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The "wisdom" of lung surfactant: balancing host defense and surface tension-reducing functions

The mixture of lipids and proteins that comprises pulmonary surfactant is both complex and multifunctional. Although surfactant was originally identified as a lipoprotein complex that reduces surface tension at the air-liquid interface of the lung (4, 20), both in vitro and in vivo studies support a second important role for surfactant in modulating lung host defense (reviewed in Refs. 12, 13, 23). The surfactant lipoprotein complex consists predominately of lipids and four proteins known as surfactant protein (SP) -A, -B, -C, and -D; all these components are synthesized and secreted by alveolar epithelial type II cells in response to a variety of stimuli, including a deep breath and exercise. Upon secretion into the liquid hypophase that covers the alveolar surface, surfactant lipids form a monolayer at the air-liquid interface and thereby reduce surface tension and the work of breathing. SP-B and SP-C are small, hydrophobic proteins that function in conjunction with lipids to reduce surface tension (reviewed in Ref. 19). A deficiency of surfactant, frequently observed in babies born prematurely, results in impaired lung function and gas exchange that is known as infant respiratory distress syndrome (4). Abnormalities in protein expression due to mutations in the genes for the SP proteins have been associated with fetal neonatal lung disease for SP-B and chronic lung disease for SP-C (reviewed in Ref. 19).

The concept that surfactant may be involved in pulmonary host defense was generated, at least in part, by the finding of multifunctional roles in host defense. A second key observation made by Drickamer and colleagues (7) was that SP-A and SP-D are members of a family of mammalian C-type lectins that have in common an NH2-terminal collagen-like region and a COOH-terminal lectin or carbohydrate recognition domain (CRD) (Fig. 1). This family of collagen-like lectins is known as the "collectin" family and includes the mannose binding lectin (6). The collectins are "pattern recognition molecules" that bind via their CRDs to oligosaccharides found on the surface of microorganisms. Numerous in vitro studies have shown that both SP-A and SP-D opsonize and frequently aggregate bacteria and viruses and enhance their uptake by immune cells such as alveolar macrophages and neutrophils (reviewed in Refs. 13 and 23). In vivo studies have provided concordant data showing that SP-A and SP-D null mice are more susceptible to bacterial and viral infections and, in general, that they have higher viral and bacterial loads and a greater inflammatory response (recently reviewed in Ref. 13). In addition to enhancing phagocytosis, SP-A and SP-D also regulate cytokine and free radical production and the uptake of apoptotic cells and have direct bactericidal activity (Fig. 2). Both SP-A and SP-D have been shown to bind to a variety of allergens, such as house dust mite and Aspergillus fumigatus, and intranasal administration of SP-A and SP-D to mice reduces the eosinophilia and specific antibody levels in mouse models of allergic bronchopulmonary aspergillosis and house dust mite-induced allergy (16).

In addition to mediating innate immune responses, SP-A and SP-D have more recently been implicated in modulation of the adaptive immune response (reviewed in Ref. 23). Both SP-A and SP-D bind to dendritic cells in a calcium-dependent manner; SP-D enhances dendritic cell antigen presentation (3), whereas SP-A inhibits dendritic cell maturation (2). Both SP-A and SP-D also inhibit T cell proliferation, in part by inhibiting calcium signaling (1). Recent studies suggest that transforming growth factor (TGF)-β present in SP-A preparations may account for at least some of the inhibition of T cell proliferation by SP-A (14). Whether or not SP-D inhibits T cell proliferation via TGF-β-independent mechanisms is not known. A role for SP-D in regulating T cell responses in vivo is supported by studies showing that lungs of SP-D null mice contain activated lymphocytes as evidenced by an increased percentage of both CD4+ and CD8+ T cells expressing CD69 and CD25 (8). Furthermore, SP-D null mice had elevated CD4+ cells and increases in IL-13 and chemokine levels following allergic sensitization (10). In aggregate, the studies briefly summarized above, and many others that cannot be included here due to space limitations, suggest that SP-A and SP-D mediate multiple and varied functions of many different types of immune cells, and, in some cases, elicit both pro- and anti-inflammatory responses.

