Review

Cellular Physiology and Biochemistry

Cell Physiol Biochem 2010;25:13-26

Accepted: September 16, 2009

Pulmonary Surfactant: An Immunological Perspective

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Key Words

Lung • Surfactant protein • Alveolar macrophages • Collectin • Receptor • Inflammation• Innate immunity

Abstract

Pulmonary surfactant has two crucial roles in respiratory function; first, as a biophysical entity it reduces surface tension at the air water interface, facilitating gas exchange and alveolar stability during breathing, and, second, as an innate component of the lung's immune system it helps maintain sterility and balance immune reactions in the distal airways. Pulmonary surfactant consists of 90% lipids and 10% protein. There are four surfactant proteins named SP-A, SP-B, SP-C, and SP-D; their distinct interactions with surfactant phospholipids are necessary for the ultra-structural organization, stability, metabolism, and lowering of surface tension. In addition, SP-A and SP-D bind pathogens, inflict damage to microbial membranes, and regulate microbial phagocytosis and activation or deactivation of inflammatory responses by alveolar macrophages. SP-A and SP-D, also known as pulmonary collectins, mediate microbial phagocytosis via SP-A and SP-D receptors and the coordinated induction of other innate receptors. Several receptors (SP-R210, CD91/calreticulin, SIRPα, and toll-like receptors) mediate the immunological functions of SP-A and SP-D. However, accumulating evidence indicate that SP-B and SP-C and one or more lipid constituents of surfactant share similar immuno-regulatory properties as SP-A and SP-D. The present review discusses current knowledge on the interaction of surfactant with lung innate host defense.

Introduction

Pulmonary surfactant, a complex of lipids and proteins lining the alveolar surface, is responsible for lowering surface tension at the air-liquid interface thereby preventing alveolar collapse at the end of expiration [1, 2]. However, lung surfactant is also an integral component of the lung's innate immune system helping to control inflammation and to prevent microbial infections of the distal lung [3, 4]. Inside the alveolus, large and small aggregate vesicles of pulmonary surfactant lipids are

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spatially and dynamically coordinated with the surface active monolayer at the air-liquid interface [5]. Surfactant composition and pool size is controlled by several physiological processes, including secretion, re-uptake, and recycling by alveolar type II epithelial cells and degradation by both alveolar type II epithelial cells and macrophages [6, 7]. All surfactant proteins contribute to the internalization of surfactant subtypes by type II epithelial cells [8-11]. The principal lipid constituents of surfactant are phospholipids, 80-85%, and cholesterol, 8-10% by weight. Phosphatidyl choline species comprise about 75% of surfactant phospholipid. Saturated dipalmitoyl phosphatidyl choline (DPPC) is the most abundant and critical surface-active phospholipid species that constitutes 50% (w/w) or more of lung surfactant phospholipid. Remaining phospholipids include phosphatidyl glycerol (12%), phosphatidyl ethanolamine (5%), phosphatidyl inositol (4%), phosphatidyl serine (1.5%), sphingomyelin (1%), and lysophospholipid (<1%). Optimal surfactant function requires the presence of four proteins named SP-A, SP-B, SP-C, and SP-D. Of the four, SP-A is the most abundant comprising 50-70% of surfactant proteins (w/w). However, SP-B, which comprises 10% (w/w) of surfactant protein is the most critical; its absence or dysfunction due to mutations results in respiratory failure and death shortly after birth [12-15]. Secreted surfactant consists of different subtypes that can be distinguished by differential or density gradient centrifugation as surface active large aggregate (LA) and surface inactive or "spent" small aggregate surfactant (SA) forms [16]. The LA and SA forms can be isolated by differential centrifugation at 40,000 and 100,000 x g, respectively. Greater than 95% of SP-A, SP-B, and SP-C fractionate with LA surfactant [17], while less than 10% of SP-D associates with LA surfactant [11]. The LA surfactant contains several morphologically distinct forms that are referred to as lamellar body-like, tubular myelin, and multilamellar vesicles. SP-A and SP-B are necessary for the conversion of lamellar bodies into tubular myelin [13, 18-20], while SP-D modulates conversion of LA to SA surfactant [11, 21]. Recent findings in inducible SP-D transgenic mice showed that SP-D preferentially interacts with newly synthesized LA surfactant enriched in phosphatidyl inositol, an action that helps maintain surfactant pool size in neonatal and adult lung through conversion of LA surfactant into catabolically active SA forms [11]. In this study most of induced SP-D fractionated with SA surfactant [11]. Earlier studies identified phosphatidyl inositol as the major phospholipid binding site for SP-D in lamellar body enriched surfactant [22]. SP-B and SP-C facilitate the formation and stability of interfacial films and surface active monolayer at the air-water interface [5]. Among surfactant components, SP-A and SP-D have been extensively characterized as host defense components of pulmonary surfactant [3, 23]. However, increasing evidence indicates that all surfactant proteins and one or more surfactant phospholipids regulate immunological homeostasis, inflammation, and innate lung host defense [4, 24].

