Lung Surfactant

The Indispensable Component of Respiratory Mechanics

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Lung surfactant, a lipo-protein complex, is a highly surface-active material found in the fluid lining the air-liquid interface of the alveolar surface. Surfactant plays a dual function of preventing alveolar collapse during breathing cycle and protection of the lungs from injuries and infections caused by foreign bodies and pathogens. Varying degrees of structure-function abnormalities of surfactant have been associated with obstructive lung diseases, respiratory infections, respiratory distress syndromes, interstitial lung diseases, pulmonary alveolar proteinosis, cardiopulmonary bypass surgery and smoking. For some pulmonary conditions, especially respiratory distress syndrome, surfactant therapy is on the horizon.

Introduction

Lungs differ considerably in structure, embryological origin, and function between vertebrate groups. But all lungs have a few common characteristics, *viz.* they are internal, fluid lined, gas-holding structures that inflate and deflate cyclically. As a result, all lungs face potential problems related to the surface tension of the fluid as well as protection from the potential immunological attack from pathogens, allergens, and pollutants. To counteract these problems, pulmonary surfactant is produced in the lungs to play dual functions of maintenance of normal respiratory cycle as well as protection against immunological burdens [1].

Keywords
Surfactant proteins; surfactant phospholipids, surface activity, pulmonary diseases, surfactant dysfunction.

Pulmonary Surfactant: The Vital Component of Respiratory Cycle

Pulmonary surfactant is essential for normal breathing, alveolar stability and host defense system in the lungs. Basically, three very interesting biophysical properties of pulmonary surfactant underlie its physiological and immunological functions:

1) Once secreted to the alveolar spaces, surfactant adsorbs rapidly to the air-liquid interface (this happens during a newborn baby's first breath).

2) Once at the interface, surfactant films reduce surface tension to extremely low values when compressed during expiration (this means that our lungs don't collapse when we breath out).

3) Surfactant proteins recognize bacterial, fungal and viral surface oligosaccharides and thus can opsonize these pathogens.

The lung surfactant evolved when vertebrates began air breathing between 320 and 420 million years ago. After the discovery of the basic functional principle of pulmonary surfactant more than 70 years ago, the

pulmonary surfactant system has been intensively investigated and more than 9000 publications have revealed numerous aspects of surfactant synthesis, secretion, metabolism and various functions in the alveolar compartment.

The human pulmonary surfactant is an array of approximately 80% phospholipids, 8% neutral lipids (cholesterol and free fatty acids) and 12% proteins, which is produced, secreted, and recycled by Type II pneumocytes [2]. The most abundant phospholipid is phosphatidylcholine (PC), especially dipalmitoylphosphatidylcholine (DPPC). DPPC is the main component of surfactant that reduces surface tension. The other lipid components of the surfactant are phosphatidylglycerol, phosphatidylinositol and cholesterol, which facilitate the adsorption of DPPC with the help of hydrophobic surfactant proteins [2]. In addition to lipids, there are four surfactant proteins (SPs) expressed by respiratory epithelial cells, designated as SP-A, SP-B, SP-C and SP-D. Out of these, SP-A and SP-D are large glycosylated water-soluble proteins and members of the calcium-dependent carbohydrate-binding collectin family, which have a role in the host defence of the lung. SP-A is also important in the organization and function of the surfactant complex regulating surfactant recycling and secretion. While, SP-B and SP-C are highly hydrophobic small peptides that confer surface tension-lowering properties and are important for the adsorption and spreading of the surfactant.

With the exception of SP-A, surfactant proteins are synthesized in polyribosomes, modified in the endoplasmic reticulum, golgi apparatus and multivesicular bodies and stored in lamellar bodies before secretion. Surfactant phospholipids are synthesized in the endoplasmic reticulum, transported through the golgi apparatus into multivesicular bodies and packaged into lamellar bodies. After exocytosis of lamellar bodies, surfactant phospholipids, in the presence of SP-A, SP-B and Ca^{2+}, are organized into a lattice structure called tubular myelin (TM), which forms a lipid-rich layer at the air-liquid interface of the alveolus. Most of the extracellular surfactant is taken up by type II cells, catabolized and transported into lamellar bodies for recycling [2] (*Figure* 1).

