



Pulmonary Surfactants: a New Therapeutic Target in Asthma

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Abstract

Purpose of Review Lung tissues are highly susceptible to airway inflammation as they are inevitably exposed to inhaled pathogens and allergens. In the lungs, clearance of infectious agents and regulation of inflammatory responses are important for the first-line defense, where surfactants play a role in host defense mechanisms. In this review, clinical significance of pulmonary surfactants in asthma has been highlighted.

Recent Findings Surfactants, such as surfactant protein A (SP-A) and SP-D released from alveolar epithelium, reduce pathogen infection and control immune-cell activation. Especially, SP-D directly binds to eosinophil surface, leading to inhibition of extracellular trap formation and reduction in airway inflammation. Production of surfactants is commonly determined by both genetic (single nucleotide polymorphisms) and environmental factors influencing processes involved in the development of asthma. In addition, nintedanib (an intracellular inhibitor of tyrosine kinases) could increase SP-D levels and is used in patients with idiopathic pulmonary fibrosis. These findings may provide a possible application of SP-D in asthma.

Summary Surfactants are key players contributing to host defense through maintaining the immune system. As clinical implications of surfactants involved in asthma have been suggested, further translational studies are needed to apply surfactants as an effective therapeutic target in patients with asthma.

Keywords Asthma · Eosinophil · Epithelium · Surfactant · Airway inflammation · Therapy

Introduction

Pulmonary surfactants, a unique mixture of lipids and proteins, form a layer between the aqueous airway liquid and the inspired air throughout the lungs. To date, they have been intensively studied to characterize their synthesis, secretion, metabolism, and function [1]. Initially, surfactants were regarded as a biophysical factor, but recent work has suggested an important role in innate and adaptive immunity of the lungs due to their immunomodulatory properties [2]. In addition, the pathogenetic relevance of surfactants in various lung diseases, such as acute respiratory distress syndrome, idiopathic pulmonary fibrosis, and pneumonia, has been revealed [3]. The possible involvement of surfactants in the

pathophysiology of asthma with a predominant disturbance in the airways has also been demonstrated [4]. The following sections review characteristics, functions, and potential therapeutic applications of surfactants in asthma.

Association Between Surfactants and Asthma

Asthma is a major health problem in society, and it is estimated that more than 300 million people worldwide suffer from the disease. This number contributes to the high health care expenditure associated with this disease [5]. This chronic airway disease seriously affects children as well as adults and is considerably increased in urban areas and high-income countries [6]. Most patients with asthma have mild to moderate symptoms; however, some patients (approximately 5–10% of adult asthmatic patients) show more severe symptoms, high comorbid burden, and frequent asthma exacerbations. In addition, patients with severe asthma are in poorly controlled status despite daily uses of high doses of inhaled corticosteroids and additional treatments [7–9]. Because asthma treatment remains a constant clinical challenge, further studies

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about asthma pathophysiology and therapeutics are needed to improve health, reduce societal costs, and to improve individual quality of life.

Asthma is commonly characterized by type 2 airway inflammation with typical symptoms such as coughing, wheezing, and dyspnea [10]. However, asthma is likely to be not a single disease, but a heterogeneous disease as multiple phenotypes or endotypes have been reported, depending on the combination of clinical, demographic, and pathological characteristics of asthma [11, 12]. Moreover, several immune cells (mast cells, eosinophils, neutrophils, and innate lymphoid cells) as well as structural cells (epithelial cells, vessels, nerves) and released cytokines/mediators have been shown to contribute to the pathogenesis of asthma [13, 14]. Such a complexity in pathogenesis and heterogeneity in treatment responses require further investigations of pathophysiologic mechanisms and future targets.

Many risk factors, such as genetic predisposition, viral infection, exposure to allergens or pollutants, and changes in microbiome, are important determinants in various steps of asthma pathogenesis [15–18]. When environmental factors are introduced, the airway epithelium is considered a central regulator (initiation and maintaining) of immune responses [19]. This first-line barrier not only expresses pattern recognition receptors but also secretes several components, including enzymes, mucins, and surfactants as well as cytokines upon damage to the epithelium [20]. Previously, altered levels of surfactants in bronchoalveolar lavage fluid or serum samples were demonstrated to be associated with multiple lung diseases including asthma [21•] (Table 1). In addition, recent studies have revealed that surfactants play an essential role in the development of asthma with eosinophilia [22, 23]. To date, application of surfactants in asthma is still lacking, but recent studies suggest that surfactants may act beneficially by supporting pulmonary host defense in some conditions.

Table 1 Altered levels of pulmonary surfactants in patients with asthma

Phenotype	Surfactant	Sample	Observation	Reference
Bronchial asthma	SP-A/SP-D	BALF	Increase	[76]
	SP-D	Salivary	Increase	[77]
	SP-D	Serum	Stable/increase	[78], [79]
	SP-D	Tissue	Increase	[80]
Severe asthma	SP-D	BALF	Decrease/increase	[81•], [82]
	SP-D	Serum	Increase	[81•], [83]
	SP-D	Sputum	Increase	[82]
Obese asthma	SP-A	BALF	Decrease	[84]
AERD	SP-D	Serum	Decrease	[59]

AERD, aspirin-exacerbated respiratory disease; BALF, bronchoalveolar lavage fluid; SP, surfactant protein

Basic Characteristics of Surfactants

Surfactants are composed of approximately 90% lipids and 10% proteins synthesized by alveolar epithelial cells (also called pneumocytes) enriched in the endoplasmic reticulum and lamellar bodies (specialized surfactant-storing organelles). In addition, these lipid and protein mixtures are assembled, transported, secreted, and recycled in the alveolar space [24]. Surfactants are highly dynamic molecules in the context of a surface exposed to constant compression–expansion dynamics (stress and stretch forces) [25, 26]. Although lipid homeostasis is well regulated under normal physiological conditions, abnormal surfactant metabolism due to oxidation, proteolytic degradation, and inhibition of surfactants leads to respiratory distress with attendant morbidity and mortality [27].

Surfactant-specific proteins comprise 2 types: hydrophilic surfactants (surfactant protein A (SP-A) and SP-D) and hydrophobic surfactants (SP-B, SP-C) [28]. The hydrophilic surfactants play an important physical role in lowering the alveolar surface-tension, whereas the hydrophobic surfactants are associated with immune defense mechanisms in the alveolar space [29]. Particularly, SP-A and SP-D are a subgroup of mammalian lectins called collectins or C-type lectins which are composed of oligomers with C-terminal carbohydrate recognition domains in association with N-terminal collagen-like domains [30]. In addition to 4 surfactants, 2 novel surfactant proteins, including SP-G and SP-H, have also been identified in the lungs [31]; nevertheless, the significance of SP-A and SP-D in asthma has mostly been highlighted.

SP-B and SP-C are small proteins encoded by single genes on chromosome 2 and on chromosome 8, respectively [32]. However, both SP-A and SP-D are structurally related multimeric proteins encoded by a multigene family on chromosome 10 located near other members of the collectin family [33]. The secreted SP-A is an octadecamer comprising 6 trimeric subunits, but the released SP-D is a dodecamer consisting of 4 trimeric subunits [34]. Although the degree of multimerization is different between species and even between individuals, all collectins form multimers to increase their affinity to pathogens and immune cells [35]. Among the collectins, SP-D has the largest and most flexible collagen domain interacting with various bound organisms or cells (Table 2).

Immunological Aspects of Surfactants

The immune system needs to properly respond to harmful, but not to harmless molecules to avoid an inappropriate immune response. Especially, the innate immune system is available for host defense against initial infection linked to the adaptive immune system [36]. In the lungs, emerging evidence has revealed that SP-A and SP-D play an important role in the

Table 2 Summary of the domains presented within each surfactant protein

Type	Structure	Function
SP-A/SP-D	N-terminal domain	Stabilization of the oligomeric structure through cysteine-rich region (disulfide bond)
	Collagen-like domain	Maintenance of molecule shape
	Neck domain	Nucleation point for refolding
	Carbohydrate recognition domain	Binding to lipopolysaccharide or carbohydrates at the surface of microorganisms
SP-B/SP-C	N-terminal domain	Dimerization through Cys residues (SP-B) Formation of an amphipathic β -hairpin (SP-C)
	C-terminal domain	Additional saposin-like domains in proSP-B (SP-B) Stabilization of the proper folding of extremely hydrophobic transmembrane (SP-C)

maintenance of immune balance [37]. Increased expressions of SP-A and SP-D are associated with reduced allergic immune responses [38]; however, surfactant deficiency contributes to enhanced allergic immune responses [39], indicating these molecules are a potential negative regulator in asthma. Functions of SP-A and SP-D in the pathogenesis of asthma are summarized in Table 3.

Function of Surfactants in Host Defense

SP-A and SP-D act as a pattern recognition receptor facilitating phagocytosis by binding to viruses, bacteria, and fungi. The association between viral infections and asthma exacerbations is well defined; human rhinovirus, respiratory syncytial virus, and influenza A virus are predominantly associated with development or exacerbation of asthma [40, 41]. The severity of asthma exacerbations is commonly due to the lack of specific antiviral agents. However, surfactants enhance clearance of viruses via a carbohydrate recognition domain (CRD)-dependent manner [42••]. More recently, certain strains of coronavirus have also been revealed to be involved in asthma exacerbations [43]. A glycoprotein on coronavirus was specifically recognized by SP-D, but not by mannan-binding lectin [44].

In addition to viral infection, bacterial infection has been shown to increase the probability of asthma exacerbation. Especially, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* enhance the risk for more severe respiratory illnesses and asthma exacerbations [45]. For *S. pneumoniae*, SP-A and SP-D bind to the bacterial cell wall components, such as lipoteichoic acid and peptidoglycan, via a CRD region [46]. Moreover, these surfactants have been demonstrated to play an important role in innate immune responses to *H. influenzae* [47]. Although SP-A and SP-D recognize most species of gram-negative bacteria composed of lipopolysaccharide, studies about the effect of surfactants against *M. catarrhalis* are still limited. Nevertheless, surfactants have been revealed to respond to other pathogenic bacteria including *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.

A close association between fungal sensitization and asthma severity was well established by skin-test reactivity to one or more fungi such as *Alternaria tenuis*, *Cladosporium cladosporioides*, *Helminthosorium maydis*, and *Epicoccum nigrum* [48]. In addition, allergic bronchopulmonary aspergillosis occurs in susceptible patients with asthma due to colonization of *Aspergillus fumigatus* [49]. SP-A and SP-D bind to *A. fumigatus*, leading to phagocytosis by alveolar macrophages and neutrophils [50, 51]. Furthermore, a recent study has shown that SP-D inhibits adhesion of *A. fumigatus* to the

Table 3 Several functions of pulmonary surfactants in asthma

Surfactant	Function	Target	
SP-A/SP-D	Host defense	Binding to pathogen	Virus, bacteria, and fungi
		Induction of phagocytosis	Pathogens and apoptotic cells
	Immune regulation	Suppression of cell maturation (SP-A)	Dendritic cells
		Enhancement of antigen presentation (SP-D)	Dendritic cells
		Reduction of cell activation/proliferation	Lymphocytes (T cells)
		Modulation of cell migration/recruitment	Monocytes and neutrophils
SP-B/SP-C	Surface film formation	Inhibition of extracellular trap formation (SP-D)	Eosinophils
		Reduction of surface tension	Air-liquid interface

epithelium surface [52]. These suggest that surfactants are a key player of pulmonary defense against infections.

Function of Surfactants in Immune Modulation

The role of surfactants in the modulation of immune responses is becoming increasingly clear. Eosinophilia in blood or sputum is commonly found in asthmatics with more severe symptoms, worse management, and worse prognosis [53]. Previously, SP-A has been demonstrated to suppress the production of interleukin (IL)-8 by eosinophils [54]. Although multiple functions of eosinophils were suggested, recent studies have highlighted the role of eosinophil extracellular traps (EETs) in the type 2 inflammation of severe eosinophilic asthma [55, 56]. Especially, eosinophil granule proteins (eosinophil-derived neurotoxin) localized in EETs may be related to asthma severity and lung function decline [57]. However, SP-D directly binds to the eosinophil membrane and inhibits extracellular trap formation in concentration- and carbohydrate-dependent manners [58]. A recent study demonstrated a critical role of SP-D (a negative regulatory feedback) in asthma; SP-D deficiency could enhance eosinophil-mediated airway inflammation/remodeling in patients with aspirin-exacerbated respiratory disease [59].

Proliferation and activation of lymphocytes are critical for the induction of the adaptive immune system in asthma. For example, T lymphocytes release IL-5 which leads to the differentiation, recruitment, activation, and survival of eosinophils [60], but lymphocyte activity was downregulated by SP-A and SP-D [61]. Moreover, surfactant treatment inhibited the ability of lymphocytes to produce IL-2 [62, 63] which is a key cytokine for the induction of allergic immune responses [64]. However, dramatically augmented IL-13 concentration was found in SP-A or SP-D deficiency [65, 66], leading to goblet cell hyperplasia, airway hyperactivity, and tissue remodeling [67]. Furthermore, SP-A and SP-D decrease proliferation of lymphocytes in response to house dust mite allergens in a dose-dependent manner [68]. Taken together, surfactants have a potential benefit in 2 aspects of asthma pathogenesis: reduction of asthma exacerbation and attenuation of type 2 airway inflammation (Fig. 1).

Potential Therapeutic Applications of Surfactants

Surfactant replacement was established as a novel therapeutic strategy in patients with surfactant deficiency. In the 1960s, the first attempt of exogenous surfactant administration was made in respiratory distress syndrome (RDS) in preterm infants, leading to reduction in mortality, the incidence of

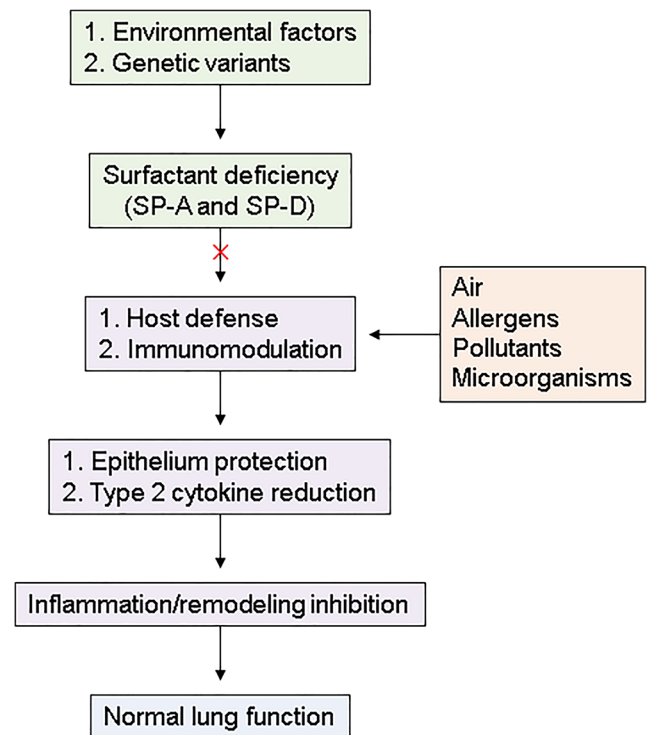


Fig. 1 Roles of pulmonary surfactants in maintenance of normal lung function. In asthmatic patients, environmental or genetic factors cause deficiency of surfactants, which are important for host defense and immunomodulation. In the absence of surfactants, inhaled exposures such as allergens, pollutants, and microorganisms enhance epithelium damage or cytokine production, leading to airway inflammation/remodeling associated with lung dysfunction. SP, surfactant protein

pulmonary air leak, and the risk of chronic lung disease [69]. In addition, surfactant therapy was beneficial in infants with pneumonia and in children with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS); however, extension of surfactant therapy to adults with ALI or ARDS failed [70, 71]. This failure may be associated with an inability of the surfactants to substantially impact the underlying pathophysiology of ALI and ARDS in adults. Although numerous subsequent trials were performed in neonatal RDS, clinical applications have not been conducted in asthma. