complex alleles with the secretion of TNF-α and TNF-β by human mononuclear cells: a possible link to insulin-dependent diabetes mellitus. Eur J Immunol 1993; 23:224–231


Mutations in the Surfactant Protein C Gene Associated With Interstitial Lung Disease*

Lawrence M. Nogee, MD; Alston E. Dunbar III, MD; Susan Wert, PhD; Frederic Askin, MD, FCCP; Aaron Hamans; and Jeffrey A. Whitsett, MD

(CHEST 2002; 121:20S–21S)

Abbreviations: ILD = interstitial lung disease; SP-C = surfactant protein C

The molecular basis for most forms of interstitial lung disease (ILD) is unknown. We recently identified a splicing mutation (c.460 + 1G > A) in the gene encoding surfactant protein C (SP-C) in two affected individuals with familial ILD.1 To test the hypothesis that SP-C mutations cause both sporadic and familial lung disease, we analyzed the SP-C gene sequence in infants with chronic lung diseases of unknown etiology. Mutations on one allele of the SP-C gene were identified in 11 of 34 patients evaluated. One infant had a mutation in the same location, but with a different nucleotide substitution (G > T) as the patients with the c.460 + 1G > A mutation. The clinical, histopathologic, and biochemical findings of these patients were similar, and included skipping of exon 4, expression of an aberrantly migrating proprotein corresponding to the size of the deletion, and reduced amounts of normal pro-SP-C. However, neither parent had a history of lung disease or carried the mutation. The occurrence of a de novo mutation functionally

*From Johns Hopkins University (Drs. Nogee, Dunbar, and Askin), Baltimore, MD; University of Cincinnati (Drs. Wert and Whitsett), Cincinnati, OH; and Washington University (Dr. Hamans), St. Louis, MO.

Correspondence to: Lawrence M. Nogee, MD, Division of Neonatology, CMSC 6-104, Johns Hopkins Hospital, 600 N. Wolfe St, Baltimore, MD 21287

Thomas L. Petty 44th Annual Aspen Lung Conference: Pulmonary Genetics, Genomics, Gene Therapy

identical to a familial mutation in infants with the same phenotype strongly supports the hypothesis that the mutations were causally related to their lung disease. Missense SP-C mutations that resulted in amino-acid substitutions in residues highly conserved across species (P30 L, I73T, G100V, Y104H, P115 L, I126R, T187N, and L188R), as well as a frameshift mutation (140delA) associated with expression of a stable transcript, were identified in 10 other infants, 6 of whom had a family history of lung disease. None of the identified mutations were found on 100 control chromosomes, indicating that they are not common polymorphisms. We conclude that mutations in the SP-C gene are a cause of both familial and sporadic ILD. While the pathophysiologic mechanisms remain to be elucidated, the finding of mutations on one allele suggests a dominant negative effect on SP-C or pro-SP-C function or metabolism.

**Mapping Susceptibility Genes for the Induction of Pulmonary Fibrosis in Mice**

Richard K. Barth, PhD; LeRoy A. Hanchett, PhD; and Clare M. Baecher-Allan, PhD

References


**Uses of Expression Microarrays in Studies of Pulmonary Fibrosis, Asthma, Acute Lung Injury, and Emphysema**

Roger S. Mitchell Lecture

Dean Sheppard, MD

Expression microarrays are a powerful tool that could provide new information about the molecular pathways regulating common lung diseases. To exemplify how this tool can be useful, selected examples of informative experiments are reviewed. In studies relevant to asthma, the cytokine interleukin-13 has been shown to produce many of the phenotypic features of this disease, but the cellular targets in the airways and the molecular pathways activated are largely unknown. We have used microarrays to begin to dissect the different transcriptional responses of primary lung cells to this cytokine. In experiments designed to identify global transcriptional programs responsible for regulating lung inflammation and pulmonary fibrosis, we performed microarray experiments on lung tissue from wild-type mice and mice lacking a member of the integrin family known to be involved in activation of latent transforming growth factor (TGF)-β. In addition to identifying distinct cluster of genes involved in each of these processes, these studies led to the identification of novel pathways by which TGF-β can regulate acute lung injury and emphysema. Together, these examples demonstrate how careful using quantitative trait locus (QTL) analysis has led to the chromosomal assignment of two of these susceptibility loci. One susceptibility gene is located within a subregion of chromosome 6 that contains a cluster of genes that are members of the tumor necrosis factor (TNF)-receptor family, including the 55-kd TNF-α1 receptor. The second susceptibility gene has been mapped to the telomeric end of chromosome 13, within an interval encompassing fibroblast growth factor (FGF)-10, a member of the FGF gene family that is expressed predominantly in the developing lung. Analysis of allelic variation in these candidate genes is underway in order to evaluate their utility as genetic markers for fibrosis susceptibility and to elucidate their possible role in influencing the disease process.