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Surfactant and its role in the pathobiology of pulmonary infection

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Abstract

Pulmonary surfactant is a complex surface-active substance comprised of key phospholipids and proteins that has many essential functions. Surfactant's unique composition is integrally related to its surface-active properties, its critical role in host defense, and emerging immunomodulatory activities ascribed to surfactant lipids. Together these effector functions provide for lung stability and protection from a barrage of potentially virulent infectious pathogens.

Keywords

Surfactant; collectin; phospholipid; infection

1. Introduction

The human lung is continually exposed to a multitude of various particulates, microorganisms, and gases, all of which potentially could have a detrimental effect on lung homeostasis and vulnerability to infection [1, 2]. Because of its enormous alveolar surface area and constant contact with ambient factors within the environment, the lungs remain the major site of infection [3]. Despite exposure to possible toxins and pathogens during respiration, the frequency of severe lower tract infection and injury is relatively low in healthy individuals [1, 2]. The intrinsic ability of the respiratory system to remain relatively resistant to infection from virulent pathogens is largely due to the effectiveness of the host defense system [1, 2].

Pulmonary host defense structurally consists of the airway and alveolar epithelium that lines the inner surface of the lung acting as a physical barrier to particles and microorganisms that enter the respiratory tract. In particular the airway columnar epithelia cells utilize mucociliary clearance mechanisms to remove invading pathogens and particulate matter. The epithelium also has an auxiliary role by elaborating cytokines, chemokines, and growth factors with the continued goal to clear infection [2]. Other cells, including neutrophils,

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macrophages, and lymphocytes can be recruited to sites of infection as major bioeffectors involved in the eradication and disposal of pathogens, or, if needed, partake in the adaptive immune response. Epithelial cells also synthesize and secrete a variety of antimicrobial intermediates, peptides, and proteins that can kill microorganisms directly or be used by neutrophils or macrophages to facilitate bacterial clearance [2]. Interestingly, many of these bioactive products released by host cells also interact with surfactant, a major component within the host defense system that has unique properties displaying both lung stabilizing and anti-microbial properties to facilitate clearance of a variety of pathogens.

1.1. Surfactant and its role in lung homeostasis

It has been established that a primary role of surfactant is to lower surface tension in the alveoli thereby stabilizing these structures to prevent alveolar collapse [3–12]; in this manner, surfactant reduces the work associated with breathing [1, 3, 7]. This surface material also serves as a barrier to pathogens [7], improves mucociliary transport [8], helps limit evolution of high-surface-tension pulmonary edema [8], and inhibits leakage of serum components into the airway [3]. The biological role of surfactant, however, as an integral component of the host defense system that exerts immunomodulatory activity has now emerged as an intriguing focus of several investigations using animal models of pulmonary infection and consideration in surfactant replacement therapies [6, 13–15]. Taken together, the demonstration of key physiological and biological activities of this material has kept investigations of surfactant as a major focus in both basic as well as translational studies.

1.2. Surfactant composition, synthesis, and secretion

Pulmonary surfactant is a complex mixture of lipids and proteins that forms a monomolecular film that lines the alveolar air-surface interface [4–6]. Surfactant is comprised of roughly 90% lipids; 80–85% of which are phospholipids, 5–10% are neutral lipids [16–20], and 10% are proteins (Figure 1) [4, 7, 8]. Phosphatidylcholine (PC) is the most predominant phospholipid in surfactant, accounting for ~75–80% of total phospholipid weight; this fraction of lipid is highly conserved across mammalian species [8, 11, 16, 18]. The major surface-active species of PC, termed dipalmitoylphosphatidylcholine (DPPC), is a saturated phospholipid comprising ~ 50% of PC that largely provides for the surface-tension lowering ability of this material. Phosphatidylglycerol (PG) and phosphatidylinositol (PI) account for 8–15% of the phospholipid portion [8, 11, 18]. Other minor phospholipids and neutral lipids are also detectable [8, 19, 21]. Although proteins make up a small fraction of surfactant, the four surfactant-associated proteins, surfactant protein (SP)-A, SP-B, SP-C, and SP-D [2, 6], all perform important roles in regulating surfactant function.

