MedicalXpress

Protein associated with allergic response causes airway changes in asthma patients

March 22 2011

Changes that occur in the airways of asthma patients are in part caused by the naturally occurring protein interleukin-13 (IL-13) which stimulates invasion of airway cells called fibroblasts, according to a study conducted by researchers at Duke University. The study is the latest effort by researchers to better understand the processes that are involved in airway remodeling that can cause breathing difficulties in patients with asthma.
The findings were published online ahead of the print edition of the American Thoracic Society's American Journal of Respiratory and Critical Care Medicine.

"In the present study, we show for the first time that airway fibroblasts, isolated directly from patients with asthma and stimulated with IL-13, invade in significantly greater numbers than those isolated from normal control subjects," said Jennifer Ingram, PhD, assistant research professor of medicine at Duke University.

"In this novel mechanism of airway remodeling in asthma patients, IL-13 acts in combination with other mediators produced by cells in the airways: transforming growth factor-β1 (TGF-β1), which causes cellular changes, and matrix metalloproteinases (MMPs), which act to break down proteins," she added. "Together, these agents cause cellular changes that lead to loss of lung function in asthma patients."

Airway remodeling occurs in patients in whom asthma is not adequately controlled over a long period of time. In these patients, persistent

inflammation of the airways can cause an increased thickness in airway walls, increased mucus production and proliferation of blood vessels in the airways, all of which can interfere with normal breathing.

Many of the fibroblast responses that occur in airway remodeling are comparable to the interaction between cancer cells and connective tissue cells called stromal fibroblasts. Studies have shown these fibroblasts actively produce pro-invasive factors that result in metastasis. Fibroblast production of TGF-β1 has been implicated as a key pro-invasive factor in colon, breast and squamous carcinomas. IL-13, a critical regulator of the allergic response, has been implicated in cellular invasion in cancer and rheumatoid arthritis.

"The invasion of fibroblasts into the airway in asthmatic patients is one of several key features of airway remodeling," Dr. Ingram noted. "In a normal response, fibroblasts begin wound healing by depositing proteins and interacting with inflammatory cells. In asthma, this wound healing and remodeling response in the airway becomes deranged and uncontrolled, leading to increased numbers of fibroblasts invading the airway and contributing to fibrosis with diminished lung function over time."

In this study, researchers enrolled 37 subjects, including 20 men and women with mild asthma who were not taking inhaled corticosteroids, and 17 healthy controls. All asthmatic subjects had been diagnosed with asthma for at least one year prior to study enrollment. Airway cells were collected from all patients using bronchoscopy and studied in a laboratory setting. After application of IL-13, invading cells were counted using microscopy.

At baseline, no significant difference in airway fibroblast invasion was observed between asthmatic subjects and controls. However, the addition of IL-13 resulted in a significant increase in airway fibroblast

invasion in asthma as compared to normal controls. In addition, airway fibroblasts of asthmatic subjects invaded in greater numbers than those of control subjects.

"These data indicate that IL-13 stimulates airway fibroblasts to invade and that this effect is specific for asthmatic airway fibroblasts," Dr. Ingram said. "We also demonstrated that this invasion response in asthma is mediated by both MMPs and TGF-β1, suggesting that both are critical mediators of the IL-13 pathway for invasion in asthma."

Because this study focused on the effect of IL-13 in patients with mild asthma, Dr. Ingram said future studies should be conducted to determine whether fibroblasts in severe asthmatics are more invasive.

"In addition, goals of future studies should focus on specific MMPs that are involved in remodeling, as well as characterization of the gene profiles of invading fibroblasts in order to further define this feature of airway remodeling," she said. "Development of therapies specifically targeting IL-13 may play a key role in preventing airway remodeling in asthma."

Provided by American Thoracic Society