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Review article

Evaluation and management of inherited disorders of surfactant metabolism

Aaron Hamvas

Keywords: *respiratory distress syndrome; newborn; genetics; lung transplantation*

Objective To review the pathophysiology, evaluation, management, and outcomes of children with inherited disorders of surfactant metabolism due to mutations in the genes encoding surfactant proteins-B or -C (*SFTPB*, *SFTPC*), ATP binding cassette member A3 (*ABCA3*), and thyroid transcription factor (*NKX2.1*).

Data sources Review of the literature, previous work from the author's and collaborators' laboratories, St. Louis Children's Hospital Lung Transplant Database.

Study selection Key articles in the field, author's work.

Results Inherited disorders of surfactant metabolism present as acute, severe respiratory dysfunction in the neonatal period (*SFTPB*, *ABCA3*, *NKX2.1*) or as chronic respiratory insufficiency in later infancy and childhood which is of variable onset, severity, and course (*SFTPC*, *ABCA3*, *NKX2.1*). Diagnosis is established with sequencing the relevant genes; lung biopsy with electron microscopy is a useful adjunct. For surfactant protein-B and *ABCA3* deficiency presenting with acute neonatal disease, treatment options are limited to lung transplantation or compassionate care. For the more chronic presentations of surfactant protein-C, *ABCA3*, and *NKX2.1* associated disease, the natural history is variable and therefore individualized, supportive care is appropriate,

Conclusions Inherited disorders of surfactant metabolism are rare, but informative diseases that provide unique opportunities for understanding mechanisms of respiratory disease in newborns and children.

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The pulmonary surfactant is a unique phospholipid and protein complex that is synthesized, packaged, and secreted by alveolar type II cells.¹⁻³ The phospholipid components constitute approximately 90% by weight of pulmonary surfactant, of which 70%–80% is phosphatidylcholine (PC). The protein components constitute approximately 10% by weight of pulmonary surfactant, half of which consists of four surfactant-associated proteins, surfactant proteins A, B, C, and D (SP-A, SP-B, SP-C, and SP-D). Pulmonary surfactant is unique in its abundance of dipalmitoylated PC (DPPC), which, along with SP-B and SP-C, lowers surface tension and prevents atelectasis at end-expiration. SP-A and SP-D participate in host defense in the lung. A regulated cycle of synthesis, secretion, and recycling involves both the phospholipid and protein components of pulmonary surfactant; SP-A and granulocyte-macrophage colony stimulating factor (GM-CSF) contribute to surfactant recycling and catabolism. The ATP binding cassette member A3 (*ABCA3*) is a transporter protein that is thought to transport phospholipid into lamellar bodies, the organelles within the alveolar type II cell in which the final processing and assembly of the surfactant components occurs prior to secretion. Thyroid transcription factor 1, encoded by the *NKX2.1* gene, regulates expression of many genes essential for lung development and function, including those encoding SP-B and SP-C (*SFTPB* and *SFTPC*, respectively).

INHERITED DISORDERS OF PULMONARY SURFACTANT METABOLISM

An overview of the known disorders of pulmonary surfactant metabolism associated with mutations in the surfactant proteins-B and C, *ABCA3*, and thyroid transcription factor genes is provided in Table 1. To date, no inherited deficiencies of SP-A or SP-D have been identified in the newborn period, although mutations in the gene encoding SP-A (*SFTPA2*) have been associated with idiopathic pulmonary fibrosis in adults.⁴

Two types of clinical presentation bring infants and children with inherited disorders of surfactant metabolism to attention. In the first and most dramatic, term newborns develop severe respiratory failure shortly after birth that requires significant ventilatory support, is minimally or transiently responsive to surfactant replacement, may require extracorporeal membrane oxygenation (ECMO), and fails to improve after the first week of life. Secondary pulmonary hypertension may accompany the clinical syndrome and may be partially responsive to inhaled nitric oxide. On chest X-rays,

