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Xenobiotic Enzymes and Genetics of COPD

To the Editor:

In a recent issue of CHEST (May 2004), Molfino1 reported that current knowledge of the genetics of COPD is limited. He clearly indicated that the inconsistent results from association studies of candidate genes and COPD may be due to the phenotype definitions used or to ethnic differences among the patients in the studies. That is why some preliminary conclusions can be drawn.

Although he cited many articles on candidate gene-association studies and linkage analyses, which have been reported for COPD patients, the pathogenesis of COPD associated with the xenobiotic enzyme has been totally neglected. It has been suggested that genetic polymorphisms in xenobiotic enzymes may have a role in individual susceptibility to oxidant-related lung disease.2-4 The first-pass metabolism of foreign compounds in the lung is an important protective mechanism against oxidative stress. The polymorphisms in the genes for cytochrome P450, microsomal epoxide hydrolase (mEPHX) and glutathione S-transferase (GST) P1, which are the enzymes involved in this protective process, had some bearing on individual susceptibility to the development of COPD.2-4 As shown in Figure 1, xenobiotics are closely associated with the oxidant-antioxidant imbalance, which is one of the two major hypotheses in the pathogenesis of smoke-related COPD. Further, oxidant-antioxidant imbalance causes the oxidative inactivation of antiproteases, alveolar epithelial injury, increased sequestration of neutrophils in the pulmonary microvasculature, and gene expression of proinflammatory mediators.

Each puff of a cigarette contains $10^{17}$ free radicals and about 4,000 substrates, including carcinogenic agents and other possible causative agents of COPD such as volatile aldehydes and hydrogen cyanide.5 Thus, defects in the detoxification of these xenobiotics and increased activity of oxidants play an important role in the development of COPD.6-8

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**Figure 1.** Hypothesis of genetic susceptibility to COPD.
reactive species may predispose smokers to airflow obstruction and emphysema. Indeed, mEPHX activity was significantly higher in patients with COPD, when compared to healthy control subjects. These findings have been supported by the study of Sandford and colleagues, who assessed a well-characterized cohort of patients from the Lung Health Study.

We have reported that the genetic polymorphism of exon 5 of smokers with GSTP1 is associated with the development of COPD in smokers. Because the GSTP1/Ile105 genotype is predominantly found in smokers with COPD (72%), but not in smokers without airflow limitation (52%), the GSTP1/Ile105 genotype may be less protective against the xenobiotics in tobacco smoke. Recent data further support the idea that the GSTP1/Ile105 homozygote is associated with an increase in IgE and histamine after challenge with diesel exhaust particles and allergens. Although cigarette smoking is the most important risk factor for the development of COPD, allergic airway inflammation, long-standing asthma, air pollutants, diesel exhaust particles, and xenobiotics also may cause irreversible airflow limitation such as COPD. It has been reported that tunnel workers being exposed to gases and particles from blasting and diesel exhausts are likely to develop COPD. Therefore, subjects exposed to diesel exhaust particles are susceptible to the accelerated decline of lung function, resulting in COPD.

There is growing evidence for the role of xenobiotics and antioxidant imbalance in the pathogenesis of airflow obstruction, which is supported by the results of association studies between COPD and variants in epoxide hydrolase and GSTs that detoxify free radicals and other tobacco products. Nevertheless, I would like to propose to Dr. Teramoto that, despite these findings, genetics may only take us this far. A more complete interpretation of how genes play a role in human lung disease requires a higher level of integration with computational genomics, proteomics, and lung physiology. Thus, isolated findings in one gene or gene family, while helpful in moving the field forward, may not provide a comprehensive answer.

Let’s Blame It on the Computer!

Inaccurate Spirometry Results?

To the Editor:

I read the article by Townsend et al (May 2004) with great interest as well as consternation. Although the authors would have the reader believe that the errors referred to are due to equipment error, based on the examples given, whether or not there is a hardware problem (eg, flow-sensor “zero error”) or a software problem (eg, the inability to delete inaccurate volume-time or flow-volume curves), the individual who is administering

12 Teramoto S, Kume H. The role of nuclear factor-κ B activation in airway inflammation following adenovirus infection and COPD. Chest 2001; 119:1294–1295

To the Editor:

I fully agree with Dr. Teramoto’s comments that xenobiotic enzymes seem to play a role in protecting the lung compartment but that their exact role in the pathogenesis of COPD is not clear. This is mentioned in my review (pages 1932 to 1933). Most of the findings described by Dr. Teramoto were also mentioned and referenced in my review.

Nevertheless, I would like to propose to Dr. Teramoto that, despite these findings, genetics may only take us this far. A more complete interpretation of how genes play a role in human lung disease requires a higher level of integration with computational genomics, proteomics, and lung physiology. Thus, isolated findings in one gene or gene family, while helpful in moving the field forward, may not provide a comprehensive answer.

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