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Good and bad lipids in the lung

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Abstract

Bacterial pneumonia can be a life-threatening disease that causes lung injury. A new study shows that accumulation of a phospholipid in the lung fluid in mice and humans worsens gas exchange during the microbial infection (pages 1120–1127). Clearance of this lipid may improve lung function during infection.

The maintenance of efficient gas exchange, the main physiological function of the mammalian lung, is essential for life. Normal gas exchange in the mammalian lung requires the production of pulmonary surfactant, a mixture of phospholipids and proteins produced by type II alveolar cells that reduce surface tension in the alveoli (Fig. 1). Deficiencies in surfactant due to premature birth result in infant respiratory distress syndrome and profound impairment in gas exchange¹. Surfactant replacement therapy in preterm newborns can reduce surface tension, prevent alveolar collapse and improve gas exchange and survival². Surfactant is pre-stored in lamellar bodies in type II alveolar epithelial cells and requires transport and exocytosis (Fig. 1). Recently, mutations in a member of the ATP-binding cassette family of transporters, ABCA3, have been shown to result in fatal surfactant deficiency in neonates³. The maintenance of normal surfactant homeostasis, therefore, is crucial for mammalian survival.

Many insults can perturb normal surfactant homeostasis, such as hemorrhage, trauma, inhaled toxins and infectious agents. These insults can manifest clinically as acute respiratory distress syndrome (ARDS), which consists of alveolar collapse, fibrin deposits and hemorrhage that result in reduced lung function, alveolar collapse and markedly impaired gas exchange. It has been proposed that infectious agents can lead to ARDS through direct impairment of surfactant exocytosis and/or type II cell death, each of which can lead to abnormal amounts of surfactant in the alveolus⁴. Under this setting, the ability of the surfactant to reduce surface tension in the alveolus is compromised, resulting in collapse of alveoli and reduced gas exchange across these crucial structures. In addition to phospholipids, pulmonary surfactant also contains proteins with immunoregulatory roles⁴.

In this issue of *Nature Medicine*, Ray *et al.*⁵ now add another mechanism to the list of potential causative agents of lung injury during bacterial pneumonia. The authors show that a host-derived phospholipid, cardiolipin, is increased in the lungs of mice with experimental pneumonia as well as in tracheal aspirates from humans with pneumonia. Cardiolipin disrupts the activity of the surfactant and impairs lung function in mice with bacterial pneumonia, causing increased surface tension in the alveoli and edema in mice. Cardiolipin also causes lung epithelial cell death, worsening lung function during pneumonia. Decreasing the amounts of cardiolipin in the lung fluid may represent a new therapeutic avenue to treat lung injury during pneumonia.

Phospholipids are major components of cell membranes, and their positioning in the cell membrane is controlled by a class of proteins called phospholipid flippases⁶. These ATPase proteins transport lipids across bilayers such as the endoplasmic reticulum, Golgi and plasma membranes⁷. ATP8b1 is a member of this protein family and is expressed in bile canaliculi to transport bile acid⁸. Individuals with mutations in ATP8b1 develop progressive familial intrahepatic cholestasis type 1 or Byler disease, gastrointestinal tract diseases and also have an increase risk for pneumonia⁹, yet the mechanisms of the increased risk of pneumonia in these individuals are unclear.

The authors then explored whether ATP8b1 might be involved in phospholipid transport in the lung and specifically in the regulation of cardiolipin abundance in the lung fluid, given that this phospholipid modified lung function when administered directly to the lung⁵. Moreover, they showed that during experimental bacterial pneumonia most of the cardiolipin is host derived, indicating that transport mechanisms may exist to regulate cardiolipin content in the airway⁵. They hypothesized that ATP8b1 may be expressed in the lung epithelium and serve as a functional lipid transporter that decreases the amounts of injurious cardiolipin from distal airways to preserve pulmonary homeostasis⁵ (Fig. 1). Ray *et al.*⁵ found that overexpression of ATP8b1 increases cardiolipin uptake *in vitro*, and overexpression of ATP8b1 in the lung, via a recombinant adenovirus encoding the protein, improves lung compliance and survival in mice undergoing experimental pneumonia.

In contrast, knockdown of *ATP8B1* expression *in vitro* in immortalized human alveolar type II cells decreased cardiolipin uptake. Furthermore, mice with a homozygous missense mutation in *Atp8b1* that affects bile salt accumulation, were more prone to bacterial-induced lung injury. These mutant mice also showed increased concentrations of cardiolipin in lung lining fluid. What's more, the authors used a cardiolipin-binding domain peptide that blocks cardiolipin accumulation in the lung lining fluid and found that it also blocked bacterial lung injury⁵, demonstrating that manipulation of cardiolipin abundance by altering its transport through ATP8b1 might be used to treat severe bacterial pneumonia in the clinic.

Ray *et al.*⁵ found that the cardiolipin obtained from human and mouse samples originates from mammalian cells and not from bacterial derived lipid. It is plausible, therefore, that cardiolipin could induce acute lung injury even in a sterile environment in a similar fashion to mitochondrial DNA in trauma¹⁰. It will be crucial to determine the contributions of this lipid transport pathway in other causes of ARDS such as sepsis or trauma where the initial injury may be in the pulmonary endothelium, which is exposed to the systemic circulation,

versus pneumonia or severe viral infection where the insult initiates on the epithelial side of the alveolar capillary membrane.

Future studies will also need to define how cardiolipin transport is affected in ARDS or pneumonia. For instance, is it defective due to dysfunction of type II pneumocytes or is it, in some cases, due to defective cell loss? If these type II pneumocytes are the major expressors of ATP8b1 and this is the predominate pathway in which cardiolipin is transported, then targeting this pathway may be insufficient in severe viral or bacterial pneumonia where type II cells, the source of surfactant phospholipid, may be beyond recovery. Ectopic expression of ATP8b1 in other cells may be insufficient to reduce cardiolipin levels in the lung.

We know from high-resolution computed tomography scan studies that both ARDS and pneumonia are diseases that affect different portions of the lung¹¹, so strategies aimed to maintain or augment ATP8b1 function in relatively unaffected lung may also improve outcomes in severe pneumonia and ARDS. Preserving lung function by pharmacologically maintaining or augmenting ATP8b1 function, even in relatively unaffected areas of the lung, may result in a reduced need for supportive care such as mechanical ventilation, which, although supportive, carries an increased risk of ventilator-associated pneumonia itself.

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Figure 1.

Surfactant homeostasis and proposed new model of lung dysfunction by cardiolipin in pneumonia. In the healthy lung, the alveoli contain pulmonary surfactant (green), a complex mixture of phospholipids and proteins prepackaged in lamellar bodies in alveolar type II pneumocytes and secreted into the alveolar lumen to reduce surface tension and prevent alveolar collapse during expiration. Surfactant homeostasis is crucial for normal gas exchange across the alveolar capillary membrane in mammals (left). In pulmonary alveoli of a lung affected by pneumonia and other causes of ARDS, there is fibrin deposition and reduced surfactant function that results in alveolar collapse and impaired gas exchange. In the study by Ray *et al.*⁵, the authors show that the lungs of individuals with pneumonia and the lungs from mice with experimentally induced pneumonia show high levels of cardiolipin, which disrupts the surface tension by reducing the capability of pulmonary surfactant, resulting in reduced lung compliance. The lipid transporter ATP8b1 regulates cardiolipin abundance in the alveolar lumen of the lung. Increasing the lipid transport of cardiolipin via ATP8b1 results in its clearance from the lumen, increased surfactant homeostasis and improved lung function during bacterial pneumonia.