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Table 1. Characteristics of surfactant disorders

Items	SP-B deficiency	ABCA3 deficiency		SP-C associated disorders	NKX2.1
		Acute	Chronic		
Presentation	Acute, neonatal period	Neonatal period	Interstitial lung disease in infancy and childhood	Interstitial lung disease in infancy and childhood	Acute neonatal RDS and older presentation of chronic lung disease
Frequency	1 per million		Unknown	Unknown	Unknown
Natural history	Lethal in newborn period	Lethal	Variable	Variable	Variable, associated with hypothyroidism and chorea
Inheritance	Recessive		Recessive	Dominant Sporadic and inherited	Dominant Sporadic and inherited
Diagnosis	Genetic analysis		Genetic analysis	Genetic analysis	Genetic analysis

diffuse haziness and air bronchograms mimic the appearance of RDS in premature infants. This acute presentation is typical for infants with loss of function mutations in *SFTPB* or *ABCA3*, but has also been seen in a small number of infants with mutations in *SFTPC* and *NKX2.1*, as well.⁵⁻⁸

A more chronic clinical presentation and variable course of disease has been seen in children with mutations in *SFTPC*, *ABCA3* and *NKX2.1*.⁸⁻¹¹ Some children may present in the newborn period with milder respiratory dysfunction that is ascribed to transient tachypnea of the newborn or congenital pneumonia while those presenting beyond the newborn period develop gradual onset of respiratory insufficiency, hypoxemia, failure to thrive and interstitial lung disease on chest radiographs. While some cases have had a history of an associated viral illness or chronic aspiration, these features have not consistently been elicited, suggesting that other genetic or environmental modifiers influence the presentation of disease. This variability in severity and course of the disease is not mutation specific and thus precludes accurate assessment of prognosis for an individual.

Although many premature infants have been evaluated, SP-B deficiency has not been identified in infants <30 weeks gestation, though no systematic analysis of the prevalence of disease in premature infants has been performed. In contrast, *ABCA3* mutations have been identified in premature infants whose respiratory dysfunction is more severe than would be anticipated for gestational age, which raises the question as to whether mutations in *ABCA3* may provide a genetic susceptibility for the risk and severity of RDS in newborns.¹²

SP-B deficiency

This autosomal recessive disorder is rare, with a disease frequency of approximately 1 per million live births in the United States. Over 30 mutations in *SFTPB* have been identified that result in partial to complete absence of SP-B protein. The most common mutation, a GAA substitution for C in codon 121, the "121ins2" mutation, is associated with approximately 70% of the cases of SP-B deficiency; the carrier frequency is approximately 1 per 1000 individuals.¹³ Though SP-B deficiency has been recognized in diverse racial and ethnic groups, a common haplotype bearing the 121ins2 mutation suggests a founder effect among people of European descent.¹⁴ Most

of the other identified mutations are family-specific and have all been inherited; no spontaneous mutations in *SFTPB* have been identified.

The absence of SP-B, the presence of an incompletely processed proSP-C, and a generalized disruption of surfactant metabolism cause surfactant dysfunction and the clinical syndrome. The threshold of mature SP-B expression required for normal surfactant function in humans is unknown. Patients with partial SP-B deficiency and approximately 10% of normal SP-B expression have a clinical picture similar to that of infants while heterozygous parents with presumably 50% of normal SP-B expression have normal respiratory function. Murine models that conditionally express SP-B develop respiratory failure when SP-B expression is approximately 25% of normal values.^{15,16} Thus, there appears to be a limited margin of SP-B expression that permits normal surfactant function, and any environmental or developmental condition that disrupts SP-B expression may result in significant respiratory dysfunction in genetically susceptible individuals.

