Biochimica et Biophysica Acta xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamem

Review

Structure-function relationships in pulmonary surfactant membranes: From biophysics to therapy ☆

Elena Lopez-Rodriguez [a,b,c], Jesús Pérez-Gil [a,*]

[a] Departamento de Bioquimica y Biologia Molecular, Facultad de Biologia, Universidad Complutense de Madrid, Madrid, Spain
[b] Institute for Functional and Applied Anatomy, Hannover Medical School, Hannover, Germany
[c] Biomedical Research in End Stage and Obstructive Lung Disease Hannover (BREATH), German Center for Lung Research, Hannover, Germany

ARTICLE INFO

Article history:
Received 3 November 2013
Received in revised form 22 January 2014
Accepted 27 January 2014
Available online xxxx

Keywords:
Air–liquid interface
Lung
Lipid–protein interactions
Membrane domains
ARDS
Surface tension

ABSTRACT

Pulmonary surfactant is an essential lipid–protein complex to maintain an operative respiratory surface at the mammalian lungs. It reduces surface tension at the alveolar air–liquid interface to stabilise the lungs against physical forces operating along the compression–expansion breathing cycles. At the same time, surfactant integrates elements establishing a primary barrier against the entry of pathogens. Lack or deficiencies of the surfactant system are associated with respiratory pathologies, which treatment often includes supplementation with exogenous materials. The present review summarises current models on the molecular mechanisms of surfactant function, with particular emphasis in its biophysical properties to stabilise the lungs and the molecular alterations connecting impaired surfactant with diseased organs. It also provides a perspective on the current surfactant-based strategies to treat respiratory pathologies. This article is part of a Special Issue entitled: Membrane structure and function: Relevance in the cell's physiology, pathology and therapy.

Contents

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* Corresponding author at: Department of Biochemistry, Faculty of Biology, Universidad Complutense, Jose Antonio Novais 2, 28040 Madrid, Spain. Tel.: +34 91 3944994; fax: +34 91 3944672.

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http://dx.doi.org/10.1016/j.bbamem.2014.01.028

1. Pulmonary surfactant

The presence of a pulmonary surfactant was directly linked with respiratory failure by Richard Pattle in England and John Clemens in the USA while studying the effects of nerve gases in the lungs [1]. A few years later, Mary Ellen Avery demonstrated that hyaline membrane disease (later known as respiratory distress syndrome, RDS) in new-borns that died after birth was caused by a lack of surfactant [2]. Consequently, hyaline membrane disease was associated with the absence of a surface-active material; under normal conditions, this material produces a surface tension of around 8 dyn/cm. In babies suffering from hyaline membrane disease, the surface tension exceeded 30 dyn/cm. The first successful animal experiments with natural surfactants were performed by Enhorning and Robertson in Stockholm, demonstrating improved survival in preterm rabbits [3,4]. Later, Adams and Fujiwara in the USA showed the same beneficial effects of natural surfactants in preterm lambs [5,6]. Once the connection between the surfactant and lung diseases in neonates was established [7–9], exogenous surfactant therapies were developed. Surfactant replacement therapy (SRT) is currently used as a prophylactic treatment in neonates of less than 35 weeks in gestational age, decreasing the mortality of premature babies up to 80%. SRT today currently enables premature babies to breathe and survive at only 25 weeks of gestational age [10]. Moreover, surfactant research has been growing and expanding to cover other lung pathologies. The primary objective of surfactant research is to understand the molecular and physical mechanisms associated with surfactant function as well as the processes interfering with the surfactant's activity and contribution to lung diseases. A better understanding of the primary or secondary implications of surfactants in respiratory pathologies is also required to facilitate the development of successful treatments and efficient clinical surfactant preparations.

1.1. Surfactant composition and structure

Pulmonary surfactant is produced in the lungs and is essential during breathing. Because it is placed at the air–liquid alveolar interface, pulmonary surfactant reduces the surface tension of the thin layer of water that covers the lung epithelium. A low surface tension reduces the work of breathing and prevents alveolar collapse. Moreover, surfactant is the first barrier that pathogens encounter within one of the largest exposed surfaces of the human body [11–13]. The lung surface area has been calculated as approximately 100 m^2 and facilitates essential gas exchange activity. For this reason, respiratory pathologies cause 13.6% of the deaths worldwide, according to the World Health Organisation (2008).

