



Genetic disorders of surfactant homeostasis

Jeffrey A. Whitsett*

Division of Pulmonary Biology, MLC 7029, Department of Pediatrics, Cincinnati Children's Hospital Medical Center and the University of Cincinnati College of Medicine, 3333 Burnet Avenue, Cincinnati, OH 45229-3039, USA

KEYWORDS

pulmonary surfactant;
respiratory distress;
gene mutations

Summary Pulmonary surfactant reduces surface tension at the air-liquid interface in the alveolus, thereby maintaining lung volumes during the respiratory cycle. In premature newborn infants, the lack of surfactant causes atelectasis and respiratory failure, characteristic of respiratory of distress syndrome. Surfactant is comprised of lipids and associated proteins that are required for surfactant function. Surfactant proteins B and C and a lamellar body associated transport protein, ABCA3 play critical roles in surfactant synthesis and function. Mutations in the genes encoding these proteins cause lethal respiratory distress in newborn infants. This review discusses the clinical and pathological findings associated with these inherited disorders of alveolar homeostasis.

© 2006 Elsevier Ltd. All rights reserved.

Pulmonary surfactant is required for the reduction of surface tension at the air-liquid interface in the alveoli of the lung. Surfactant lipids and proteins are packaged and secreted by type II epithelial cells that line peripheral air-spaces. Surfactant function is dependent upon the interactions among the hydrophobic proteins, SP-B and SP-C, and surfactant phospholipids that contribute to the structural organization, spreading, and stability of surfactant in the alveolus. Mutations in genes encoding SP-B, SP-C, and ABCA3 (the latter required for formation of lamellar bodies), cause acute and chronic lung disease after birth. While it is well known that surfactant deficiency causes respiratory distress syndrome (RDS) in preterm infants, defects in pulmonary surfactant function are associated with various lung disorders in both children and adults. During the last decade, both clinical and animal studies have led to the recognition that mutations in the genes encoding the surfactant proteins SP-B and SP-C (SFTPB and SFTPC, respectively), and a lipid transport protein ABCA3 disrupt

surfactant homeostasis, and cause acute and chronic lung disease.^{1,2}

HEREDITARY SP-B DEFICIENCY CAUSED BY MUTATIONS IN SFTPB

SP-B is a 79 amino acid amphipathic protein. SP-B is packaged with phospholipids in the lamellar bodies, and secreted into the alveolus, where it stabilizes lipid films to reduce surface tension. SP-B or its precursor, proSP-B, regulate many aspects of surfactant homeostasis, being required for the processing of proSP-C, the formation of lamellar bodies, production of tubular myelin, the formation of active surfactant films, and the recycling of surfactant lipids and proteins. Deletion of the SP-B gene causes fatal RDS in newborn mice without the disruption of lung morphogenesis. Similarly, a number of mutations in the human gene encoding SP-B (SFTPB) cause fatal respiratory distress in newborn infants.³ In human infants, SP-B deficiency is inherited as an autosomal recessive gene that generally causes respiratory failure in the newborn period. Hereditary SP-B deficiency presents in full-term infants with refractory respiratory distress following birth. The diagnosis

* Tel.: +1 513 636 4830; Fax: +1 513 636 7868.

E-mail address: jeff.whitsett@cchmc.org.

can be made by the identification of mutations in the abnormal SFTPB genes. In general, SP-B is undetectable in lung lavage or tracheal aspirate fluid as assessed by ELISA or Western blot analysis. A partially processed proSP-C peptide accumulates in the airspaces, indicating that SP-B is required for the normal proteolytic processing or trafficking of SP-C. Abnormal accumulations of the mutant proSP-C protein are readily detected in the alveolar space by Western blot or immunohistochemistry. SP-B deficient infants do not have sustained responses to exogenous surfactant replacement, and generally die of respiratory failure in the first months of life. Lung transplantation has extended survival and improved the quality of life in a number of infants with hereditary SP-B deficiency.