Pulmonary surfactant in lung disease

Abnormal surfactant levels and composition in humans have been associated with respiratory dysfunction and inflammation in ALI/ARDS [25, 26], pulmonary fibrosis [27], emphysema [9, 28], cystic fibrosis [29], COPD [30], and RDS in newborns [1]. Genetic variation or deletion in surfactant protein genes is associated with COPD [31, 32], interstitial lung diseases [33, 34], cancer [35, 36], pulmonary infections [37, 38], congenital alveolar proteinosis [14, 39, 40], and enhanced development of broncho-pulmonary dysplasia [41]. In parallel, studies in SP-A, SP-B, SP-C, and SP-D-deficient mice support the crucial roles for surfactant proteins in surfactant stability and monolayer formation [13, 19, 21, 28, 42], metabolism [10, 21, 43, 44], pathogenesis of acute and chronic inflammation [28, 45-50], respiratory distress [13, 51, 52], lung injury [51, 53-55], and susceptibility to infection [46, 48, 56-58]. Deficiencies in surfactant protein components is associated with dys-regulated inflammatory responses [28, 43, 48, 49, 56] and presence of abnormal surfactant vesicles [26, 27]. Collectively, the results from genetically manipulated mice support the concept that genetic polymorphisms in one or more surfactant protein genes enhance susceptibility to pulmonary inflammatory disease in humans.

Genetic susceptibility may alter interactions between surfactant and alveolar cells promoting the development of lung disease. An inducible mouse model of SP-B expression was used to demonstrate that re-expression of SP-B in the lungs of SP-B-deficient mice suppressed inflammation caused by surfactant dysfunction [49]. SP-B is critical for the biophysical action of surfactant that lowers surface tension at the air-liquid interface; its absence, and by extension impaired surfactant function, resulted in activation of inflammatory pathways in alveolar macrophages and alveolar type II epithelial cells. Notable in this case is the activation of the transcription factor STAT3, which mediates the inflammatory as well anti-

inflammatory pathways of IL-6 family and IL-10 receptors in macrophages [59], respectively. In addition, recent studies demonstrated that STAT3 expression in alveolar type II epithelial cells is critical for pulmonary homeostasis; STAT3 regulates surfactant lipid synthesis and secretion [60, 61], oxidant stress [62, 63], and it protects epithelial cells from acute lung injury by LPS or adenoviral infections [60, 62].

A combination of genetic and environmental modifications of surfactant may further enhance the development of pulmonary disorders. In this regard, oxidative stress defined as the loss of balance between oxidant and antioxidant pathways underlies the pathogenesis of several inflammatory lung diseases including ARDS, COPD, and fibrosis [64]. Air pollution and ozone in particular, infections, and smoking are among environmental exposures that contribute to pulmonary oxidant stress [65]. Oxidized surfactant displays inferior anti-inflammatory and surface tension lowering properties [66, 67]. Reactive oxygen species alter the structure of surfactant lipids and proteins inactivating biophysical and immunological properties of surfactant components [68-76]. The macrophage scavenger receptors SR-A and MARCO clear oxidized surfactant lipids as a source of inflammation in the alveolus [77]. Under conditions of oxidative stress, SP-A, the major protein component of surfactant, plays a protective role against oxidative modification and in preserving the surface tension lowering properties of surfactant lipids [66, 78]. Genetic polymorphisms in SP-A may influence oxidant induced dysfunction of surfactant.