Biophysical Functions of Pulmonary Surfactant

The surface tension of the alveolar air-water interface provides the retractive force opposing lung inflation. The presence of surfactant in the fluid film can lower air-water surface tensions to near zero values. This ensures that the alveolar space is open during the whole respiratory cycle preventing intra-pulmonary shunts resulting in inadequate oxygenation of the blood. Thus, the net benefit is reduced work of breathing.[1] Further, it also improves mucociliary transport and facilitates removal of particles and debris from the alveoli into the large

[1] Without lung surfactant, every breath requires tremendous force, like blowing up a new balloon!!

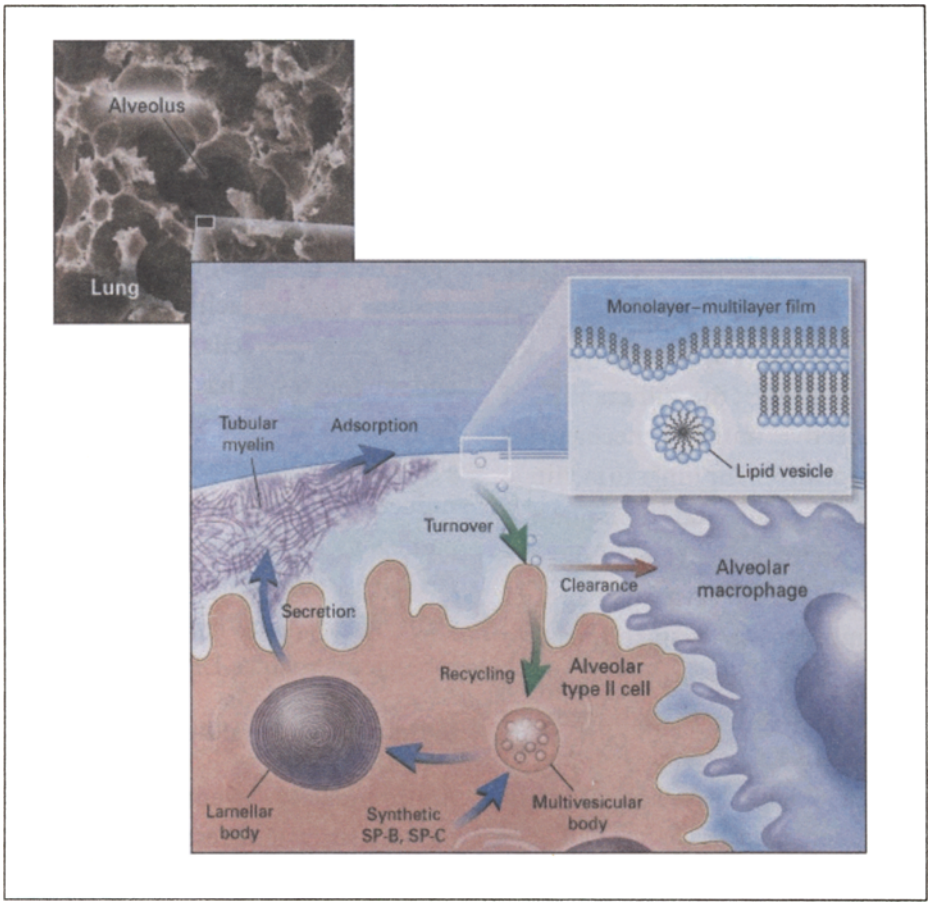

Figure 1. Freeze-frame view of the alveolar space with a magnified view of the air–liquid interface, with formation of pulmonary surfactant films.