ABCA3 deficiency

ABCA3 is most highly expressed in lung tissue, more specifically, on the limiting membrane of lamellar bodies in alveolar Type II cells, but is also expressed in the heart, brain, pancreas, kidney, and platelets.¹⁷⁻¹⁹ The frequency of disease due to recessive mutations in *ABCA3* in the population is unknown although preliminary studies suggest that *ABCA3* deficiency may be the most common of these disorders of surfactant homeostasis. Over 180 mutations in *ABCA3* have been identified in association with lethal RDS in newborns and with chronic respiratory insufficiency in children. One variant, a substitution of valine for glutamic acid in codon 292 (E292V) has been found in approximately 0.4% of the general population and in 4% of a cohort of infants with RDS, suggesting that this variant contributes to the risk or severity of respiratory disease in susceptible individuals.¹²

While the exact role of *ABCA3* in surfactant metabolism remains unknown, data from humans and mice suggest that *ABCA3* mediates PC and phosphatidylglycerol transport into lamellar bodies. This disrupted phospholipid transport leads to reduced surfactant function.^{5,20-22} The function of *ABCA3* in other tissues remains unknown.

Surfactant protein-C disorders

SP-C is a lung specific peptide that functions to lower surface tension. The frequency of disease due to mutations in *SFTPC* in the population is unknown. Over 35 dominant mutations in *SFTPC* have been identified in association with familial and sporadic acute and chronic lung disease in patients ranging in age from newborn to adult. The most common mutation is a threonine substitution for isoleucine in codon 73 (I73T) and is associated with 25% of the cases of both sporadic and inherited SP-C associated disease, but we failed to find it in a population-based screen of over 4000 individuals.^{10,12} A high degree of recombination within *SFTPC* may contribute to the high rate of spontaneous disease-causing mutations.²³

Mutations in *SFTPC* result in production of misfolded proSP-C that accumulates within cellular secretory pathways (endoplasmic reticulum and Golgi) in the alveolar type II cell resulting in activation of cell stress responses and apoptosis.^{24,25} It is unclear if the presence of proSP-C or the absence of mature SP-C impairs surfactant function, and furthermore, if this altered surfactant function contributes to the pathogenesis of symptomatic disease.

Disease associated with mutations in *NKX2.1*

Thyroid transcription factor is expressed in the brain, thyroid gland, and lung and is critical for the development of these organs. Dominantly expressed mutations in *NKX2.1* result in a constellation of hypothyroidism, choreoathetosis and respiratory disease: the "brain-thyroid-lung syndrome".^{8,26,27} The respiratory disease, if present, may manifest as RDS in the newborn period or as recurrent pulmonary infections or interstitial lung disease in later childhood. The frequency of disease and mutations is unknown. Over 20 mutations have been reported in the literature, but no common mutations have been identified. Similar to mutations in *SFTPC*, approximately half arise spontaneously.

Other lung diseases associated with surfactant-related genes

Mutations in the gene encoding the α -subunit of the granulocyte-macrophage colony stimulating factor receptor (*CSF2RA*) have been associated with pulmonary alveolar proteinosis in children and mutations in the surfactant protein A gene (*SFTPA2*) have been associated with idiopathic pulmonary fibrosis and lung cancer in adulthood.^{4,28}

DIAGNOSIS OF INHERITED DISORDERS OF SURFACTANT METABOLISM

Genetic analysis

Establishing a diagnosis of an inherited disorder of surfactant metabolism should occur promptly so that deliberate discussions of therapeutic options can proceed, especially in the cases of acute neonatal presentation.

Sequence analysis of the relevant genes, *SFTPB* and *ABCA3* for acute neonatal presentation and *SFTPC* and *ABCA3* for later onset presentation, provides the most direct means to establish a diagnosis, and is available in clinical and research laboratories. Associated hypothyroidism should prompt sequence analysis of *NKX2.1*. The relatively small sizes of *SFTPB* and *SFTPC* permit rapid results that can be incorporated into clinical discussions and decisions, whereas the significantly larger size of *ABCA3* makes the analysis more time consuming and more difficult to incorporate into clinical decisions in the face of a critically ill, rapidly deteriorating child. Further complicating genetic analysis is the fact that in all these genes, most mutations are family specific and distinguishing true disease causing mutations from rare yet benign sequence variants can be difficult.