Decreased catabolism of surface-inactive surfactant aggregate forms is associated with respiratory dysfunction in patients with asthma, cystic fibrosis, and pneumonia [79, 80]. Impaired surfactant catabolism by alveolar macrophages results in accumulation of surfactant and eventual respiratory failure in patients with primary or secondary alveolar proteinosis (PAP) [81-84]. Loss of GM-CSF function is the main cause of primary PAP. GM-CSF is critical for the local differentiation of alveolar macrophages and their ability to degrade surfactant lipids and proteins [82, 85]. This discovery revealed the importance of alveolar macrophages in surfactant catabolism. In mice, alveolar macrophages contribute about 50% of surfactant catabolism [86]. Correspondingly, temporary depletion of alveolar macrophages results in as 8-10 fold increase in surfactant pool size [87] in rats. A variety of conditions including immunodeficiency syndromes, chronic infection, hematologic malignancies, and environmental exposures contribute to the development of secondary PAP [84]. It is not clear how conditions that lead to secondary PAP impair alveolar macrophage function. However, secondary PAP in *Pneumocystis carinii* pneumonia involves stimulation of surfactant protein synthesis through the interaction between epithelial cell CD40 and CD154 on immune cells [88]. Moreover, accumulation of surfactant in this model is associated with re-distribution of SP-A and SP-D from large aggregate to small aggregate surfactant, oxidative de-oligomerization of SP-D, and alterations in relative expression levels of SP-B and SP-C [89-91]. Structural modifications and redistribution of surfactant proteins are known to occur in primary PAP surfactant as well [92, 93]. Congenital PAP, a rare group of genetic disorders caused by mutations in SP-B and SP-C genes [14, 39, 40], is characterized by mis-processing of SP-B and SP-C pro-proteins and secretion of metabolically inept surfactant containing abnormal forms of SP-B and SP-C [94, 95]. These studies emphasize that alveolar macrophage dysfunction on one hand, and endogenous or exogenous biochemical disruption of surfactant on the other, disturb the interaction of metabolic and immune processes signifying the development of lung disease.

SP-A and SP-D

Structural characterizations of SP-A and SP-D have led to the recognition that SP-A and SP-D interface critical physiological and immune functions of pulmonary surfactant. Both SP-A and SP-D are members of the collectin family of proteins, a classification that is based on homologous amino-terminal collagen-like domains and carboxy-terminal carbohydrate recognition domains (CRD). Mannose binding lectin (MBL), the founding member of the collectin family, is the first component of the lectin pathway of complement in the circulation [96]. Collectins are a subgroup of a large superfamily of proteins containing Ca^{++}-dependent CRD domains. However, the CRD domains of SP-A and SP-D are adapted to interact with distinct surfactant phospholipids [97, 98]. The collagen-like domain of collectins forms trimers and disulfide-dependent oligomerization of trimers then results in deca-octameric SP-A or MBL structures resembling a bouquet of flowers, or cross-hatched SP-D dodecamers. Thus formed, collectins serve as humoral pattern recognition molecules where multiple CRD domains bind, in a calcium-dependent manner, carbohydrate-based ligands on the surface of diverse microorganisms [96]. On the other hand, SP-A and SP-D serve discrete but

complementary roles in intra-alveolar surfactant dynamics and modulation of surfactant turnover by alveolar macrophages and type II epithelial cells, thus contributing to physiological and immunological integrity of the distal airspace. Swapping of amino-terminal segments including the collagen-like domains between SP-A and SP-D is not sufficient to interchange SP-A with SP-D function *in vivo* indicating that SP-A and SP-D are not physiologically redundant. SP-A binds and aggregates phosphatidyl choline, an interaction that facilitates formation of tubular myelin in large aggregate surfactant [99, 100]. Binding of SP-D to phosphatidyl inositol facilitates conversion of large aggregate surfactant to smaller lamellar forms that are metabolized by alveolar type II epithelial cells [18]. Proper surfactant ultrastructure appears critical for the post-natal SP-D-mediated surfactant maturation and the turnover of surfactant lipids by alveolar type II epithelial cells [10, 18, 19, 21, 43, 44, 99, 101-106].

