The Relationship Between Alpha-1 and COPD: Why Alpha-1 Matters to You Even If You Do Not Have It

In the fall of 2003, a distinguished scientific journal, the American Journal of Respiratory and Critical Care Medicine, published a special supplement, "Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency." This landmark publication aimed to do nothing less than change the way health professionals think about Alpha-1.

In probing Alpha-1's effects on the lung, researchers ask questions relevant to all COPD patients. They have difficulty breathing even on short walks. They wheeze or cough during the mildest exertion. And they may number as many as 32 million in the U.S. They are people with chronic obstructive pulmonary disease (COPD), a broad term that includes emphysema, chronic bronchitis, and other obstruction in the lungs. Not all COPD sufferers are Alphas. But in adults, Alpha-1 often manifests itself first as COPD.

The Alpha-1 community is an excellent study group for COPD for a variety of reasons. Alpha-1 is easily diagnosed, sufferers are often younger and have fewer co-morbidities (other health problems contributing to illness) than other pulmonary diseases, and Alpha-1 has a rapid progression. That's why the connection between Alpha-1 research and COPD research seems natural. In learning more precisely how Alpha-1 Antitrypsin (AAT) deficiency attacks the lungs, scientists also learn more about COPD.

Science is still looking for answers about the exact mechanism of COPD in general and Alpha-1-related lung disease in particular. With its resources and expertise, however, the Alpha-1 Foundation has contributed to taking the first steps—asking the right questions.

What Are Researchers Looking For?

• What role does AAT play in lung inflammation? "Inflammation is a hot topic in Alpha-1 research, if you'll pardon that choice of words," says Dr. Bruce Trapnell of the University of Cincinnati School Medicine, the Foundation's scientific director. For decades, scientists have blamed a protease-antiprotease imbalance for Alpha-1-related lung inflammation. Too little protective antiprotease (AAT) allows the body's infection-fighting proteases to attack lung tissue itself. But some researchers wonder, "Is it that simple?" Is something else at work—something that might inactivate AAT? Alpha-1 researchers investigating the anti-inflammatory role of AAT may also shed light on other forms of COPD.

• What role do proteases and antiproteases play in tissue injury? Since agents in cigarette smoke are capable of rapidly inactivating the antiprotease activity of even normal alpha-1 antitrypsin, some have suggested that all of COPD may be due to a deficiency of this important protein. The deficiency is genetic in those with Alpha-1 but in individuals with non-Alpha-1 COPD, the deficiency is a functional deficiency caused by the action of cigarette smoke, as well as other environmental agents, on the alpha-1 antitrypsin protein. Thus research on Alpha-1 has much broader application to COPD in general.

• What role does abnormal AAT play? Maybe this protease-antiprotease imbalance has nothing to do with inflammation at all. People with the "Z" gene not only produce low levels of AAT; the AAT that they do produce is abnormal. According to conventional medical wisdom, expression of this abnormal AAT primarily causes liver disease; lung disease is a secondary effect. But recent research indicates that abnormal AAT *itself* causes inflammation in the lung. Scientists would like to know why and how.

• How significant is lung inflammation in the presence of infection? "When you get pneumonia, for example, you get a ton of neutrophils in the lung to kill bacteria," says Trapnell. "There so many, the lung looks like cheese." In non-Alpha's with pneumonia, AAT protects the lung tissue from these massive armies of neutrophils. But in Alphas (who have limited AAT protection at best), the neutrophil armies may exacerbate (make even worse) a pre-existing, low-level inflammation. In other words, Alphas may suffer a spectrum of lung damage, from a low-level inflammation in the absence of infection to severe inflammation during a bout of pneumonia. Research is exploring this spectrum further and gauging its significance.

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