Surfactant Dysfunction Disorder: A Mini-review
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Abstract
Disorders of pulmonary surfactant proteins are rare but provide important insights into the mechanisms of surfactant dysfunction. Mutations in the surfactant protein-B and the ATP-binding cassette family member A3 (ABCA3) genes usually present as lethal neonatal respiratory syndrome. Dominant mutations in the surfactant protein-C gene result in interstitial lung disease in older infants and children. Surfactant protein A and D deficiency cause significant susceptibility to bacterial and viral infections, delayed microbial clearance, and over-expression of proinflammatory cytokines but require further studies in the future. (J Pediatr Resp Dis 2014;10:24-27)

Key words: surfactant dysfunction, ABCA3 mutation, pulmonary alveolar proteinosis

INTRODUCTION
The surfactant proteins (SP) play important roles in the structure, function, and metabolism of the surfactant. Inadequate production of pulmonary surfactant causes respiratory distress syndrome (RDS) in premature infants. Genetic mutations can cause surfactant production deficiency and diffuse lung disease in full-term infants with the radiographic resemblances of RDS. Surfactant is produced in alveolar type II cells (AEC2s). Four specific proteins have so far been described: SP-A, SP-B, SP-C, and SP-D. Surfactant protein B (SP-B) and C (SP-C) are hydrophobic and confers the surface tension lowering properties. SP-A and SP-D are of the collectin family with function of innate immunity.

SP-A and SP-D deficiency
SP-A and SP-D are associated with immune cells, and activate various cellular functions and act as opsonins with macrophages resulting in modulation of phagocytosis or production of reactive oxygen species. The pulmonary collectins possess direct inhibitory effects on bacterial growth; and collectins associate with cell surface pattern-recognition receptors. SP-A and SP-D regulate inflammatory cellular responses by the release of lipopolysaccharides-induced proinflammatory cytokines. Animal models of SP-A or SP-D deficiency reveal significant defect in host defense. Significant susceptibility to bacterial and viral infections, delayed microbial clearance, and over-expression of proinflammatory cytokines are observed. Rats that do not produce SP-D possess an increased pool of lipids in the tissues and alveolus without an increase of the surfactant proteins; these rats develop emphysema. Congenital SP-D deficiency has so far not been reported in humans.

Surfactant B deficiency
SP-B is a hydrophobic protein encoded on chromosome 2, and infants with SP-B deficiency is autosomal recessive. Mutations of SP-B are exclusively neonatal lethal and develop pulmonary symptoms and signs within hours of birth. Radiographically, infants often present with diffuse lung disease which resembles RDS in prematurely born infants. The majority of affected infants die within 3 months after birth despite surfactant replacement or even extracorporal membrane oxygenation.

Diagnosis is confirmed by the demonstration of
disease-carrying mutations on both alleles. The most common mutation is 121ins2. The only current effective therapy for severely affected infants who were not able to produce SP-B is lung transplantation.\textsuperscript{10, 11}

**Surfactant C deficiency**

The age of onset of disease of infants with SP-C deficiency varies with SFTPC mutations. The clinical course varies from severe RDS in neonates to idiopathic pulmonary fibrosis in the 6\textsuperscript{th} decade.\textsuperscript{12} Young infants usually present with hypoxemia in ambient air, failure to thrive and diffuse infiltrates in chest radiographs.\textsuperscript{13, 14}

The therapy of patients with SFTPC mutation remains elusive. Corticosteroid, hydroxychloroquine had been used,\textsuperscript{15} but lung transplantation has been performed in patients with progressive deterioration in lung function.\textsuperscript{16}

**ABCA3 mutation**

TABCA3, encoded on chromosome 16, is a transporter that hydrolyzes ATP to move substances across biological membranes.\textsuperscript{17} ABCA3 is expressed in many tissues, mostly in the membrane of lamellar bodies within AEC2. ABCA3 facilitates the transport of lipids for surfactant function. In ABCA3 deficient infants, reduced surface tension-lowering ability and the amount of surfactant phospholipids, its deficiency is the most recognized surfactant dysfunction.\textsuperscript{18}

\textbf{Figure 2}. A 2-month-old baby girl with normal spontaneous delivery and no respiratory distress in the neonatal period, she began to suffer from progressive respiratory embarrassment and hypoxemina. Initial plain chest radiograph (a) shows bilateral ground glass appearance which was well demonstrated on computed tomographic scans (b) and (c). Video-assisted thoracoscopic biopsy shows prominent interstitial fibrosis with no evidence of cytomegalovirus inclusion bodies or \textit{Pneumocystis jirovecii} infection. The child’s clinical manifestations are compatible with surfactant disorder either due to SP-C or ABCA3 mutation. Further mutational analysis of surfactant protein is on-going till the publication.
ABCA3 deficiency in some patients present with severe and fatal RDS, but prolonged survival is being increasingly recognized with delayed onset with extensive allelic heterogeneity. Corticosteroids increased ABCA3 expression in vivo and provide a rationale for treatment.

**GM-CSF Receptor Deficiency**

Genetic defects in the gene encoding the α chain (CSF2RA) were recently reported as a cause for pulmonary alveolar proteinosis in children. These reports establish that genetic mechanisms disrupt GM-CSF signaling and the clinical presentations of patients with GM-CSF receptor abnormality differ from surfactant deficiency by the excessive accumulation of surfactant protein due to impaired turn over by the macrophage with proteinaceous exudates in the alveoli. (figure 3).

**CONCLUSION**

Pulmonary surfactant is required for lung function after birth, and play critical roles in the maintenance of lung volumes and respiration. Surfactant proteins A and D play important roles as components of innate immunity by enhancing their clearance by alveolar macrophages and orchestrating secondary

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<th>Locus</th>
<th>SP-B deficiency</th>
<th>SP-C dysfunction</th>
<th>ABCA3 deficiency</th>
<th>GM-CSF receptor deficiency, α chain</th>
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<tr>
<td>Chromosomal location</td>
<td>SFTPB</td>
<td>SFTPC</td>
<td>ABCA3</td>
<td>CSF2RA</td>
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<td>AR</td>
<td>AD, sporadic</td>
<td>AR</td>
<td>AR</td>
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<td>Loss of function</td>
<td>Toxic gain of function</td>
<td>Loss of function</td>
<td>Loss of function</td>
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<td>Onset of pulmonary symptoms</td>
<td>Neonate</td>
<td>Neonate &lt; infant to adult</td>
<td>Neonate, infancy, childhood</td>
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<td>Principle histology</td>
<td>SDM</td>
<td>SDM</td>
<td>SDM</td>
<td>PAP</td>
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<tr>
<td>Course</td>
<td>Severe, fatal</td>
<td>Variable</td>
<td>Variable</td>
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*AR – autosomal recessive, AD – autosomal dominant, SDM – surfactant dysfunction, metabolic; PAP – pulmonary alveolar proteinosis.
inflammatory responses in the lung. Alternation of surfactant B and C homeostasis can result in surfactant insufficiency with variable respiratory presentations such as fatal RDS, interstitial lung diseases or chronic lung diseases. Genetic defects in the gene encoding the α chain (CSF2RA) present with pulmonary alveolar proteinosis in children due to impaired degradation of surfactants in the alveoli.

REFERENCES