umetsu's team showed in 2006 that a second group of cells, known as natural killer T-cells (NKT cells), are also important in asthma, and demonstrated their presence in the lungs of asthma patients. NKT cells, they showed, can function independently of TH2 cells, for example, when asthma is induced with ozone, a major component of air pollution. Compounds targeting NKT cells are now in preclinical development.

The recognition now of a third pathway for asthma, involving natural helper cells, may reflect the diversity of triggers for asthma seen in patients.

"Clinically, we knew there were different asthma triggers, but we thought there was only one pathway for asthma," Umetsu says, adding that all of the identified pathways can coexist in one person. "We need to understand the specific asthma pathways present in each individual with asthma and when they are triggered, so we can give the right treatment at the right time."

Provided by Children's Hospital Boston