Both SP-A and SP-D serve a pivotal function in lung humoral and innate immunity; they bind a wide range of pathogens, suppress microbial growth, and damage bacterial membranes on one hand, and modulate alveolar macrophage phagocytosis of monodisperse or agglutinated microorganisms [3, 23, 107-111] on the other. In addition to binding carbohydrates, SP-A binds lipid and protein moieties on microbial cell wall molecules. Thus, SP-A binds the lipid A moiety of rough lipopolysaccharides [112], disaturated phosphatidyl glycerol on the surface of *Mycoplasma pneumoniae* [109], the 65 kDa surface cytotoxin MPN372 on *Mycoplasma pneumoniae* [113, 114], and the adhesins Apa and Eap on *Mycobacterium tuberculosis* [115] and *Staphylococcus aureus* [116], respectively. SP-D interacts with heptose in the inner core oligosaccharide of rough LPS and mannose in O-antigen carbohydrate chains of smooth LPS [117, 118]. Extraction of LPS from the cell wall of gram-negative bacteria underlies the direct bactericidal activity of SP-A and SP-D [108]. LPS is a major immunoreactive contaminant in inhaled air that can disrupt surfactant membranes. Both SP-A and SP-D are involved in clearance and detoxification of LPS by alveolar macrophages [119, 120]. Further, SP-A- and SP-D-deficient mice are unable to resolve neutrophilic inflammation caused by gram-negative bacteria or LPS [43, 58]. Clathrin-dependent endocytosis of SP-A activates a PKCζ-dependent pathway that blocks the ability of LPS to induce inflammation in alveolar macrophages [121]. Concordant to their ability to remove LPS from the surface of bacteria, SP-A and SP-D remove LPS from the membrane of surfactant vesicles [122, 123] as well, and also bind and aggregate LPS in model surfactant monolayer membranes [124, 125]. These findings support the notion that SP-A and SP-D preserve basal surfactant function through their ability to both sterilize pathogens and remove inflammatory molecules that are inhaled into airway secretions.

In different circumstances, SP-A and SP-D enhance pathogen-dependent activation of pro-inflammatory responses of alveolar macrophages during ingestion of SP-A- or SP-D-opsonized microbes *in vitro* [126-131], a proactive clearance mechanism that also operates *in vivo* during initial clearance of experimental pulmonary infections [45, 46, 58, 90, 129, 132-137]. In contrast, SP-A and SP-D suppress secretion of pro-inflammatory cytokines and oxidant intermediates when macrophages are challenged with pathogen-derived cell wall components such as lipopolysaccharide [121, 138-144] or mycobacterial cell wall extract [145]; this protective SP-A function has been noted in both *in vitro* macrophage culture and *in vivo* animal models [58, 140, 146]. SP-A initially enhances clearance of *Mycoplasma pneumoniae* [133, 134] but subsequently turns off inflammation [146], indicating that SP-A works in a temporal fashion to resolve inflammation. In this context, SP-A and SP-D regulate phagocytosis of apoptotic cells [147, 148]. In addition, SP-A enhances secretion of anti-inflammatory IL-10 and can induce secretion of TGFβ in the presence of mycobacterial cell wall antigen or apoptotic cells in peripheral blood monocytes and alveolar macrophages [145, 149], processes that may help resolve inflammation and restore steady-state concentrations of pulmonary surfactant in the long-term. In this regard, TGFβ activation by epithelial β6 integrin is necessary for the maintenance of normal surfactant pool size; lack of β6 integrin results in inflammation and development of PAP [150]. These findings indicate that precise coordination of surfactant metabolism with immune responses is necessary to resolve inflammation and restore airway homeostasis.

SP-B, SP-C, and surfactant lipids

The hydrophobic SP-B and SP-C have been characterized extensively for their ability to effect lamellar body formation, secretion, and formation of the surfactant monolayer that is critical to the lowering of surface tension at the air/water interface [5]. However, increasing evidence indicate that SP-B and SP-C are also involved in immunomodulation that is critical for the stability and host defense of the airways [24]. Inducible transgenic

mice were used to show that reduction in SP-B expression and the associated abnormalities in reducing surface tension divulged an inflammatory response in alveolar macrophages and type II epithelial cells [49]. SP-B-deficiency also impaired the ability of the lung to counteract LPS-induced inflammation [50]. SP-B is the most critical effector of the surface tension lowering properties of surfactant, a function that also influences the shape and phagocytic activity of alveolar macrophages [151].

More recently, SP-C-deficient mice were found to be susceptible to bacterial and viral infections and to suffer from excessive inflammation [48, 56]. Bleomycin-induced fibrosis was more severe in SP-C-deficient mice [152]. The role of SP-C in suppressing inflammation is in part related to the ability of its amino-terminal segment to bind LPS [153-155]. On the other hand, SP-C-containing surfactant vesicles bind and interfere with toll-like receptor mediated inflammatory responses in macrophages [56]. Exogenous surfactant and surfactant lipids in the absence of proteins exhibit anti-inflammatory properties as well [156-158]. SP-B and SP-C appear to confer differential roles in the ability of surfactant to suppress inflammation; the presence of SP-B rather than SP-C in survanta was more important in suppressing LPS-induced production of nitric oxide by alveolar macrophages [158]. Survanta is a bovine derived therapeutic surfactant lipoprotein that is used to treat respiratory distress syndrome in premature infants; it contains SP-B and SP-C but not SP-A or SP-D [159]. In addition, surfactant vesicles containing phosphatidyl glycerol (POPG) block LPS-induced inflammation by macrophages [160]. POPG is an acidic phospholipid that is uniquely present in pulmonary surfactant. It was shown that POPG binds CD14, TLR4, and MD-2, thus antagonizing the ability of LPS to induce inflammation [160]. On the other hand, surfactant lipids and dipalmitoyl phosphatidyl choline in particular block epithelial cell expressed TLR4 activation by limiting translocation of TLR4 to membrane lipid raft micro domains [161]. Phospholipid vesicles containing dipalmitoyl phosphatidyl choline, the major phospholipid in pulmonary surfactant, induced expression of several macrophage innate immune receptors [162], a property that has also been noted for purified SP-A and SP-D [163-168]. In these cases, SP-D influences alveolar macrophage differentiation as indicated by expression of CD11c [169-171], while surfactant DPPC and SP-A induced expression and function of several innate immune receptors that so far include the complement receptor CR3 (CD11b), the scavenger receptors SR-A, CD36, and LOX-1, the mannose receptor, toll-like receptors, Fc receptors and the complement receptor CR1 [157, 164, 169, 170]. Adoptive transfer experiments and studies in SP-D-inducible transgenic mice indicate that SP-D contributes to the local differentiation of freshly recruited monocytes in the alveolar space [169-171]. Surfactant lipids and proteins may subsequently become ligands for one or more of these receptors. It is also notable that phosphatidyl glycerol facilitates clearance of surfactant phospholipids by alveolar macrophages [172, 173]. These studies indicate that alveolar macrophages and alveolar type II epithelial cells coordinate surfactant metabolism and innate host defense properties of pulmonary surfactant.

SP-A and SP-D receptors

Several receptor systems have been identified that mediate homeostasis and immunomodulatory activities of SP-A and SP-D by alveolar macrophages. These include CD91/calreticulin, SIRPα, toll-like receptors, and SP-R210.

CD91/calreticulin and SIRPα

Earlier studies reported that calreticulin, an endoplasmic reticulum chaperone, appears on the cell surface of normal and malignant cells [174, 175]. In parallel, other studies identified the collagen-binding C1q receptor C1qR as calreticulin and additional studies demonstrated that the collagen-like domains of collectins (SP-A, SP-D, and MBL) also bind calreticulin [176] in macrophages. CD91, also known as lipoprotein related receptor 1 [177], was then identified as a receptor for secreted chaperones including calreticulin [178]. Gardai et al [179, 180] have subsequently demonstrated that calreticulin bridges SP-A-coated apoptotic cells and bacteria to CD91, resulting in the ingestion of SP-A-bound cargo, and a concomitant pro-inflammatory response. The same studies also showed that the CRD domains of collectins bind the signal inhibitory receptor SIRPα, thus mediating anti-inflammatory activities of collectins [179]. SIRPα was initially defined as a counter-receptor for the widely expressed CD47 [181], that transmits "eat me" vs. "don't eat me" signals to initiate phagocytosis of apoptotic cells and exogenous intruders but not intact host cells by macrophages. The CD47-SIRPa interaction inhibits "self" engulfment through de-phosphorylation of myosin IIA [182]. However, SP-A and SP-D also bind SIRPα to suppress ingestion of apoptotic cells by alveolar

