Current Views on the Functions of Surfactant Proteins

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The alveolar surfaces of the lungs are lined with a surface-active material consisting of approximately 90% lipids and about 5-10% proteins. This film of pulmonary surfactant enables healthy persons to breath effortlessly with a frequency of about 25,000 cycles per day. The surfactant lipids, with 1,2-dipalmitoylphosphatidylcholine as its major surface-active component, form a monolayer at the air-liquid interface. By decreasing surface tension, this surface film protects the alveoli against collapse at end expiration [1].

The hydrophobic surfactant proteins, SP-B and SP-C, play a prominent role in catalyzing the insertion of surfactant lipids into the surface film [1-3]. Mature SP-B is a cysteine-rich, basic peptide consisting of 79 amino acids. Under nonreducing conditions it occurs as a dimer. SP-C is an extremely hydro-phobic peptide consisting of only 35 amino acids. It contains a continuous C-terminal hydrophobic domain of 23 amino acids including a stretch of 6 contiguous valines. The mature protein has two palmitoyl groups linked to the two cysteines on positions 5 and 6. Both SP-B and SP-C are formed in type-II pneumocytes from much larger primary translation products [3]. Immuno-electron microscopy studies showed that the processing of SP-B and SP-C to their mature forms

proceeds in multivesicular bodies that are en route to lamellar bodies [4].

The evidence that SP-B and SP-C play a key role in facilitating the transfer of surfactant lipids to the surface film is overwhelming. Without these proteins, adsorption of phospholipids to the air-liquid interface would be extremely slow. Studies in vitro conclusively demonstrated that both SP-B and SP-C substantially increase the surface activity of surfactant preparations, regardless of the assay system used; preparations containing these specific proteins adsorb very rapidly to an air-liquid interface. Importantly, when administered endotra-cheally in sufficient amounts, they effectively compensate for surfactant deficiency in pre-term as well as babies with threatened or manifest respiratory distress syndrome [1, 2]. Further evidence for the functional importance of SP-B was provided by recent observations that SP-B and its mRNA were lacking in newborns with congenital alveolar proteinosis [5]. As both SP-B and SP-C are highly conserved proteins with very different structures, it is quite likely that both proteins are indispensable for optimal functioning of the surfactant system. The exact mechanisms by which SP-B and SP-C catalyze the insertion of phospholipids into the surface film are not yet fully understood. We recently performed studies aimed at elucidating the importance of the two positively charged amino acid residues at positions 11 and 12 of SP-C. The results suggested that these

residues are crucial for the binding of phospho-lipid vesicles to the monolayer, thus facilitating the insertion of lipids into the surface film [6]. The two hydrophilic proteins SP-A and SP-D both belong to the collagenous lectins or collectins. These lectins all possess a similar monomeric primary structure comprising a short N-terminal region, a collagen-like domain, a neck region, and a carbohydrate-binding globular C-terminal region [7]. In its functional form SP-A consists of six trimers that are assembled to the characteristic funnel-shaped structure reported for Clq and man-nose-binding protein, an important collectin in the circulation. The less abundant SP-D has a similar cruciform quaternary structure as conglutinin. Accumulating evidence suggests that circulating collectins such as mannose-binding protein play an important role in the innate or non-clonal immune defense system, as they can selectively recognize configuration of carbohydrates that are present on the surface of pathogenic bacteria or viruses [7]. The strong resemblance between SP-A and SP-D and their counterparts in the circulation suggested that these proteins may play a corresponding role in the first line of lung defence against pathogens in the airways. Indeed, evidence is accumulating to support such role for both SP-A and SP-D [8]. In brief, it is highly likely that alveolar macrophages possess specific receptors for both SP-A and SP-D. Both proteins specifically generate the production of oxygen radicals by alveolar macrophages, which can contribute to local killing of microorganisms. Several groups have demonstrated that SP-A enhances the complement-and immunoglobulin-mediated phagocytosis of bacteria by alveolar macrophages and mono-cytes. It has also been shown that SP-A can act as opsonin in the phagocytosis of some viruses and gram-negative bacteria. Both SP-A and SP-D can bind to lipopolysaccharide of a variety of gram-negative bacteria and thus inhibit binding of lipopolysaccharides to their regular target cells. Interestingly, both SP-A and SP-D can, at least in vitro, lower the infectivity of some viruses, such as influenza virus A.

It is interesting to note that in some of these effects, e.g. in the activation of alveolar macrophages, the major surfactant lipids exert an effect that is opposite to that of SP-A. It is quite feasible that the local ratio between surfactant lipids and hydrophilic proteins may determine the net effect on the target cell and that disturbances in these ratios, which occur in various lung diseases, could lead to dysregulation of the defense function of pulmonary surfactant.

References

- Van Golde LMG, Batenburg JJ, Robertson B: The pulmonary surfactant system. NIPS 1994;9:13-20.
- Johansson J, Curstedt T, Robertson B: The proteins of the surfactant system. Eur Respir J 1994;7:372-391.
- Weaver TA, Whitsett JA: Function and regulation of expression of pulmonary surfactant-associated proteins. Biochem J 1991;273:249-264.
- Voorhout WF, Weaver TE, Haagsman HP, Geuze HJ, Van Golde LMG: Biosynthetic routing of pulmonary surfactant proteins in alveolar type II cells. Microsc Res Techn 1993;26:366-373.
- Hamvas A, Nogee LM, deMello DE, Cole FS: Pathophysiology and treatment of surfactant protein-B deficiency. Biol Neonate 1995;67(suppl 1): 18-31.
- Creuwels LAJM, Boer EH, Demel RA, Van Golde LMG, Haagsman HP: Neutralization of the positive charge of SP-C: Effects on structure and function. J Biol Chem 1995; 270:16225-16229.
- Holmskov U, Malhotra R, Sim RB, Jensenius JC: Collectins: Collagenous C-type lectins of the

innate immune defense system. Immunol Today 1994;15:67-74. Van Golde LMG: Potential role of surfactant proteins A and D in innate lung defense against pathogens. Biol Neonate 1995;67(suppl 1):2-17.

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