Surfactant is synthesized within the alveolar type II epithelial cells [6–9, 22]. After its biosynthesis, the surfactant components are packaged within lamellar bodies prior to secretion into the alveolar surface via calcium-dependent exocytosis (Figure 2) [21–23]. β-adrenergic agents, and changes in ventilatory pattern are physiological triggers for surfactant secretion from alveolar epithelia, in addition to several biochemical mediators [24]. Once secreted, the components of lamellar bodies transform into tubular myelin [21], a lattice-like structure that is believed to be the precursor to the surfactant monolayer that forms and spreads over the air-liquid interface [4, 6, 22]. The surfactant film is formed by the rapid adsorption of the tubular myelin on the alveolar surface [4, 11, 21]. The film compresses, thus facilitating reduction in surface tension and is also purified during the breathing cycle as certain protein components are squeezed out of the film [21]. As surfactant is actively being secreted, materials are constantly being exchanged from the film and are recycled into the type II epithelial cells to maintain constant surfactant pool size [4, 11, 21]. Thus, many recycled alveolar surfactant components traffic back into newly formed lamellar bodies (Figure 2)[21].

1.3. Lipids in Surfactant Behavior

The lipid portion of surfactant is primarily responsible for the surface activity of the film [4, 7, 19], though it is not the sole component contributing to this function. The film is enriched in DPPC [11], the main component conferring reduced surface activity although other saturated molecular species of PC also may exert similar properties [25]; DPPC becomes a highly packed monomolecular film with a squeeze out of other unsaturated lipids during compression phases of the respiratory cycle to achieve the low surface tensions needed to protect alveoli from atelectasis during end-expiration [7, 19]. Other phospholipids including the anionic phospholipids, PG and PI, are believed to enhance adsorption into the film [11]. These phospholipids may also interact with the hydrophobic surfactant proteins, SP-B and SP-C, to stabilize the film [6, 8]. Optimal surface tension-reducing capabilities are observed when these components in surfactant act together, specifically the phospholipids, neutral lipids, SP-B, and SP-C [1]. Cholesterol is the predominant surfactant neutral lipid and addition of cholesterol and the other neutral lipids into DPPC or DPPC-PG films increases adsorption rates [8, 11, 17]. This process could result in increased fluidity of the film and regulate its re-distribution [7, 11, 17, 18]. Improper amounts of surfactant cholesterol may also disrupt surface tension lowering ability [8, 17, 18].

1.4. Surfactant Proteins

Surfactant contains four associated proteins, SP-A, SP-B, SP-C, and SP-D, all of which have been well studied and contribute importantly to surfactant behavior. SP-A and SP-D are larger, hydrophilic glycoproteins [4, 8, 16, 23] that play a significant role in the host defense system [1, 2, 6, 22]. SP-B and SP-C on the other hand are much smaller polypeptides, highly hydrophobic, and often co-isolate with lipids [4, 8, 16, 18]. These hydrophobic proteins play key roles in alveolar stability to assist in reducing surface tension thereby preventing alveolar collapse [1, 26], aiding in phospholipid adsorption and redistribution in surfactant films [2, 4, 7, 8, 20], and regulating surfactant production [1]. PLUNC (Palate, Lung, Nasal Epithelial Clone) appears to be a relatively new surfactant-like protein found in the upper airways [27]. PLUNC behaves similarly to SP-B and SP-C through its surface tension reducing properties but also resembles SP-A ad SP-D via its role in immunity [27]. PLUNC impairs *Pseudomonas aeruginosa* ability to form biofilms. In addition, related family members of PLUNC, specifically bactericidal/permeability-increasing protein (BPI) and lipopolysaccharide binding protein (LBP), react to gram negative bacteria to perhaps exert antimicrobial activity [27].