macrophages [148]; this interaction is thought to maintain a low rate of alveolar macrophage phagocytosis in the resting state without inciting inflammation. In this model, the interaction of lung collectins with apoptotic cells or bacteria increases the affinity of SP-A or SP-D with calreticulin, which favors the inflammatory/clearance CD91/calreticulin pathway over the basal inhibitory SIRPα pathway. On the other hand, LPS-mediated suppression of SIRPα [183] correlates with the enhanced ability of exudate macrophages to ingest apoptotic cells [148]. However, recent studies in transgenic mice and CD91-deficient cells showed that CD91 is not the only cell-surface receptor for calreticulin [184, 185]. Other studies identified the class A scavenger receptor SR-A as a calreticulin receptor on antigen presenting cells [186]. Interestingly, the pairing of CD47 with SIRPα inhibits phagocytosis via IgG Fc or complement receptors [187], but does not affect the phagocytosis of senescent or oxidized erythrocytes via scavenger receptors [188]. Therefore, SP-A and SP-D engagement of SIRPα may suppress phagocytosis via some but not all innate immune receptors. On the other hand, more recent studies demonstrated that CD91/calreticulin acts as a receptor for modified SP-D [76]. S-nitrosylation of thiols in the SP-D collagen domain enhanced the interaction of SP-D with CD91/calreticulin in the absence of apoptotic cell or bacterial targets. The increased binding of S-nitrosylated SP-D with calreticulin was associated with reduction in the oligomerization state of nitrosylated SP-D. In this case, posttranslational modification of SP-D and its binding to calreticulin may overcome SIRPα-mediated local immunosuppression by SP-D. This alternative engagement of the CD91/calreticulin receptor has pathophysiological significance in that SP-D is subject to modification by reactive nitrogen and oxygen radicals during inflammation *in vivo* [75]. Modified SP-D exacerbates inflammation and injury through recruitment of inflammatory cells during *Pneumocystis carinii* pneumonia [89].

CD14 and toll-like receptors

Several studies have demonstrated that both SP-A and SP-D antagonize the inflammatory actions of pathogen-derived molecules through their ability to directly bind the LPS receptor CD14 and the toll-like receptors TLR2 and TLR4 [189-193], and the TLR4 adaptor MD-2 [194]. SP-A and SP-D were shown to bind these innate receptors via their CRD domains. SP-A and SP-D binding blocks the interaction of pathogen immuno-stimulatory molecules with TLR receptor components. On the other hand, SP-A can also modulate expression and function of TLRs in human alveolar macrophages indirectly [165]. As mentioned above, all surfactant proteins and lipids modulate, directly or indirectly, the activity of toll-like receptors in the airway.

SP-R210

The 210 kDa SP-A receptor was identified in rat lung and human U937 cell membranes [195]. Polyclonal antibodies to SP-R210 blocked SP-A binding to alveolar macrophages and type II epithelial cells and also blocked the ability of SP-A to inhibit surfactant phospholipid secretion in alveolar type II epithelial cells. These studies provided initial evidence that SP-R210 is involved in surfactant metabolism. Subsequent studies defined the role of SP-R210 in immunological responses [126, 127, 145, 196]. SP-R210 facilitates phagocytosis and killing of SP-A-opsonized *Mycobacterium bovis* BCG, by a mechanism involving induction of nitric oxide and secretion of TNFα [126, 127]. Interestingly, SP-R210 was shown to inhibit T lymphocyte proliferation [196] in peripheral blood mononuclear cells, indicating that SP-R210 can also act to suppress inflammation. Antibodies against the SP-A binding domain confirmed the ability of SP-R210 to inhibit Th1 lymphocyte proliferation in the context of an immune response to mycobacterial antigen [145]. The suppression of lymphocyte proliferation by SP-R210 was mediated via induction of the anti-inflammatory cytokines IL-10 and TGFβ. A molecule with properties similar to SP-R210 was recently identified in myometrial membranes where it mediates the anti-inflammatory response of SP-A during late gestation [197]. LPS and mycobacterial cell wall antigen stimulate inflammatory responses via CD14 and toll-like receptors [190, 193, 198]. In this regard, ligation of SP-R210 elicited secretion of IL-10 and suppressed, but did not abolish mycobacterial antigen-stimulated secretion of TNFα [145]. Thus, it appears that SP-A, via SP-R210, enhances macrophage activation inducing ingestion and killing of SP-A-opsonized pathogens but subsequently, it works to suppress inflammation.

