Researchers identify new regulator in allergic diseases

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Researchers have taken a critical step in understanding how allergic reactions occur after identifying a genetic signature for regulation of a key immune hormone, interleukin (IL-13).

Scientists from Cincinnati Children's Hospital Medical Center say the finding opens the potential for new molecular targets to treat allergic disease. They report on March 28 in *Mucosal Immunology* that a particular microRNA, miR-375, is regulated by IL-13, and in turns regulates how IL-13 induces pro-allergic changes, particularly in epithelial cells in the lung and esophagus.

The data support a role for miR-375 in asthma and in eosinophilic esophagitis (EoE), a severe, often painful food allergy that renders children unable to eat a wide variety of foods. EoE can also cause weight loss, vomiting, heartburn and swallowing difficulties.

"The identification of a microRNA that regulates IL-13-induced changes and inflammatory pathways is a significant advancement for the understanding and future treatment of allergic disease," says Marc E. Rothenberg, MD, senior investigator on the study and director of the Division of Allergy and Immunology and Center for Eosinophilic Disorders at Cincinnati Children's. "MiR-375 is proof of principle that microRNAs are involved in fine-tuning IL-13-mediated responses, which opens up a set of new possibilities for novel therapeutic targets for treatment of allergic disease."

IL-13 induces changes in epithelial gene and protein expression that are important in the onset of many allergic diseases, including EoE. Notably, expression of miR-375 was consistently downregulated after IL-13 stimulated human esophageal squamous and bronchial epithelial cells. Viral overexpression of miR-375 in epithelial cell cultures markedly modified the IL-13-associated immunoinflammatory pathways.

MicroRNAs are short segments of RNA that can regulate whether genetic messengers (mRNAs) are degraded or translated into protein.

In the current study, investigators stimulated esophageal and bronchial human epithelial cells with IL-13 and analyzed for differential microRNA expression. Decreases in miR-375 were observed in the human cells and also in an IL-13 transgenic mouse model. The researchers subsequently assessed miR-375 in patients with EoE, a human allergic disease characterized by IL-13 overproduction, and in healthy individuals.

Interestingly, the researchers found that decreased expression of miR-375 correlates significantly with disease activity, the degree of allergic inflammation and that miR-375 expression normalizes with disease remission. While this suggests miR-375's potential use as a disease activity biomarker for certain allergic diseases, changes in IL-13-mediated inflammatory pathways with viral overexpression of miR-375 in epithelial cell cultures also hint at its therapeutic potential.

Allergic diseases have been on the rise over the past 20 years, with approximately one of every 13 children having food allergies and over 2.5 million children suffering from allergic asthma. Only recently recognized as a distinct condition, the incidence of EoE has also been increasing. Rothenberg and his laboratory team pioneered research showing EoE's reported incidence is estimated to be at least one in 1,000 people. Its hallmark is swelling and inflammation in the esophagus,

accompanied by high levels of immune cells called eosinophils.

EoE can affect people of any age, but is more common among young men who have a history of other allergic diseases, such as asthma and eczema. EoE is often first discovered in children with feeding difficulties and failure to thrive, but it is often misunderstood and not well known, delaying proper diagnosis and treatment.

Provided by Cincinnati Children's Hospital Medical Center