1.5. Hydrophobic surfactant proteins

Mutations in the gene encoding SP-B within chromosome 2 or reduced amounts of SP-B protein cause severe or even fatal respiratory failure in newborns [7, 8]. SP-B is synthesized as a dimeric structure, stored, and secreted from the lamellar bodies along with the surfactant phospholipids [7, 20]. This dimer is integral in fostering stability of compressed films and enhancing surface tension-reducing properties [7, 20]. Some studies suggest that SP-B may be involved in host defense by helping to initiate the clustering and eventual killing of bacteria, including *Pseudomonas aeruginosa* and *Staphylococcus aureus* [8]. Hence, SP-B is crucial for survival [18].

SP-C has many similar functions to SP-B. SP-C is a very small protein (~4.2 kDa) whose gene is localized to chromosome 8 [1, 4]. Like SP-B, it is stored and secreted from the lamellar bodies in conjunction with the phospholipids [7]. SP-C is a membrane protein harboring a transmembrane fragment that is capable of operating as a signal peptide [7, 8]. This transmembrane portion assists SP-C to link the surfactant monolayer at the interface with the lipid bilayer [2, 7]. SP-C promotes adsorption and recycling of phospholipids and the spreading of lipids at the interface to optimize surfactant activity [2, 7, 8, 21]. Along

with its roles in regulating surface activity, SP-C may be involved in host defense as it interacts with both lipopolysaccharide (LPS) and the pattern recognition molecule CD-14 found on phagocytes to reduce LPS-elicited responses [1, 8, 28]. Studies have demonstrated that SP-C binding to LPS may depend on the structure of LPS as well as its glycolipid components [1]. The ability of SP-C to associate with CD-14 suggests a role for this protein to contribute to the removal of pathogens although this requires further study [1]. Interestingly, targeted disruption of SP-C in mice is not lethal, but the absence of SP-C or the presence of misfolded SP-C proteins may be associated with interstitial lung disease [29, 30]. These results demonstrate that even though SP-C may not be as critical for some activities ascribed to surfactant, its deficiency may be linked to a broad range of regulatory events as an integral component of surfactant.

1.6. Hydrophilic surfactant proteins

SP-A and SP-D are the large, hydrophilic proteins found in surfactant. Both proteins are members of the collectin family of proteins, which are calcium-dependent carbohydrate binding lectins [2, 8, 21]. Encoded in rodents from genes located at the same locus on chromosome 10 [4, 13], SP-A and SP-D monomers entail four core domains: the NH_2-terminal domain, a collagen domain, the neck region, and the C-terminal domain known as the carbohydrate recognition domain (CRD) (Figure 3) [2, 14, 16, 31]. These monomers come together as a trimer [16], at which point SP-A forms an octadecamer or bouquet-like structure [2, 4, 13, 15] and SP-D forms a dodecamer, or crucible-like structure (Figure 3)[2, 15]. SP-A has been shown to facilitate the formation of tubular myelin from lamellar bodies, specifically when SP-B, SP-C and calcium are also present [2, 4, 22, 32]. Mice devoid of SP-A lack tubular myelin [2]. Additionally, similar experiments have demonstrated that lack of SP-D causes disruptions in surfactant homeostasis [2]. In addition to the important roles played by SP-A and SP-D in surfactant structure and metabolism, these collectins are critical components within the host defense system.

2. Role of collectins in infection

There is mounting data indicating that the hydrophilic proteins SP-A and SP-D may have an indispensible role as elements involved in the innate defense system. These functions include the ability to aggregate and control the clearance of pathogens as well as the ability to modify macrophage function [33]. Both proteins are capable of binding to a multitude of different pathogens including fungi and yeast, Gram-negative and Gram-positive bacteria, mycobacteria, mycoplasma, and viruses [14, 16]. In most cases, binding is contingent upon the CRD region of the proteins [13, 31–34]. The variable patterns of spacing of the CRDs between SP-A and SP-D, along with the multimeric structure of the proteins, enable them to differentially bind and recognize a broad range of microbial agents [2, 35]. This ability to respond to such a wide array of pathogens might explain, in part, why healthy individuals so rarely develop severe respiratory tract infections [14]. The response of these collectins adjusts according to the type of pathogen and the needs of the host, which makes it a very efficient system.