Macrophage expressed SP-R210 was recently identified as a short trans-membrane isoform of the novel myosin 18A (Myo18A) [199] that was named as SP-$R210_S$. The Myo18A gene was also identified by Obinata and colleagues in fibroblasts [200]. Subsequent independent studies showed that the *Myo18A* gene encodes two major splice variants of Myo18A that are differentially expressed in somatic and immune cells [199, 201]. With the exception of alveolar type II epithelial cells

[195, 199], non-immune cells and tissues express a long intracellular isoform with an amino-terminal PDZ domain [199, 201] that was also named SP-R210$_L$. The long SP-R210$_L$ isoform regulates retrograde membrane flow; this function involves formation of a tripartite complex that bridges the PDZ domain of SP-R210$_L$ with LRAP35a and myosin IIA [202]. The size of SP-R210$_L$ mRNA varies from 7.5-8.5 kbases in different tissues. SP-R210$_S$ does not contain the amino-terminal PDZ domain; it is expressed as a type II membrane protein on the surface of macrophages where it acts as an SP-A receptor. The size of the SP-R210$_S$ mRNA ranges between 6.5-7.0 kbases in different macrophage populations and cell lines. Macrophages also express a third 150-170 kDa splice variant called SP-R210$_{S1}$ [145] expressed from 6.0-6.5 kbase mRNA species. SP-R210$_S$ is the predominant isoform expressed on alveolar macrophages while SP-R210$_{S1}$ is expressed in monocytes. The role of macrophage SP-R210 isoforms in surfactant catabolism is inferred from results in GM-CSF-deficient alveolar macrophages. Alveolar macrophages from GM-CSF-deficient mice lack high affinity binding sites for SP-A, and exhibit decreased uptake and degradation of LA surfactant [82].

Conclusions

Tightly controlled mechanisms exist to preserve surfactant homeostasis and eradicate a myriad of airborne pathogens to keep the lung sterile. This complex mixture of lipids and proteins lowers surface tension at the air-liquid interface preventing collapse of alveolar sacs during exhalation on one hand and intimately involved in innate host defense of the distal airways on the other. A host of studies in humans, animal models, and in cultured cells indicate that the integrity of surfactant and its various biophysical forms are critical components of the lung innate immune system. Studies on partial or individual surfactant components have revealed various mechanisms by which surfactant and its components interact with alveolar macrophages to prevent infection and precisely regulate inflammatory responses. The ability of several surfactant components to modulate innate immune receptors on alveolar macrophages, which are variously involved in phagocytosis of microbes (scavenger, complement, and mannose receptors), and uptake of damaged proteins and lipids (scavenger receptors) may help eliminate infectious agents and immunoreactive macromolecules from airway secretions.

It appears that considerable effort is invested to suppress the inflammatory actions of toll-like receptors in alveolar epithelial cells and macrophages as several surfactant proteins and a combination of surfactant lipids and proteins bind and antagonize the effects of LPS and infectious organisms. Within this realm, recent studies showed that TLR4 is an important immunological source of acute lung injury caused by acid inspiration, influenza, pulmonary contusion, and hemorrhagic shock [203-205]; these injury models did not involve administration of LPS indicating that insults that activate TLR inflammatory pathways are not restricted to specific pathogens or infection. The domain-dependent interactions of SP-A and SP-D with CD91/calreticulin and SIRPα control opposing macrophage reactions that maintain basal responses but enhance the clearance of apoptotic cells under inflammatory conditions that suppress SIRPα. The CD91/calreticulin pathway may contribute to oxidant-induced lung injury through recognition of nitrosylated SP-D. SP-R210 appears to coordinate macrophage activation with ingestion of SP-A-opsonized mycobacteria but to suppress antigen-mediated inflammation. Differential expression of SP-R210 isoforms in resident and recruited macrophages may mediate opposing inflammatory activities of SP-A during resolution of inflammation. SP-R210 isoforms, via secretion of IL-10, TGFβ, and modulation of surfactant secretion may have reciprocal roles in surfactant metabolism by alveolar type II epithelial cells and macrophages.

Abbreviations

ALI (acute lung injury); ARDS (adult respiratory distress syndrome); COPD (chronic obstructive pulmonary disease); RDS (respiratory distress syndrome); PAP (pulmonary alveolar proteinosis); LA (large aggregate); SA (small aggregate); CRD (carbohydrate recognition domain); GM-CSF (granulocyte macrophage colony stimulating factor); SP (surfactant protein); TLR (toll-like receptors).

Acknowledgements

We acknowledge the financial support of the Juvenile Diabetes Researsch Foundation, Potts Memorial Foundation, University of Texas Health Science Center President's Council grants, and NIH/NHLBI Public Health grant HL068127.

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