Pulmonary surfactant is a complex mixture of lipids and proteins, and lipids account for more than 90% of the surfactant by mass (see Fig. 1). The qualitative and quantitative compositions of the lipids in the surfactant vary between species and according to environmental conditions, such as body temperature [14]. Surfactant also changes according to physiological constraints, such as the breathing rate or hibernation [15], or due to pathological situations, particularly lung injury [16,17]. However, the protein composition is also critical for normal surfactant function. Surfactant proteins A (SP-A) and D (SP-D) belong to the collectin protein family. They are directly related to the innate host defence of the lung and recognise, bind and eliminate pathogens [18–20]. Surfactant proteins B (SP-B) and C (SP-C) are small hydrophobic proteins that are deeply embedded into the surfactant phospholipids; they enhance interfacial adsorption of surface active molecules into the air–liquid interface and contribute to mechanical stability of the interfacial films [21]. Animal models show that deficiencies in surfactant proteins lead to respiratory pathologies, demonstrating a direct relationship between surfactant activity and normal lung performance. Deficiencies in SP-A and SP-D are not critical at first, although animal models deficient in SP-A develop lung infections more frequently [22]. SP-D deficiency might be related to emphysema [23] and chronic obstructive pulmonary disease (COPD) [24]. On the other hand, SP-C deficiency is associated with chronic respiratory pathologies [25], and complete SP-B deficiency results in death shortly after birth [26,27].

1.1.1. Surfactant lipids

Phospholipids are amphipathic molecules that have a polar and hydrophilic moiety and non-polar or hydrophobic chains. This type of molecule adopts a particular arrangement at the air–liquid interface, minimising the contact between the hydrophobic region and water molecules. Phospholipids thus adopt an energetically favourable orientation, pointing the polar heads toward the water phase, while the non-polar chains are oriented toward the air.

As shown in Fig. 1, the most abundant component in surfactant is dipalmitoylphosphatidylcholine (DPPC), representing approximately 40% of the total surfactant mass. DPPC is essential for producing the very low surface tension observed during compression; its saturated acyl chains can adopt a highly lateral packed state. Surfactant contains other saturated phosphatidylcholines (PC), such as palmitoylmirystoyl-PC (PMPC, 16:0/14:0), and unsaturated PCs, such as palmitoyloleoyl-PC

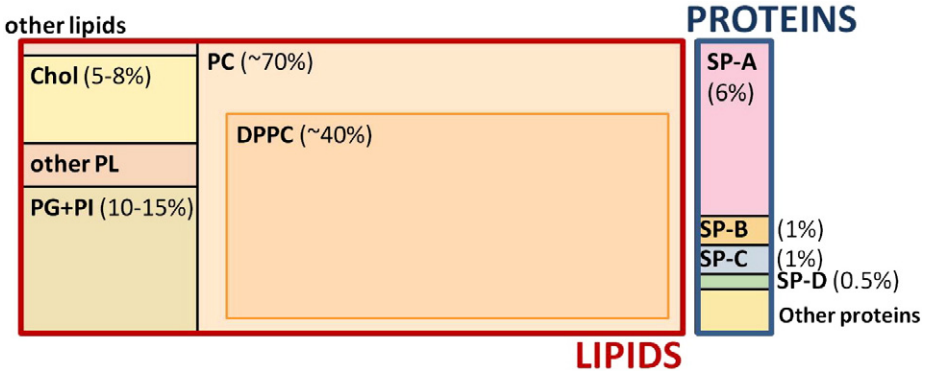

Fig. 1. Composition of lung surfactant. Proportions of the different lipid and protein components in pulmonary surfactant, represented as occupying proportional areas with respect to total surfactant mass.

Please cite this article as: E. Lopez-Rodriguez, J. Pérez-Gil, Structure-function relationships in pulmonary surfactant membranes: From biophysics to therapy, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbamem.2014.01.028