2.1. Responding to pathogens

Bacteria—SP-A and SP-D are able to bind and neutralize both Gram-negative and Gram-positive bacteria by acting as opsonins. Often these proteins induce bacterial aggregation that serves as an appropriate physical context for phagocytosis [2, 32]. These surfactant proteins interact with *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli* (specifically the rough strains), *Salmonella minnesota*, *Streptococcus pneumoniae*, *group B streptococci*, *Haemophilus influenza*, and *Staphylococcus aureus* [13, 32, 33, 35]. Both SP-A and SP-D bind to LPS, but they interact with LPS via different components: SP-D binds

to LPS through the core oligosaccharides [32, 33], whereas SP-A binds to the lipid A domain [13, 33, 34]. SP-D binds Gram-positive bacteria though peptidoglycan and lipoteichoic acid [14, 16]. SP-A is unable to interact with these components but instead utilizes the extracellular adhesin protein, Eap, on Gram-positive *S. aureus* for opsonization [36]. After binding to bacteria, SP-A and SP-D facilitate their clearance through numerous mechanisms. SP-A and SP-D may also act as opsonins to enhance bacterial phagocytic removal [13, 15, 16]. Additionally, these collectins appear to exhibit antimicrobial effects on bacteria by potentially increasing the permeability of their membranes [35, 37]. SP-D is not capable of effectively aggregating *P. aeruginosa* [13, 33] and SP-A appears not to interact directly with this pathogen [13]. These collectins promote phagocytosis indirectly, by stimulating the activity of alveolar macrophages [13, 16]. The interaction of SP-A with *S. aureus* is more specialized compared to interaction with other microbes. SP-A mediates opsonization by binding to Eap expressing *S. aureus* [36]. *S. aureus* is opsonized by SP-A and then interacts with the putative SP-A receptor 210 (SP-R210) on alveolar macrophages for phagocytosis [36]. SP-R210 is also utilized to kill *Mycobacterium bovis* (bacillus Calmette-Guerin) that has been opsonized by SP-A [36].

Mycoplasma, fungi, and yeasts—SP-A and SP-D are both able to bind to *Mycoplasma pneumonia* [32][31], and SP-A in particular is highly effective in its clearance [38]. SP-A is also effective in limiting pro-inflammatory biological signals triggered by *Mycoplasma pneumoniae* [15]. Pulmonary infection with *Mycoplasma* is limited by SP-A which serves as a growth inhibitory signal for the microbe [35]. SP-A and SP-D also facilitate removal of fungi and yeasts from the pulmonary system. SP-D utilizes its CRD domain to bind to fungi and yeast, such as *Saccharomyces cerevisiae* and *Candida albicans*, via its surface glycoproteins [35]. Both collectins can bind fungi or yeast to aid in their aggregation [16, 35]. This interaction acts at times to inhibit growth, specifically for *C. albicans*, as phagocytosis may be inhibited due to the size of the resulting aggregates [16]. *Aspergillus fumigatus* [35], on the other hand, is phagocytized by macrophages following binding by SP-A or SP-D [32].

Viruses—Viruses differ in infectivity from many other pathogens due to the fact that they require entry into cells for subsequent replication [16]. Viral infections can have devastating effects on respiration if they are not efficiently removed from the system, an effect observed by the morbidity of past influenza pandemics [39]. SP-A and SP-D are both able to bind, agglutinate and enhance phagocytosis of numerous viruses, including influenza A virus, adenovirus, respiratory syncytial virus (RSV), and herpes simplex virus type 1 [13, 32, 35]. The collectins bind to these viruses via their CRD domains to glycoproteins on the surface of the viruses [32, 33]. SP-A and SP-D bind to different glycoproteins on RSV, yet both diminish infectivity [16, 32, 35]. SP-A and SP-D can promote phagocytosis of virions through both opsonic and non-opsonic mechanisms [15, 16, 35]. Collectin binding to influenza A virus occurs by recognition of hemagglutinin and neuraminidase glycans on the surface of the virus thereby hindering the ability of the virus for cell entry [35, 39]. This mechanism leads to aggregation and inactivation of the virion [35, 39]. It is possible that hemagglutinins found on influenza A viruses involved in past influenza outbreaks exhibited antigenic variations that resulted in reduced collectin binding, leading to greater virulence and subsequent high mortality and morbidity in patients [39].

