Personalized therapy for asthma and COPD could soon be here

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Researchers at Washington University School of Medicine in St. Louis have defined a new type of immune response that is activated in patients with severe asthma and COPD (chronic obstructive pulmonary disease). Their discovery could dramatically improve diagnosis and treatment of patients with chronic inflammatory lung disease.

"We've cracked the first part of the molecular code that links a viral infection to the later development of chronic inflammatory diseases like asthma and COPD," says senior author Michael Holtzman, M.D., the Selma and Herman Seldin Professor of Medicine, director of the Division of Pulmonary and Critical Care Medicine and a pulmonary specialist at Barnes-Jewish Hospital. "With this information, we can more precisely diagnose and monitor these types of diseases and then better target our treatment to specific abnormalities. That's a big step forward from simply monitoring breathing status."

The findings, published online May 18, 2008, in *Nature Medicine*, promise a way to determine whether a patient's asthma or COPD is the result of a chronic immune response that can be turned on by a respiratory viral infection. Guided by these new findings, this type of immune response could be detected by monitoring specific types of inflammatory cells or molecules in the lung or potentially in the bloodstream, giving physicians a more precise approach to diagnosis and treatment of lung disease.

This type of testing could eventually tell physicians whether a patient's

condition is mild, moderate or severe, as well as track the effectiveness of treatment. It could also lead to the development of new types of drugs that target the underlying cause of inflammatory lung disease.

"With our results, we can now work on developing more rational ways to diagnose and monitor lung conditions such as asthma and COPD," Holtzman says. "As it stands now, the diagnosis of chronic lung disease generally depends on clinical judgment and standardized tests of lung function, but we have little that tells us what's going on in the patient's lungs at the cellular and molecular level."

Asthma and COPD are both serious lung diseases that cause shortness of breath, wheezing, coughing and fatigue. In the United States, about 20 million people have been diagnosed with asthma and about 12 million with COPD, which includes emphysema and chronic bronchitis. Holtzman's research aims to find therapies for these disorders that modify the underlying causes of the disease instead of simply suppressing symptoms as most present-day treatments do.

In this study, Holtzman and colleagues found that a common type of viral infection of the lung can leave behind a persistent trace of the virus. This viral remnant likely becomes an ongoing stimulus for a chronic immune response, which could last for long periods, even a lifetime. This response causes the cells in the lung passages to overproduce mucus and become hyper-reactive to irritants.

The research team uncovered the details of this immune process by studying mice that are infected with a respiratory virus that is very close to the type of viruses that cause similar infections in humans. When the mice got over their infection, they were left with chronic airway disease characterized by mucus production and increased airway reactivity to an inhaled irritant.

A key molecular feature of this chronic disease was the production of a powerful natural inflammatory substance, interleukin-13 (IL-13). Investigating the source of IL-13, the researchers tracked down a previously undescribed type of immune pathway. This pathway is part of the immune system that is supposed to be activated for only short periods of time. However, the investigators found that the pathway can also be persistently activated after viral infection, likely due to the pathway's ability to respond to viral remnants.

Under these conditions, they also found that the pathway is set up to amplify its own activity. This combination of persistent activity and positive feedback leads to the long-term production of IL-13 as well as other substances that then cause continuous inflammation in the lung tissue and the development of chronic lung disease.

The team of investigators confirmed that the same immune process could also be detected in the lungs of people with severe asthma and COPD. This type of immune response is typically associated with parasitic infections and allergic disease, but here it appears to be linked to viral infection and chronic inflammatory disease. Importantly, the response produces a specific array of compounds that can be detected in the lung and likely in the blood to serve as diagnostic markers of disease. The research team is now working to verify that the profile of biomarkers for this immune response can be used to diagnose patients with asthma and COPD.

In another recent article, Holtzman and colleagues identified another new type of immune mechanism that developed after respiratory viral infection and led to inflammatory lung disease. In this case, the virus triggered an allergic-type antibody response to cause the later development of disease. This pathway did not stay active quite as long but it still caused changes in the airways of the lungs that were similar to the disease found in humans with chronic asthma. The new findings

show that patients with severe asthma and COPD may also share some mechanisms that cause their disease.

"Now, we have identified two new immune pathways that lead to chronic lung disease, and we already have evidence for additional pathways," Holtzman says. "Our goal is to find distinct biological markers for each pathway. This will tell us how to diagnose and what to treat. Then, we must develop therapeutics that are directed to each type of response so that physicians can deliver a treatment that is tailored to the specific type of asthma or COPD found in that patient."

Deciphering these unique immune pathways also can identify new targets for drugs that could block the harmful immune responses, according to Holtzman. He says the findings could also make drug development much more accurate.

"There appear to be many distinct ways to cause asthma or COPD. If an experimental drug works on only one of these causes, it is likely to fail in drug trials that include a broad range of patients," he explains. "But if we can set up trials so the test drug is targeting a specific immune response and is given only to those who have that type of response, then we can more accurately determine whether the drug is beneficial."

Citation: Kim EY, Battaile JT, Patel AC, You Y, Agapov E, Grayson MH, Benoit LA, Byers DE, Alevy Y, Tucker J, Swanson S, Tidwell R, Tyner JW, Morton JD, Castro M, Polineni D, Patterson GA, Schwendener RA, Allard JD, Peltz G, Holtzman MJ. Persistent activation of an innate NKT cell-macrophage immune axis that translates respiratory viral infection into chronic lung disease. *Nature Medicine*, May 18, 2008 (advance online publication).

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