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Discovery of Impaired Barrier Function in Eosinophilic Esophagitis

CINCINNATI - Researchers have identified impaired barrier function in eosinophilic esophagitis (EoE), a severe, often painful food allergy that renders children unable to eat a wide variety of foods.

Eosinophils are normal cellular components of the blood, but when the body produces too many eosinophils they can cause a variety of eosinophilic disorders. These are disorders involving chronic inflammation resulting in tissue damage, often in the gastrointestinal system.

Researchers from Cincinnati Children's Hospital Medical Center, University of North Carolina School of Medicine and Nestle Research Centre in Switzerland investigated desmosomal cadherin desmoglein 1 (DSG-1), an essential intercellular adhesion molecule that is altered in various human skin disorders. Examining esophageal biopsies from patients with EoE, the investigators observed a specific decrease in DSG-1. They further demonstrated that decreasing expression of DSG-1 weakened the barrier function of the esophageal epithelium, suggesting a potential mechanism by which patients with EoE are hypersensitized to food antigens.

In addition, the research team showed that decreased levels of DSG-1induced similar changes in gene expression to the changes observed in the inflamed esophageal mucosa of patients. Notably, the most induced overlapping gene was periostin, a multipotent proinflammatory extracellular matrix molecule. Further experiments identified a direct connection between DSG-1 and periostin, with decreased DSG-1 leading to periostin expression.

"This finding is incredibly exciting," says Marc Rothenberg, MD, PhD, the Director of the Division of Allergy and Immunology and Cincinnati Center for Eosinophilic Disorders at Cincinnati Children's and corresponding author of the study, "Periostin is currently one of the most interesting and hottest molecules in the allergy and asthma field. In this study, we have identified a mechanism by which impaired barrier function, triggered by decreased DSG-1, induces allergic responses by triggering induction of periostin."

This study, published online in *Mucosal Immunology*, is the first to identify impaired barrier function in EoE, as well as the underlying mechanism, and has broad implications for treating allergic diseases – particularly eosinophil-associated disorders.

"On the basis of these findings, therapeutics designed to improve barrier function may be a new approach for treatment," says Joseph Sherrill, PhD, a faculty research instructor at the Division of Allergy and Immunology at Cincinnati Children's and first author of the study.

These findings combined with the recent report by Dr. Eli Sphrecher's group (Samuelov *Nat Genet*. 2013;45(10):1244-8) showing that genetic defects in DSG-1 induce a severe allergic state including EoE in humans definitively points to this pathway as a cause of atopy.

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.

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