Elevated Levels of Extracellular Superoxide Dismutase in Chronic Lung Disease and Characterization of Genetic Variants*

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Extracellular superoxide dismutase (EC-SOD) is the major extracellular antioxidant enzyme and is present at high levels in the lung. The biological role EC-SOD plays in normal and pathologic lung processes is not yet understood.

To begin to investigate whether or not this enzyme is involved in the pathogenesis of chronic lung disease, we surveyed serum EC-SOD levels in 155 consecutive pulmonary patients seen in the pulmonary outpatient clinics at Duke University. These patients represented a variety of lung diseases. In addition, 18 healthy individuals served as control subjects.

We found that those with chronic lung disease had a 30% elevation in serum EC-SOD levels compared with control subjects (p=0.0025). This statistically significant increase was preserved for both obstructive and restrictive lung diseases. Four of the patients with lung disease had markedly elevated serum levels (>10-fold above average). Subsequent characterization of these four outliers by Western blot and allele-specific reverse transcriptase-polymerase chain reaction (RT-PCR) analysis demonstrated that three of them contain a single base pair G to C missense mutation in the carboxy-terminal coding region of EC-SOD. This results in a single amino acid substitution of glycine for arginine (R213G) located in the positively charged heparin-binding region at position 213 of the mature protein, a position that may interfere with tissue localization and/or proteolytic cleavage. Allele-specific RT-PCR of DNA from the fourth individual using wild-type and R213G-specific primers failed to amplify a product, suggesting that this individual contains an undefined EC-SOD variant.

These results suggest that EC-SOD levels may be altered in pulmonary disease and that mutations in the heparin-binding region are associated with dramatic elevations in serum EC-SOD.

Genetics of Atopy and Asthma*

The Rationale Behind Promoter-Based Candidate Gene Studies

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Over the past 8 years, a tremendous interest has grown in identifying the genetics of a number of diseases, some of which may be unigenic in their transmission and hence adhere to mendelian principles. Others are complex and their elucidation of contribution of major genes represents a considerable effort aimed at identifying multiple loci and their interaction. The value of this sort of study is highlighted by our understanding of the genetic basis of diseases such as cystic fibrosis, the most common mendelian-based genetic disease in man, as well as more complex diseases such as Alzheimer’s disease. The study of the genetics of asthma is important to identify the contribution of multiple sets of genes that interact in producing the asthmatic syndrome in conjunction with proper environmental exposure to protein allergens or chemical sensitizers or even viral or bacterial products. This would be critical in identifying those populations at greater risk at different times in their lives and/or development.1,5 Therefore, in a complex syndrome like asthma, the predominance of a single gene or even the sole influence of a single gene or a single set of genes is very unlikely. A more credible scenario would involve the interaction of multiple sets of genes, each contributing a small amount to the pathophysiologic condition of asthma. Elucidation of these many genes will be critical to develop strategies aimed at genetic counseling and screening of individuals at risk as well as to inform us of potential mechanisms of disease that might serve as therapeutic targets in asthma. We are just at the beginning of this process and have only uncovered a few candidate genes at present (HLA, TCR, chromosome 5q cytokines, chromosome 11q FcERI, etc). With the identification of other candidate genes, we may come to a greater understanding of the pathogenesis of the asthmatic syndrome and we may then design new therapeutic options.

GENERAL APPROACHES

The development of techniques to actually sequence the human genome as outlined by the Human Genome Project, and worldwide attempts to collaborate with the genome project through efforts in western Europe, have made the genetic analysis of complex disease much more attractive over the past 5 to 6 years.6 In fact, the original approach of functional candidate gene cloning followed by chromosomal localization and case-control and family

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