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REVIEW ARTICLE

LUNG SURFACTANT

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ABSTRACT

Residing at the interface of the body, the lung is a uniquely vulnerable organ optimized for gas exchange, having a very thin, delicate epithelium, abundant blood flow, and a vast surface area. Lung surfactant is a surface active material composed of both lipids and proteins that is produced by alveolar type II pneumocytes that provides a stable, low surface tension for the lung, thereby preventing alveolar collapse at low transpulmonary pressure. Surfactant is a secretory product, composed of lipids and proteins. Phosphatidylcholine and phosphatidylglycerol are the major lipid constituents and SP-A, SP-B, SP-C, SP-D are four types of surfactant associated proteins. The lipid and protein components are synthesized separately and are packaged into the lamellar bodies in the AT-II cells. Lamellar bodies are the main organelle for the synthesis and metabolism of surfactants. The synthesis, secretion and recycling of the surfactant lipids and proteins is regulated by complex genetic and metabolic mechanisms. Alterations in surfactant homeostasis or biophysical properties can result in surfactant insufficiency which may be responsible for diseases like respiratory distress syndrome, lung proteinosis, interstitial lung diseases and chronic lung disease.

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INTRODUCTION

The agents that decrease surface tension are known as surface active-agents or surfactants. Surface tension can be defined as the cohesive force of attraction experienced by the molecules present at the interphase of two media. The surfactants are amphipathic molecules that form a film between the two media in such a way that their interactions are thermodynamically stable and result in reduced surface tension. (Glasser and Mallampalli, 2012) Lung surfactant is a highly surface active substance that is synthesized by alveolar epithelial type II cells and composed of approximately 80% phospholipids, 10% proteins, and 10% neutral lipids. The pre-dominate phospholipids are phosphatidylcholine (PC) and phosphatidylglycerol; phosphatidylinositol and sphingomyelin contribute to the total concentration. Two of the surfactant-associated proteins, SP-A and SP-D, have important host defense properties, while the remaining two, SP-B and SP-C, are intensely hydrophobic and interact with surfactant phospholipids to optimize surface tension lowering function (Crouch and Wright, 2001). It is remarkable to note that this surfactant system also plays a vital role in pulmonary innate immune defense system against allergic threats. (Griese, 1999)

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The composition of lung surfactant

Protein composition of surfactant system including surfactant proteins and surface active lipid associated transporter, ABCA3, is of utmost important for both surface activity and immunological homeostasis (Tokieda *et al*., 1997; Whitsett, 2010). The surfactant proteins are categorized according to their water affinity, in 4 major divisions, SP-A, SP-B, SP-C and SP-D (Izzo and Rickham, 1968) all of which are formed by alveolar type-II cells (Wright, 1990; Field and Gilbert, 1997; Hobo *et al*., 1997; Hobo *et al*., 2001; Ito *et al*., 2003; Morrison *et al*., 1999; Danlois *et al*., 2003; Christmann *et al*., 2008; Danlois *et al*., 2000; Bernhard *et al*., 1997; Wright, 2005; Weaver and Conkright, 2001). The Hydrophobic Surfactant proteins include SP-B and SP-C. SP-B are the surfactant proteins indispensable for survival due to their major role in lowering surface tension by interacting with surfactant PLs (Izzo and Rickham, 1968; Whitsett and Weaver, 2002; Madsen *et al*., 2000) with additional function of forming tubular myelin and packing Phospholipids into lamellar bodies (Leth-Larsen *et al*., 2004) SP-C is the most hydrophobic small protein which also interacts with PLs to lower Surface tension (Leth-Larsen *et al*., 2004). Two of the surfactant proteins, SP-A and SP-D, are members of the collectin protein family (Crouch and Wright, 2001; Crouch *et al*., 2000), which includes the liver-derived serum mannose binding lectin. Collectins have in common an N-terminal collagen-like region and a C-terminal lectin domain that binds carbohydrates in a calcium-dependent manner . The C-type lectin domains are arrayed with spatial

orientation (Weis and Drickamer, 1994) that confers unique carbohydrate specificities, and their preferential binding sites are nonhost oligosaccharides, such as those found on bacterial and viral surfaces (Crouch, 1998). The most well-defined function of the collectins is their ability to opsonize pathogens, including bacteria and viruses, and to facilitate phagocytosis by innate immune cells such as macrophages and monocytes. SP-A and SP-D also regulate production of inflammatory mediators. Mice made deficient in SP-A or SP-D by homologous recombination have an enhanced susceptibility to infection and inflammation induced by intratracheal administration of pathogens, including Group B Streptococcus, Pseudomonas aeruginosa, respiratory syncytial virus, Haemophilus influenza, and inflammatory agents such as LPS (Lawson and Reid, 2000). Deficiencies in mannose-binding lectin have been characterized in humans and are associated with increased susceptibility to infection and autoimmune disease (Jack *et al*., 2001).

