ELSEVIER

SEMINARS IN PERINATOLOGY

ABCA3 Deficiency: Neonatal Respiratory Failure and Interstitial Lung Disease

Janine E. Bullard, MD,* Susan E. Wert, PhD,† and Lawrence M. Nogee, MD*

ABCA3 is a member of the ATP Binding Cassette family of proteins, transporters that hydrolyze ATP in order to move substrates across biological membranes. Mutations in the gene encoding ABCA3 have been found in children with severe neonatal respiratory disease and older children with some forms of interstitial lung disease. This review summarizes current knowledge concerning clinical, genetic, and pathologic features of the lung disease associated with mutations in the ABCA3 gene, and also briefly reviews some other forms of childhood interstitial lung diseases that have their antecedents in the neonatal period and may also have a genetic basis.

KEYWORDS newborn, pulmonary surfactant, respiratory distress syndrome, persistent pulmonary hypertension of the newborn, pulmonary alveolar proteinosis, desquamative interstitial pneumonitis, chronic pneumonitis of infancy, cellular interstitial pneumonitis

Hereditary SP-B deficiency was the first identified genetic cause of surfactant deficiency. Its recognition demonstrated that inborn errors of surfactant metabolism could result in severe neonatal lung disease, and suggested how genetic mechanisms could contribute to the development of neonatal lung disease.[1,2] Although many additional infants with SP-B deficiency have since been identified, there have also been reported many infants who have had similar clinical presentations as those of SP-B deficient infants, as well as similar appearing lung pathology, but for whom no mutations in the SP-B gene (*SFTPB*) could be identified.[3-5] Similarly, although SP-C gene (*SFTPC*) mutations may result in both neonatal lung disease and interstitial lung disease (ILD) in older children, they have accounted for only a minority of such cases.[6,7] These observations indicate that there are other genes in which mutations may result in both acute neonatal and chronic lung diseases. The most recently recognized genetic cause of lung disease involves mutations in the gene encoding member A3 of the ATP binding cassette (ABC) family of proteins, ABCA3; and although data are limited, mutations in this gene may prove to be the most frequent genetic cause of neonatal lung disease.

ABCA3 Gene and Protein

The ABC family of transporters is a large family of related transmembrane proteins that bind and hydrolyze ATP to translocate a wide variety of substrates across biological membranes.[8,9] These proteins share a common structure, with half-transporters having 6 membrane spanning domains and a cytoplasmic ATP-binding domain with conserved motifs and full transporters containing 12 transmembrane regions and 2 nucleotide-binding domains. The ABCA3 protein is encoded by a single gene, located on human chromosome 16 which contains 33 exons, with the first 3 exons being untranslated, and the gene is referred to as *ABCA3*.[10-16] *ABCA3* spans over 80,000 nucleotide bases and is transcribed into an approximately 6500-bp mRNA, which directs the synthesis of a 1704-amino-acid protein.[14] Although the cDNA for *ABCA3* was first isolated from thyroid tissue, it is most highly expressed in lung tissue. It is expressed at lower levels in a wide range of other human tissues, including heart, brain, and kidney, and platelets.[14,16] *ABCA3* expression in lung tissue is developmentally regulated in that its production increases with advancing gestational age and peaks around the time of delivery in the rat lung. *ABCA3* expression is also increased by glucocorticoids in vitro.[14,17]

Surfactant is a mixture of lipids and specific proteins

*Division of Neonatology, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD.
†Divisions of Neonatology and Pulmonary Biology, Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH.
Address reprint requests to Lawrence M. Nogee, MD, CMSC 6-104, 600 N. Wolfe Street, Baltimore, MD 21287-3200. E-mail: lnogee@jhmi.edu

0146-0005/06/$-see front matter
doi:10.1053/j.semperi.2005.12.001

needed to reduce alveolar surface tension and prevent end-expiratory atelectasis. Surfactant is synthesized, stored, and secreted by alveolar type II cells. ABCA3 is highly expressed in the lung and has been localized to the limiting membrane of lamellar bodies, which are the intracellular storage organelles for surfactant within the alveolar type II cells. An antibody directed against lamellar body membrane (LBM) proteins recognized a 180 kD protein, termed LBM 180, that was subsequently identified as ABCA3.[14,16,18] The function of ABCA3 is unknown. However, other members of the ABCA family of transporters are often involved in lipid transport. For example ABCA1 and ABCA4 transport cholesterol and phosphatidylethanolamine, respectively.[19] Because of the location of ABCA3 within the limiting membrane of alveolar type IIcells, the role of other ABCA subfamily proteins in lipid transport, and recent evidence demonstrating that ATPase activity is induced by lipids,[20] it is reasonable to hypothesize that ABCA3 transports phospholipids important for surfactant function. ABCA3 may either import lipids critical for surfactant function, such as disaturated phosphatidyl choline (DSPC) into lamellar bodies, or alternatively, export lipids that are deleterious to surfactant function from lamellar bodies, thereby enriching the lamellar bodies with surface active lipids.

