Study shows how flu infections may prevent asthma

December 13 2010

In a paper that suggests a new strategy to prevent asthma, scientists at Children's Hospital Boston and their colleagues report that the influenza virus infection in young mice protected the mice as adults against the development of allergic asthma. The same protective effect was achieved by treating young mice with compound isolated from the bacterium *Helicobacter pylori* (*H. pylori*), a bacterium that colonizes the stomach and is best known for causing ulcers and increasing the risk of gastric cancers.

The findings, published online December 13 in the Journal of Clinical Investigation, provide a potential immunological mechanism in support of the "hygiene hypothesis," an idea that attributes the increasing rate of asthma and allergies to the successful reduction of childhood infections with vaccines and antibiotics. The hygiene hypothesis is also supported by epidemiological studies associating certain childhood infections, such as respiratory viral infections or gastrointestinal infection with *H. pylori*, with a lower risk of developing asthma.

"Some infections appear to result in important protective effects against asthma," says Dale Umetsu, MD, PhD, of Children's Division of Immunology, a senior author of the paper, and Professor of Pediatrics at Harvard Medical School. "But we certainly don't want to give people dangerous infections to prevent asthma. So if we can understand how infections prevent asthma, we may be able to replicate the good parts and avoid the bad parts of infection and develop new treatments for children to prevent asthma."

In mice, influenza A infection appeared to confer its benefits by expanding an immature cell type in the lung known as natural killer T (NKT) cells, part of the innate immune system. The same beneficial NKT cells in the lung could be expanded by several NKT-stimulating molecules known as glycolipids, including one isolated from *H. pylori*.

The active infectious agents protected against asthma only if the mice were exposed when very young (2 weeks). "Flu infection in adult mice makes the allergic reaction worse," says Ya–Jen Chang, PhD, first author and a postdoctoral fellow in Umetsu's lab.

Previous studies examining the hygiene hypothesis have focused on the adaptive immune system, which features immune cells that are slow to respond but are able to develop long-term memory, such as those stimulated by each year's flu vaccine or those involved in seasonal allergies.

In contrast, the new paper examines the innate immune system, which responds rapidly to infections and shapes adaptive immune responses. This study specifically focuses on NKT cells, one of the first responders to many infections. Previous work by Umetsu's team implicated NKT cells as a cause of asthma.

In contrast, the latest study reports on a new subset of inhibitory NKT cells that seem to prevent allergic reactions in the airways -- if stimulated at the right time by the right infectious agents or the right glycolipid.

"In the absence of influenza A or the *H. pylori* compound, we see an expansion of NKT cells that cause asthma and allergies," says Umetsu. "We're now trying to understand how to specifically activate the inhibitory subset of NKT cells. Treatments focused on specifically expanding this inhibitory subset of cells in children might prevent the development of asthma."

The researchers want to explore the therapeutic applications of the *H. pylori* glycolipid compound, synthesized by British lipid biochemist Petr Illarionov, PhD. "It might be a good candidate for an asthma vaccine," says Chang. Umetsu wants to test the next generation of glycolipid compounds, and to illuminate their specific mechanism of action, with a more detailed characterization of the inhibitory NKT cells.

Provided by Children's Hospital Boston