Tissue analysis

Despite the severity of illness in many of these children, histopathologic evaluation of lung tissue can be a valuable adjunct to genetic diagnosis. At the time of lung biopsy, close coordination among the neonatologist or pulmonologist, surgeon, and pathologist is necessary to ensure that the tissue is prepared immediately and appropriately for electron microscopy, histopathology, and future molecular or proteomic analysis. A suggested tissue procurement procedure is outlined by Langston et al.²⁹ Sentinel findings of a surfactant metabolic disorder include diffuse alveolar type II cell hyperplasia, alveolar septal thickening and alveolar proteinosis. Examination of the lamellar body morphology with electron microscopy can also provide insight: disorganized lamellar bodies suggest SP-B deficiency while dense lamellar bodies or those with eccentric dense inclusions suggest *ABCA3* deficiency.^{7,30,31}

LUNG TRANSPLANTATION FOR INHERITED DISORDERS OF SURFACTANT METABOLISM

No mechanism-specific interventions are available for any of surfactant disorders, and thus lung transplantation provides an option to prolong survival. The determination for lung transplantation is based on combinations of interacting factors that include the specific molecular defect, the degree of illness and trajectory of the clinical course, the absence of extrapulmonary organ dysfunction, the need for and ability to transport to a pediatric lung transplant center, and, most importantly, the desire of the family to begin such an undertaking. Therefore, considerable effort goes into helping families understand the implications of a decision to pursue lung transplantation, especially the fact that transplantation substitutes a series of chronic problems for what otherwise is an imminently lethal problem.

The five year survival for infants who have undergone transplantation is approximately 50%, with short term mortality due predominantly to infection and long term

mortality due to bronchiolitis obliterans or infection (Table 2). In addition to bronchiolitis obliterans, long term mortality results from lymphoproliferative malignancy. The post-transplant outcomes of the inherited surfactant deficiency syndromes are similar, suggesting that these outcomes reflect consequences of transplantation rather than the underlying disease.^{32,33}

Table 2. Post-transplant morbidity and mortality for infants with surfactant disorders

Items	SP-B deficiency	SP-C disorders	ABCA3 deficiency	Total
Post-transplant complications (%)				
Acute rejection	12	40	58	40
PTLD	12	20	17	16
Bronchiolitis obliterans	25	60	42	40
Causes of death (n)				
Bronchiolitis obliterans infection	1	1	4	6
Gastroenteritis	3	–	1	4
Malignancy	1	–	–	1
	–	1	–	1

PTLD: Post-transplant lymphoproliferative disorder.

While the survival rate is a critical factor, the quality of that survival plays a larger role in some families' decision-making. The degree and duration of illness in the pre-transplantation period contribute to the risk of adverse neurodevelopmental outcomes, especially in infants. Nearly all of the ventilated infants have had oral-motor feeding difficulties that require long-term (1–2 years) nasogastric or gastrostomy feedings and most infants have gross motor delays that improve in the first 2 years. Patients also must adhere to an extensive immunosuppression regimen, regular monitoring of blood levels of immunosuppressive drugs, physical, occupational, and speech therapy, and feeding interventions. These significant short and long-term challenges have prompted approximately half the families of affected children to decline transplantation and choose compassionate care for their infants.

In summary, these lung-specific disorders of surfactant metabolism are ideal candidate diseases for which lung transplantation can reconstitute the function of the mutant gene and also provide a unique opportunity to understand surfactant biology. The complexities and heterogeneous outcomes of transplantation, though, necessitate deliberate and informed decision-making before proceeding. Understanding the mechanisms underlying respiratory dysfunction in these disorders holds the hope that mechanism-specific interventions can be developed in the future.

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