Mutations in other ABC genes often result in human disease. For example, ABCA1 mutations result in disrupted transport of cholesterol and phospholipids leading to the development of the disease phenotypes, Tangier disease, and familial high density cholesterol (HDL) deficiency syndrome.[21,22] ABCA4 is a rod photoreceptor associated with autosomal recessive forms of blindness caused by retinal degeneration, including Stargardt disease, age-related macular degeneration, fundus flavimaculaus, cone-rod dystrophy, and retinitis pigementosa.[19,23] ABCC7 is more commonly known as cystic fibrosis transmembrane conductance regulator (CFTR). ABCC7 gene mutations result in cystic fibrosis, the most common genetic lung disease.[24-26] Given both the likely role of ABCA3 in surfactant function and the association of other ABC proteins with human disease, we hypothesized that mutations in *ABCA3* would result in severe surfactant deficiency. To test this hypothesis, DNA was examined from 21 infants who had symptoms of severe surfactant deficiency at birth.[27] The group of infants chosen for this study was highly selected from a larger group of infants enrolled in a study to identify infants with possible inborn errors of surfactant metabolism. It included 6 pairs of siblings who had similar disease as well as infants with a family history of consanguinity, thus making a genetic mechanism for lung disease likely in this group. Hereditary SP-B deficiency and *SFTPC* mutations were excluded as potential causes for lung disease by a combination of protein and genetic studies. As an autosomal recessive inheritance pattern was postulated, single nucleotide polymorphisms (SNPs) were first examined in the sibling pairs, with the rationale that if affected siblings were discordant for their *ABCA3* alleles, this would effectively exclude the *ABCA3* locus as being involved in their disease. However, 5 of the 6 pairs were concordant for the same pattern of SNPs in their *ABCA3* genes, consistent with ABCA3 being related to their disease. The thirty coding exons and flanking splice sites of their ABCA3 gene were then sequenced. Surprisingly, 16 of the 21 infants examined were found to have mutations in their ABCA3 gene, including children who were homozygous for nonsense mutations, which would exclude all ABCA3 production, thus establishing ABCA3 deficiency as the basis for their lung disease. Although it was not entirely surprising to find some infants with *ABCA3* mutations, the finding that over 75% of the infants studied were found to have mutations was unanticipated and suggests that ABCA3 deficiency is a relatively more frequent cause of severe neonatal respiratory disease than SP-B deficiency or *SFTPC* mutations. Larger studies are needed to fully evaluate the relative prevalence of these disorders, but given the larger size of *ABCA3* in comparison to *SFTPB* (10,000 bases) and *SFTPC* (3500 bases), it is reasonable that ABCA3 deficiency may be the most common of these disorders. Population-based estimates of *ABCA3* mutations are not yet available. There was considerable allelic heterogeneity in the initial group of ABCA3 deficient infants, with 12 different mutations identified and no common mutation that might be used as a tool to study the molecular genetic epidemiology of ABCA3 deficiency, much as the *SFTPB* mutation, 121ins2, has been useful in the study of SP-B deficiency.

Pathology

Histopathology findings in newborns with *ABCA3* mutations have included alveolar type II cell hyperplasia, variable degrees of interstitial thickening, and prominent foamy macrophages in the airspaces, often embedded in variable amounts of proteinaceous material.[27] These findings were usually interpreted by pathologists reviewing the histology as consistent with the disorders termed chronic pneumontis of infancy (CPI), desquamative interstitial pneumonitis (DIP), nonspecific interstitial pneumonitis (NSIP), and pulmonary alveolar proteiniosis (PAP). Pulmonary fibrosis was also a prominent feature in those infants with fatal disease. There was considerable heterogeneity in the findings between the different infants, and it should be noted that these findings are nonspecific and similar to those observed in infants with *SFTPB* and *SFTPC* mutations. Therefore, these findings are suggestive of an inborn error disrupting surfactant metabolism, but are not specific for the disorder. Moreover, it is likely that mutations in other genes essential for normal surfactant metabolism may result in similar clinical and histopathology findings. Potential candidate genes, in which mutations could result in a similar phenotype, include the enzymes needed for the proper processing of proSP-B and proSP-C to their mature forms found in extracellular surfactant, other transporters for surfactant components, as yet unidentified proteins needed for lamellar body assembly, or proteins important in surfactant secretion. Lamellar bodies are a lysosomally derived organelle, and disorders involving abnormal trafficking of lysosomal proteins have been described in patients with some forms of the genetically heterogeneous disease, Hermansky-Pudlak Syndrome (HPS) that