SFTPC MUTATIONS AND ACUTE AND CHRONIC LUNG DISEASE

SP-C is a 34 amino acid, hydrophobic, alpha-helical protein that is selectively synthesized type II epithelial cells in the lung. Human SP-C is produced by proteolytic processing of the larger precursor protein of 191 amino acids during its routing to the lamellar bodies. SP-C is packaged with surfactant lipids before being secreted into the airspace. Like SP-B, SP-C interacts closely with the phospholipids in surfactant, enhancing their spreading and stability, and likely mediating recruitment of lipids to surface active multi-layers, and enhancing the recycling of surfactant lipids by type II cells. Defects in SP-C in transgenic mice results in alterations of surfactant stability, and in some mouse strains, cause severe interstitial lung disease with loss of alveoli, inflammation, and vascular remodeling, indicating that SP-C is required for the maintenance of normal lung structure and function. In humans, a number of mutations in the SFTPC gene have been identified in association with severe respiratory failure in newborn infants and, more commonly, with interstitial lung disease in children and adults.⁴ Disorders in SP-C metabolism are generally inherited as autosomal-dominant genes with variable penetrance. SP-C mutations cause severe interstitial lung disease with features of chronic pneumonitis of infancy (CPI) or non-specific interstitial pneumonitis (NSIP), depending on the age of presentation and therapies used to support the infants. Diagnosis of congenital SP-C related lung disease can be made by sequence of the SFTPC gene. To date, a number of mutations causing dominantly inherited lung disease, generally cause misfolding of the proSP-C peptide, resulting in incomplete processing, resulting in deficiency of SP-C in the airways. The misfolded protein is toxic to type II epithelial cells, and likely interferes with the routing and processing of the normal protein produced from the normal allele. There have been no definitive treatments identified for the therapy of SP-C related lung disease, although lung transplantation has improved longevity and

quality of life in a number of patients with severe interstitial lung disease caused by mutations in SP-C.

ABCA3 TRANSPORT PROTEIN AND RESPIRATORY FAILURE

ABCA3 is a member of a large class of Walker domain containing transmembrane proteins of ABC transporters known to translocate a number of substances across cell membranes. Related proteins include CFTR and other transmembrane proteins that are associated with human genetic diseases, including Tangiers disease, Stargardt's retinopathy, and others. Recent studies support the important role of ABCA3 in surfactant packaging and homeostasis. ABCA3 staining is found in alveolar type II epithelial cells, where it is localized to lamellar bodies. Mutations in ABCA3 in humans have been associated with autosomal recessive lung disease in newborn infants.⁵ ABCA3-related lung disease generally presents with respiratory distress in full-term infants, following birth. Respiratory distress is refractory to surfactant replacement and conventional therapies including assisted ventilation and other supportive measures. Electronmicroscopy demonstrates small, abnormally dense lamellar body-like organelles and the absence of normal lamellar bodies in type II epithelial cells from patients with ABCA3 mutations. A number of mutations have been identified in the ABCA3 gene, all inherited as autosomal-recessive alleles, primarily presenting as acute respiratory failure in newborn infants. ABCA3 mutations have been associated with chronic interstitial lung disease in older patients. The diagnosis of ABCA3 deficiency should be suspected in full-term infants with respiratory failure, failing conventional management, and with family histories of neonatal losses from respiratory distress, and consanguinity. Electronmicroscopy has been highly useful in the presence of the abnormal, dense lamellar bodies has been closely associated with mutations in ABCA3. Definitive diagnosis can be made by a gene sequence analysis, although the large size of the ABCA3 gene and heterogeneity of mutations has made this diagnosis technically difficult.

SUMMARY

In summary, mutations in the genes encoding SP-B, SP-C, and ABCA3 disrupt surfactant homeostasis within type II epithelial cells and cause respiratory distress in newborn infants. Together these genes represent a relatively rare cause of acute and chronic lung disease in newborn infants and children. Diagnosis of the inherited disorders of surfactant homeostasis should be suspected in full-term infants with acute or chronic respiratory disease that is refractory to conventional therapies. Both biochemical and genetic tests can be helpful in making a definitive diagnosis of familial disorders of surfactant homeostasis, could be useful

in management and genetic counseling of affected infants and their families.

REFERENCES

1. Whitsett JA, Weaver TE. Hydrophobic surfactant proteins in lung function and disease. *N Engl J Med* 2002; **347**: 2141–2148.
2. Whitsett JA, Wert SE, Trapnell BC. Genetic disorders influencing lung formation and function at birth. *Hum Mol Genet* 2004; **13**: R207–R215.
3. Nogee LM, Wert SE, Profitt SA, Hull WM, Whitsett JA. Allelic heterogeneity in hereditary surfactant protein B (SP-B) deficiency. *Am J Respir Crit Care Med* 2000; **161**: 973–981.
4. Nogee LM, Dunbar AE, Wert SE, Askin F, Hamvas A, Whitsett JA. A mutation in the surfactant protein C gene associated with familial interstitial lung disease. *N Engl J Med* 2001; **344**: 573–579.
5. Shulenin S, Nogee LM, Annilo T, Wert SE, Whitsett JA, Dean M. ABCA3 gene mutations in newborns with fatal surfactant deficiency. *N Engl J Med* 2004; **350**: 1296–1303.

Available online at www.sciencedirect.com