Much of what is known about the roles collectins play in innate immunity has been achieved by experiments involving mice that are deficient in either of these proteins. Loss of SP-A results in delayed clearance of many pathogens due to deficient recognition and subsequent removal by macrophages [6, 13, 14]. Even more detrimental effects could be seen from the increase in release of inflammatory agents [14, 35]. SP-D knockout mice also display a robust pulmonary inflammatory response with decreased clearance of a variety of pathogens

[6, 13, 14, 35]. These consequences can lead to an increase in growth, proliferation, and infectivity of invading microbes [35]. Thus, mice that lack SP-A and SP-D are clearly susceptible to infection and inflammation [2, 8, 13, 15, 37]. Of note, in humans there exist two genes, SP-A1 and SP-A2 that encode for SP-A1 and SP-A2 proteins [40]. The possibility that there may be subpopulations with differential vulnerabilities to microbial infection based on these species of SP-A is intriguing; however the detailed functionality of these isoforms requires further investigation. Overall, the existing data clearly demonstrate that SP-A and SP-D are potentially indispensible in the innate immune response.

2.2. Regulating inflammatory responses

The collectin proteins can also modulate the host inflammatory response independent of activities against microbial agents. For example, SP-A and SP-D play a major role in regulating inflammation by hastening the clearance of apoptotic cells and impeding the release of cytokines and other pro-inflammatory products [2, 6]. Multiple mechanisms exist by which cells remove dying cells. Apoptotic neutrophils are cleared via the interaction of SP-A and SP-D with myeloperoxidase, which is present on the surface of these cells [41]. SP-D has also been found to interact with immunoglobulin M to enhance phagocytic removal of late apoptotic cells [42]. When not interacting with pathogens, SP-A and SP-D bind to the signal inhibitory peptide (SIRP-alpha) on macrophages to attenuate release of pro- inflammatory products, specifically cytokines [2]. In some experiments using SP-A or SP-D knockout mice, the presence of pro-inflammatory cytokines is increased and inflammatory response resulting from infection is accentuated [13]. Further, these collectins are prone to nitrosylation, a modification that perturbs their tertiary structure. For example, *S*-nitrosylation of SP-D is chemoattractive for macrophages and induces pro-inflammatory signaling [43].

SP-A regulates signaling pathways in macrophages in response to microbial recognition that controls inflammation. In type II pneumocytes, SP-A can bind to various receptors, including P63 [44] and SPAR [45], to activate the phosphatidylinositol 3-kinase (PI-3K) pathway triggering phosphorylation of the downsteam kinase, Akt. Activation of the PI-3K-Akt pathway is pro-survival as Akt normally inactivates downstream pro-apoptotic signals such as glycogen synthase kinase -3β and forkhead transcription factor FKHR [45]. Akt activation leads to phosphorylation of IκBα leading to nuclear translocation of the transcription factor, NFκB, that induces expression of pro-inflammatory genes. However, in macrophages, SP-A increases the expression of Toll-like receptor (TLR) 2, and yet impairs its activity resulting in decreased Akt activation and nuclear NFκB [46]. Thus, SP-A differentially regulates critical signaling events within pulmonary cells that in turn controls inflammatory gene expression [46].

3. Role of lipids in infection

Recent studies have illuminated a potentially important role for surfactant phospholipids in altering the immune response. Phospholipids, specifically anionic lipids appear to act as immunosuppressive mediators by inhibiting responses such as release of reactive oxygen species and pro-inflammatory cytokines [8, 47, 48]. This may represent a self-preservation or feedback control mechanism to limit prolonged inflammation for these regulatory lipids.