Surfactant phospholipids and proteins are synthesized by alveolar type II cells lining the alveoli. Surfactant lipids and surfactant protein B (SP-B) precursor protein and surfactant protein C (SP-C) are transported to multivesicular bodies and, after proteolytic processing, stored in lamellar bodies. SP-B, SP-C, and surfactant lipids are secreted into the alveolar subphase and interact with surfactant protein A to form a tubular myelin reservoir from which multilayers and monolayers form a film, thus reducing surface tension at the air–liquid interface. Surfactant remnants are taken up and reutilized or catabolized by type II epithelial cells. Alveolar macrophages play a critical part in the clearance and catabolism of surfactant lipids and proteins. Formation of the active surface film is required to maintain lung volumes, thereby preventing atelectasis and respiratory failure.

airways by lowering surface tension during end-expiration [1].

Recent Excitement about Surfactant: Newly Defined Role in Host Defence

Lungs reside at the interface of the body and the environment, making it especially vulnerable to enormous immunological burden from pathogens, allergens, and pollutants. To counteract the vulnerability of lungs, the protective immune mechanisms are also located locally in the lungs to facilitate clearance of pathogens and to modulate inflammatory responses. SP-A and SP-D have recently been identified as participants of host defense mechanism against infection and inflammation [3]. These are the members of collectin protein family, which have an N-terminal collagen-like region and a C-terminal lectin domain, which binds carbohydrates in a calcium dependent manner (*Figure* 2). These C-type lectin domains are arrayed with spatial orientation that confers unique carbohydrate specificities, and their preferential binding sites for nonhost oligosaccharides, such as those found on bacterial and viral surfaces [3]. Thus they have a unique ability to opsonize pathogens, including bacteria and viruses, and to facilitate phagocytosis by innate immune cells such as macrophages and monocytes. It has been shown that mice deficient in SP-A or SP-D have an enhanced susceptibility to infection and inflammation induced by intratracheal administration of pathogens, including Group B *Streptococcus*, *Psudomonas aeruginosa*, respiratory syncytial virus, *Haemophilus influenza*, and inflammatory agents such as LPS.

Pathophysiological Relevance of Surfactant

Approximately seventy four years of pulmonary surfactant research have passed and

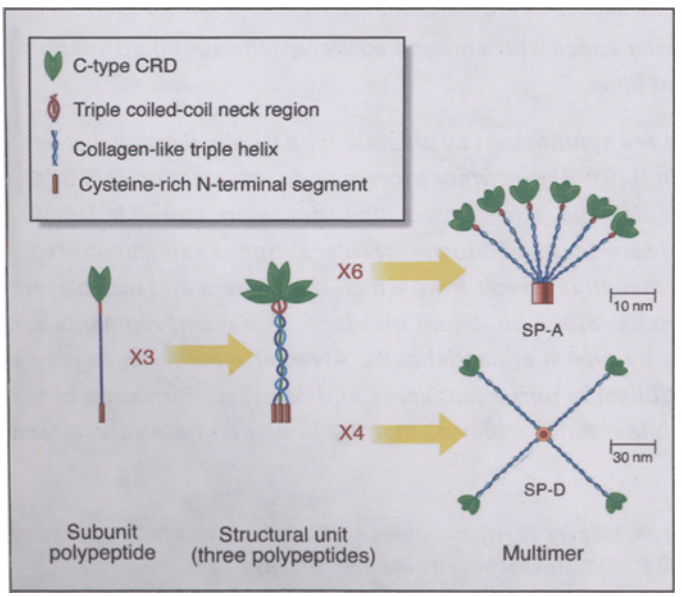

Figure 2. SP-A and SP-D are members of the collectin family of oligomeric proteins, which have collagen-like N-terminal regions and C-type carbohydrate recognition domains (CRDs). The CRDs bind carbohydrates such as those found on pathogen surfaces. SP-A consists of 6 structural units, which are assembled into a "flower bouquet" formation. SP-D consists of the tetrameric structural units assembled into an X-like structure.