An important and somewhat daunting task has been the identification of specific receptors for SP-A and SP-D. Both proteins in a promiscuous manner to a plethora of different ligands, and, perhaps not surprisingly, a number of potential receptors have been identified and include surfactant protein receptor 210 (SP-R210), glycoprotein-340 (GP-340), signal-inhibitory regulatory peptide (SIRP-α). Toll-like receptors, receptors for C1q, and the complex of CD91 and calreticulin (reviewed in Ref. 13). Gardai and coworkers’ (9) intriguing study provided data consistent with the possibility that the ability of SP-A and SP-D to modulate both pro- and anti-inflammatory responses may be a consequence of whether or not the SP is attached to a pathogen or apoptotic cell. Their data suggest that when the CRD of SP-A or SP-D is bound to a pathogen or apoptotic cell, the unobligated collagen domain interacts with CD91/calreticulin to activate NF-κB and the inflammatory signaling cascade. In contrast, in the normal uninfected lung, the CRD of SP-A or SP-D is free to bind SIRP-α and thereby suppress the inflammatory signal-
ing cascade via SRC homology 2 (SH2)-domain-containing protein tyrosine phosphatase 1-mediated inhibition of P38 (Fig. 3). These intriguing studies shed some light onto how both pro- and anti-inflammatory responses may be mediated by SP-A and SP-D; future important studies are required to define the mechanisms by which receptor expression is regulated and to determine whether specific cell types express different receptors under basal conditions and whether

Fig. 1. Structure of lung collectins and mannose binding lectin (MBL). Collectins have in common an \textit{NH}_{2}-terminal collagen-like region and a COOH-terminal carbohydrate recognition domain (CRD). Collectin trimers are assembled into oligomers of varying size. Drawing is not to scale. SP, surfactant protein. [From Wright (23).] Reproduced with permission from *Nature Reviews Immunology*, 5: 58–68 (2005), Macmillan Magazines Limited.

Fig. 2. SP-A and SP-D have multifunctional roles in host defense. SP-A and SP-D both bind to, and in many cases aggregate, pathogens and apoptotic cells and enhance their uptake and removal by immune cells such as alveolar macrophages and neutrophils. The lung collectins also have direct antimicrobial activity. Both SP-A and SP-D also regulate a variety of immune cell functions, such as production of cytokines and free radicals. [From Wright (23).] Reproduced with permission from *Nature Reviews Immunology*, 5: 58–68 (2005), Macmillan Magazines Limited.
receptor expression changes during an inflammatory or infectious episode.

Although SP-A and SP-D are known as SPs, both are found in many extrapulmonary sites (reviewed in Ref. 13). For example, SP-D mRNA has been detected in several organs, including mouse stomach and kidney; salivary, sweat, and lachrymal glands; and throughout the female reproductive tract albeit at levels lower than found in the lung. A recent intriguing study by Condon and coworkers (5) suggests that SP-A plays a role in the initiation of parturition in mice. Increases in amniotic fluid levels of SP-A paralleled increases in expression of IL-1β and NF-κB in intrauterine macrophages. Furthermore, intrauterine injection of SP-A caused premature labor. A role for SP-A in mediating host defense against *Pseudomonas aeruginosa* infections in the cornea was also recently reported (18). It seems likely that many future studies will help clarify the extrapulmonary functions of SP-A and SP-D, and, at some point in time, the appropriateness of their names may be questioned.

Although substantial progress has been made in understanding the role of the surfactant collectins in host defense in the lung and more recently in other organs, many important and unanswered questions remain. Studies in mice suggest that exogenously administered SP-A and SP-D may be effective therapy for treating allergic and bacterial inflammation and infection. To date, there have been no clinical trials in humans investigating the efficacy of surfactant preparations containing SP-A or SP-D for treatment of acute lung injury or infections, although surfactant replacement therapy with preparations containing lipids and/or SP-B and SP-C have been tested for treatment of acute lung injury with limited success (17). Also, a growing number of recent studies have provided evidence that associations exist between genetic polymorphisms of the human gene and lung disease (e.g., Refs. 15 and 21), but our investigations in this area must be expanded. In addition, a clear understanding of the regulation of SP-A and SP-D synthesis, secretion, and catabolism in diseased lungs or other organs is not well understood. Many studies have provided evidence that levels of all of the SPs and lipids are altered in a variety of lung diseases (reviewed in Ref. 11). In many cases, the alterations in levels are different for the different components, suggesting that the changes are not due to nonspecific suppression of surfactant production due to damage to the alveolar epithelium. Clearly, the lung of the healthy host requires adequate amounts of functional surfactant to both reduce surface tension and defend the lung against infection and inflammation. Exciting future investigations both in basic research and clinical studies will be required to fully understand how the wisdom of the lung is manifest in maintaining appropriate levels of the multifunctional and complex substance known as surfactant.

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REFERENCES


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