3.1. Immunosuppression by phospholipids

Recently, anionic phospholipids, such as palmitoyl-oleoyl-phosphatidylglycerol (POPG) and phosphatidylinositol (PI), relatively minor components of pulmonary surfactant, appear to exhibit immunomodulatory activity. POPG and PI were observed to inhibit LPS-induced nitric oxide and tumor necrosis factor-alpha responses in lung macrophages by interfering

with Toll-like receptor interactions with adaptor molecules, CD-14 and MD-2, involved in NF-κb induced cytokine signaling [49]. The same group demonstrated that anionic phospholipids impair pro-inflammatory signaling induced by *M. pneumoniae* and RSV [50]. Another anionic phospholipid and very minor component of surfactant, cardiolipin, was also found to be immunosuppressive after release from injured host cells in pneumonia [51]. Cardiolipin in this study was observed to potently inhibit surfactant activity.

3.2. Lipid inhibition of viral infectivity

Viruses are common pathogens that interact with surfactant phospholipids. To date, dipalmitoylphosphatidylglycerol (DPPG) has been the only phospholipid member of surfactant to inhibit viral infection, though others may also play a role [52]. Specifically, DPPG interacts with Vaccinia virus, an orthopoxvirus. Small vesicles containing DPPG inhibit viral infection by blocking attachment of the virions to host cells [52]. DPPG likely impairs interaction with cell membranes by obstructing viral ligand binding with cell surface receptors [52]. Future studies will need to determine if other phospholipids have similar effects on viral infectivity.

3.3. Facilitating viral host cell entry by lipids

A significant body of data also suggests that surfactant phospholipids facilitate the entry of viruses into host cells [53–56]. DPPC, the predominant surface-active lipid, binds and enhances adenoviral entry into alveolar epithelium [52, 53]. As surfactant DPPC is reutilized after alveolar secretion by reincorporation into alveolar cells during recycling, it would appear that adenovirus exploits this pathway for cell entry. These effects on adenoviral trafficking with lipids appear to be specific to saturated lipids (e.g. DPPC), as monounsaturated forms of PC bind the virus but impede particle entry [53].

Phosphatidylserine (PS) also enhances viral infection by increasing fusion of the virus to cell membranes [54] by masquerading as an apoptotic signal [55, 56]. In cells undergoing apoptosis, PS transmigrates from the inner to outer membrane of dying host cells as a signal for efferocytosis, a form of phagocytosis [56]. In viruses, PS is associated mainly with enveloped forms [54]. Vaccinia virus, particularly the mature viral form, by either expressing PS on its envelope or interacting with surfactant PS, is recognized by many cell types as an efferocytotic signal for internalization [55]. By exploiting this mechanism for host cell entry, which inhibits the initiation of the inflammatory response, the virus may go undetected by the immune system enabling it to spread to surrounding cells [55]. However, this ability of PS to facilitate some viruses to enter cells can also be utilized as a translational tool by using enveloped viral vectors for therapeutic gene transfer [54].

4. Role of infection on surfactant composition

Several studies demonstrate that surfactant composition is altered in human subjects with respiratory infection [7–9, 12, 13]. These observations have led to studies using animal models of pneumonia or cellular systems to better understand microbial virulence factors that might alter surfactant metabolism. Lower respiratory tract pathogens modify surfactant balance by several mechanisms that directly reduce intra-alveolar availability of both apoprotein and lipid components, decrease surfactant biosynthesis, or impair its secretion [33, 37, 57–61]. For example, virulence factors released from *P. aeruginosa* have been linked to degradation of collectins [16, 33, 37, 57–59], and bacterial exotoxins displaying lipase activity are implicated in surfactant phospholipid hydrolysis [62–64]. *P. aeruginosa* secretes elastases [33, 57] and protease IV [58] that mediate degradation of SP-A and SP-D by targeting the CRD domain [16, 33, 37, 57, 58]. Protease IV also exhibits activity against SP-B, resulting in impaired surfactant function [58]. Degradation of collectins by these

