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Review

Recent advances in alveolar biology: Evolution and function of alveolar proteins☆

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ABSTRACT

This review is focused on the evolution and function of alveolar proteins. The lung faces physical and environmental challenges, due to changing pressures/volumes and foreign pathogens, respectively. The pulmonary surfactant system is integral in protecting the lung from these challenges via two groups of surfactant proteins – the small molecular weight hydrophobic SPs, SP-B and -C, that regulate interfacial adsorption of the lipids, and the large hydrophilic SPs, SP-A and -D, which are surfactant collectins capable of inhibiting foreign pathogens. Further aiding pulmonary host defence are non-surfactant collectins and antimicrobial peptides that are expressed across the biological kingdoms. Linking to the first symposium session, which emphasised molecular structure and biophysical function of surfactant lipids and proteins, this review begins with a discussion of the role of temperature and hydrostatic pressure in shaping the evolution of SP-C in mammals. Transitioning to the role of the alveolus in innate host defence we discuss the structure, function and regulation of antimicrobial peptides, the defensins and cathelicidins. We describe the recent discovery of novel avian collectins and provide evidence for their role in preventing influenza infection. This is followed by discussions of the roles of SP-A and SP-D in mediating host defence at the alveolar surface and in mediating inflammation and the allergic response of the airways. Finally we discuss the use of animal models of lung disease including knockouts to develop an understanding of the role of these proteins in initiating and/or perpetuating disease with the aim of developing new therapeutic strategies.

1. Introduction

This review summarises the contributions in the second session of the alveolar biology symposium, which emphasised the evolution and function of various alveolar proteins. These included the small molecular weight surfactant proteins SP-B and SP-C, that are involved in surface tension regulatory functions; the large hydrophilic surfactant collectin proteins, SP-A and SP-D, that are involved in host defence; and various non-surfactant collectins, specifically newly discovered avian collectins and antimicrobial peptides, defensins and cathelicidins.

The lung is unique in that it faces both complex physical challenges associated with dynamically changing pressures and volumes, as well as environmental challenges associated with the vast array of foreign pathogens and particles to which the lung is exposed. Each of these two very diverse challenges is a consequence of the immense surface area of this dynamic fluid-lined organ. The pulmonary surfactant system is uniquely situated at the air–liquid interface of this large internal surface, such that it

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is able to play a role both in dynamically regulating the interfacial surface tension with changing lung volumes as well as actively inhibiting and inactivating a broad spectrum of foreign pathogens.

These roles are achieved by two separate groups of surfactant proteins. The small molecular weight hydrophobic SPs, SP-B and -C, are intricately associated with the surfactant lipid film at the air–liquid interface and function to regulate: (1) the initial interfacial adsorption of the lipids; (2) the reversible sequestration of the lipids into the surfactant reservoir (multilayer membrane aggregates in the hypophase that are associated with the interfacial film); and finally (3) the recruitment of lipids from the reservoir to the surface film to spread over an expanding surface area (Fig. 1). In this way they regulate the structure, integrity and composition of the surface lipid film, such that it optimally controls interfacial surface tension (Possmayer et al., 2001; Perez-Gil, 2008; Zuo et al., 2008). The large hydrophilic SPs, SP-A and -D, are members of a family of collagenous carbohydrate binding proteins, known as collectins, or calcium-dependent (C-type) lectins. Collectins consist of oligomers of trimeric subunits that are capable of recognizing, inhibiting and inactivating a broad spectrum of foreign pathogens, making them important effector molecules of the innate immune system (Haagsman and Diemel, 2001).

However, the surfactant collectins are not the only proteins involved in pulmonary innate defence. Recently, four novel collectin proteins, all highly expressed in the respiratory tract, have been described in the chicken, including an SP-A homologue named chicken lung lectin (cLL, an SP-A like protein lacking collagen) and three other chicken collectins (cCL1-3) homologous to human collectins CL-L1, CL-K1 and CL-P1, respectively (Hogenkamp et al., 2006). In addition, there is a range of antimicrobial peptides, including the two main families – the defensins and the cathelicidins.

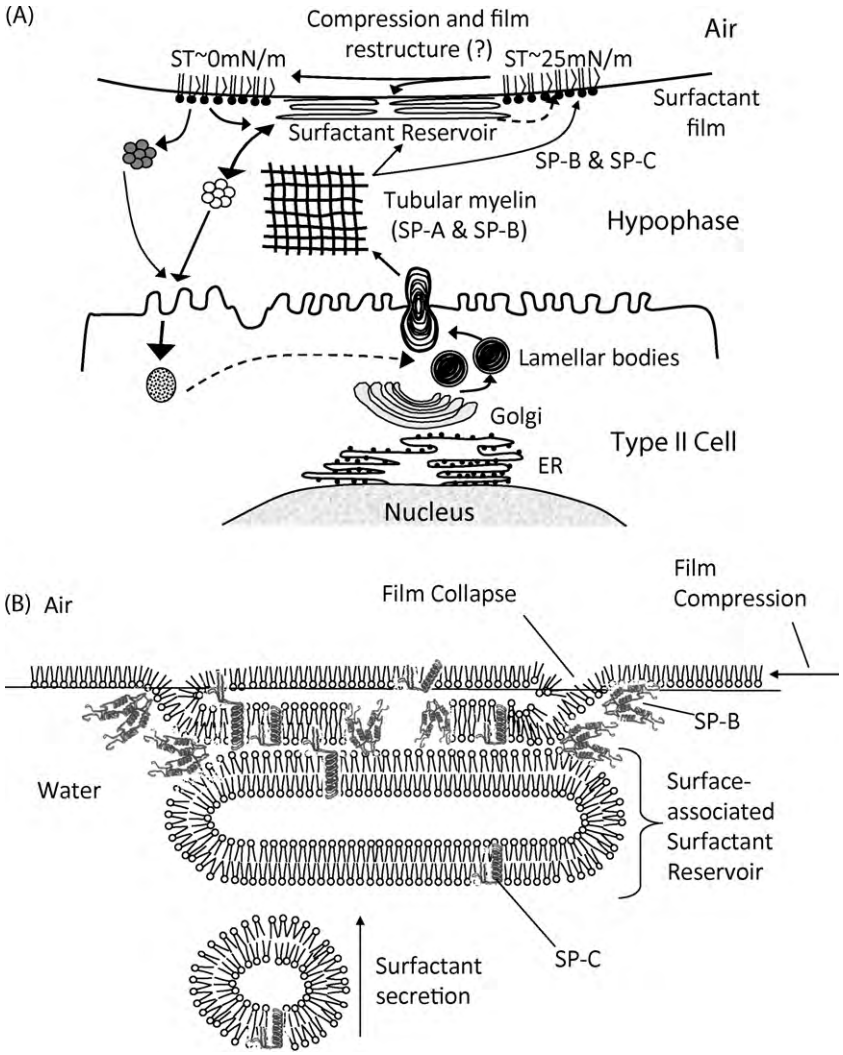

Fig. 1. (A) Schematic diagram of the life cycle of pulmonary surfactant. Pulmonary surfactant is packaged in lamellar bodies (LB) that are secreted into the liquid lining the alveoli (hypophase) via exocytosis across the type II cell plasma membrane. Here the lamellar bodies swell and unravel, forming a crosshatched structure, termed tubular myelin (TM), which consists of lipids and proteins, in particular SP-A and SP-B. This structure supplies lipids to the surface film at the air–liquid interface as well as the surfactant reservoir, which is a multilayer structure associated with the surface film. The adsorption of the lipids to the air–liquid interface is mediated by the surfactant proteins, SP-B and -C. As the mixed molecular film is compressed, lipids are squeezed out of the film into the reservoir, and the film undergoes a restructuring through as yet unknown molecular mechanisms, which renders it capable of reducing surface tension (ST) to near 0 mN/m. Upon reexpansion, some lipids from the reservoir re-enter the surface film. Lipids from the surface film and the reservoir are eventually recycled and taken back up by the type II cell via endocytosis. Figure reproduced with modifications from (Foot et al., 2006) with permission from Elsevier.
(B) Hypothetical model of the surfactant film and surface-associated surfactant reservoir demonstrating film collapse under dynamic compression. The interaction of the two hydrophobic surfactant proteins (SP-B and -C) with the lipid mono- and bilayers is indicated. This interaction aids in the regulation of movement of lipids between the interfacial film and the surface-associated reservoir. Figure adapted from the original (Perez-Gil and Keough, 1998) and reproduced with modifications from (Foot et al., 2006) with permission from Elsevier.