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Reduced amount of total surfactant complex or aberrant proportions of its components
Lipolytic or proteolytic degradation
Oxidative damage to the surfactant components
Impaired enzymatic conversion of large into small surfactant aggregates
Presence of inhibitory compounds in the alveolar airspaces (fibrinogen, amino acids)
Genetic abnormality causing the production of anomalous surfactant proteins

Table 1. Some of the potential reasons for lung surfactant impairment.

our knowledge about surfactant in research and clinical practice is still increasing exponentially. A pathophysiological role for surfactant was first appreciated in premature infants with respiratory distress syndrome (RDS) and hyaline membrane disease, a condition, which can nowadays be treated by means of exogenous surfactant replacement.[2] For years, the putative surfactant dysfunction has been ignored by clinicians in adult respiratory medicine but there is increasing evidence of its relevance in adult respiratory disorders. Deficiency and dysfunction of pulmonary surfactant have been associated with smoking[3] as well as several respiratory diseases such as acute respiratory distress syndrome, pneumonia, and cardiogenic lung edema, after cardiopulmonary bypass surgery, following lung transplantation, idiopathic pulmonary fibrosis (IPF), sarcoidosis, hypersensitive pneumonia to name a few (*Table* 1).

The possible involvement of pulmonary surfactant in the pathophysiology of obstructive lung diseases with a predominant disturbance in the conducting airways, such as asthma, chronic obstructive pulmonary disease, cystic fibrosis and pneumonia has only recently been addressed. Models of airway closure suggest a theoretical use of surfactant in asthma, and clinical studies have suggested that surfactant from asthmatics is functionally impaired. The main mechanism of such impairment appears to be the influx of inhibitory proteins into the airways. Also, products of inflammatory cells (including proteases and reactive oxygen and nitrogen species) and airway edema may also contribute

[2] Surfactant is formed relatively late in fetal life. The premature infants born without adequate amounts experience respiratory distress and may die!! Surfactant replacement therapy has been shown to reduce mortality rates by 30 to 50 percent for infants with neonatal respiratory distress syndrome. The first FDA-approved surfactant was Exosurf Pediatric, a synthetic compound made by Burroughs Wellcome Co. of Research Triangle Park, NC.

[3] Environmental tobacco smoke (ETS) exposure significantly degrades the performance of the lipids in lung surfactants. The main features of this degradation are an increase in the minimum surface tension on inhalation and a decrease in the respreading of the surfactant over the alveolar surfaces on inhalation.

to surfactant dysfunction. SP-A being critical for host defence against pathogens, any structure-function abnormality in this renders the CF subjects susceptible to respiratory infections. In a separate study, the BAL fluid recovered from patients with pneumonia showed reduced levels of PC, PG and alterations in fatty acid composition. In addition, amount of SP-A is also decreased and surfactant function is impaired.

Mutations of surfactant protein encoding genes are associated with several multifactorial respiratory airway diseases. Allelic variations of the SP-A and SP-B genes have been shown to be important genetic determinants in individual susceptibility to respiratory distress syndrome, which is a good general model for a multifactorial pulmonary disease resulting from complex interactions between several environmental and genetic factors. Because SP-A and SP-D act directly in the clearance of common lung pathogens, the genes encoding these proteins have been implicated as candidates in a few infectious diseases, including respiratory syncytial virus (RSV) infections and tuberculosis.

Conclusion

Investigations on pulmonary surfactant system in humans has advanced our understanding of lung physiology in health and disease, which may lead to the development of new approaches to the treatment of respiratory pathological conditions. The success of intratracheal instillation of surfactant in neonatal RDS has stimulated its potential utility in adult respiratory diseases with possible surfactant abnormalities such as ARDS, pneumonia, COPD, asthma and emphysema. Since these respiratory diseases are of heterogenous nature and not all patients are responders to certain treatment strategies, a possible link with genetic predisposition to such diseases appears likely. Thus, it is important to study potential genetic markers, such as surfactant proteins, in order to understand these disease mechanisms clearly.

Suggested Reading

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