Functions of lung surfactant

Pulmonary mechanics

Beyond the importance of low alveolar surface tension in promoting lung stability, (Goerke, 1986) one should also consider the effects of surfactant adsorption and desorption kinetics on surfactant function. More detailed kinetic studies and some computer model-building will be required (Schürch *et al*., 1992) and (Schürch *et al*., 1994). Clinically evident repetitive collapse and re-expansion of lungs may be a result of kinetic dysfunctions (Schürch *et al*., 1995), and a better understanding of lung damage from overinflation should follow a better picture of how surfactant function is linked to mechanics (Dische *et al*., 1998) and (Goerke, 1992).

Surfactant in airways

Surfactant also has roles to play in small airways. Thus it can act to maintain patency (Goerke, 1995), to prevent resistance increase in allergen-challenged animals (Taskar *et al*., 1997), and to enhance mucociliary clearance of unwanted contaminants (Bjorklund *et al*., 1997) and (Wada *et al*., 1997).

Pulmonary vessels and blood flow

Not surprisingly, surfactant effects on lung mechanics have also been found to produce concomitant lung circulatory changes (Enhorning, 1977).

Means of assessing alveolar-stabilizing function of surfactant

Adequately measuring surfactant function in vitro and in vivo has proven to be very difficult. Different techniques are required to answer different questions, one size does not fit all.

(a)Wilhelmy balance

The modified Langmuir-Wilhelmy surface balance, usually consisting of a Teflon trough with either tightly fitting or ribbon barriers, has been used for a longer time than most other lung surfactant methods, and is still being suitably employed. For example, recent work on the respreading of used surfactant has made appropriate use of this technique (Liu *et al*., 1996)

(b)Captive bubble surfactometer

Because films with very low tensions could not be adequately contained in Langmuir-Wilhelmy balances at physiological temperatures, Schürch and colleagues developed several models of a captive bubble surfactometer (Im Hof *et al*., 1997; De Sanctis *et al*., 1994; Wagner *et al*., 1996; Wang *et al*., 1995). The use of such a balance was critical in demonstrating the importance of low film compressibility as an indicator of good surfactant function (Putz *et al*., 1994). Reaching near-zero surface tension with a mere 15–20% film area compression is probably the most difficult goal to achieve, and represents the hallmark of excellent surfactant function. It is becoming apparent from these in vitro studies that surfactant concentrations of at least 1 mg phosphor lipid/ml must be present to obtain optimal results.

(c) Pulsating bubble surfactometer

The pulsating bubble surfactometer, developed by Enhorning (Putz *et al*., 1994), is a predecessor of the captive bubble device, and is still in more common use in spite of some surface leakage difficulties. It offers a much smaller sample size and far greater ease of use than its derivative machine, but falls short when asked to provide critical information from the first film compression. A comparison of both bubble devices with a recommendation for addressing surface leakage problems with the pulsating bubble surfactometer has been published (Schoel *et al*., 1994). Most studies using this latter device ignore first compression isotherm data, and report the lowest surface tensions found in 50–100 cyclic bubble compressions (Putz *et al*., 1994).

Conclusion

Pulmonary surfactant, a mixture of lipids and proteins, is very important for proper lung function. It decreases surface tension at the alveolar interphase, prevents collapse of alveoli during expiration and prevents the emptying of smaller alveoli into the larger ones. The maintenance of lung compliance and ventilatory capacity is also a function of the pulmonary surfactant. In addition, it plays an important role in host defense and other immunoprotective functions. The surfactant is synthesized and secreted from specific cuboidal cells present in the alveolar epithelium called type II pneumocytes (AT-II). AT-II cells contain membrane bound organelles called lamellar bodies. The components of the surfactant are synthesized separately and are packed into the lamellar bodies which are mainly involved in surfactant metabolism. The synthesis, secretion and recycling of surfactant is highly regulated. Though most of the underlying mechanisms are known, the specific signaling and regulatory pathways are yet to be identified. Any genetic or metabolic abnormalities in surfactant homeostasis can result in surfactant deficiency. Deficiency of surfactant is seen in diseases like respiratory distress syndrome, chronic lung diseases, interstitial lung diseases etc. A Combination of surfactant (natural or synthetic) and hormones or other pharmacological agents associated with surfactant homeostasis are useful in treating these diseases. However, the exact formulation of combinational therapy is yet to be done. The detailed knowledge about surfactant with respect to the pathophysiological alterations in various lung diseases would be helpful in designing novel surfactant supplements.

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