proteases can potentially leave the host vulnerable to developing severe infection [57]. A mucoid strain of *P. aeruginosa* also reduces levels of surfactant phospholipids by inhibiting gene transcription of the rate-limiting enzyme, cytidylyltransferase, required for PC synthesis [59]. Mucoid strains also inhibit gene transcription of SP-B and SP-C, compounding surfactant deficiency that impairs stability of surfactant films [59]. In addition, other components of gram-negative bacteria, such as LPS inhibit phospholipid synthesis and secretion [59, 60]. Bacterial suppression of surfactant production may also be indirect via release of host cell cytokines, including tumor necrosis factor -α, which targets surfactant biosynthetic enzymes for degradation[57–60]. Human adenovirus can also alter surfactant phospholipid composition [61], whereas *Aspergillus fumigatus* and *Pneumocystis carinii* can downregulate SP-B and SP-C protein and mRNA expression [1]. In some studies, pathogens induce expression of collectins [65–67].

5. Concluding Remarks

Even though a great deal is known about the composition of surfactant and the roles these components play in lung balance, there is still much to learn. Surfactant phospholipids, along with SP-B and SP-C, are crucial to maintain surface activity. Deficiencies or alterations to these components can have devastating effects on pulmonary function resulting in lung injury. SP-A and SP-D play an integral role in regulating innate host defense. Additional research is needed to fully understand the biological and clinical relevance of these surfactant components to human disease. It is anticipated that the next phase of investigation will capture newer tools of genomics, proteonomics, and lipidomics to link this work with personalized medicine to enhance our understanding of the fundamental roles of surfactant. These approaches can be used in the future to identify high-risk populations for lower tract infection or to devise novel strategies to optimize lung function in the setting of pulmonary infection and inflammation. More work is needed to examine how newer, emerging virulent pathogens evade the protective responses of the surfactant system to initiate and sustain infection. Enhancing this knowledge will potentially help improve the outcome of patients with severe respiratory illness.

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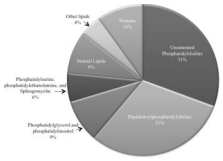

Figure 1.
Breakdown of Surfactant Composition. Surfactant is composed of about 90% lipids and 10% proteins. The largest portion of this are the phospholipids, composed of phosphatidylcholine (half of which is dipalmitoylphosphatidylcholine), phosphatidylglycerol, phosphatidylinositol, and others. Neutral lipids in surfactant are predominantly cholesterol, but also include free fatty acids, monoglycerides, diglycerides, and triglycerides. Proteins represent the remaining portion of surfactant of which surfactant-associated proteins are key components.

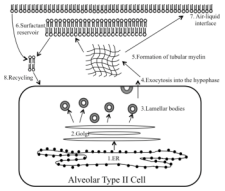

Figure 2.

Surfactant synthesis, secretion, and recycling. (1)Surfactant component are synthesized in the endoplasmic reticulum (ER) of the alveolar type II cells and are then transported to the Golgi (2) where they are modified. (3) The phospholipid and protein components of surfactant are then stored in the lamellar bodies until they are secreted (4) via exocytosis into the hypophase. The surfactant constituents then form (5) tubular myelin which can either be transported to the surfactant reservoir (6) for later use or directly to the air-liquid interface (7) to form the surfactant film that protects the alveoli. The phospholipids are recycled (8) back to the type II cells to be stored in lamellar bodies until reuse.

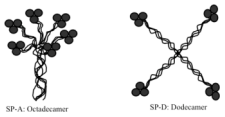

Figure 3.
Structure of surfactant proteins A and D. Both SP-A and SP-D are composed of a NH2-terminal domain, a collagen domain, a neck region, and a carbohydrate recognition domain. These four domains come together to form a trimer. In SP-A, these trimers form an octadecamer while in SP-D they form a dodecamer.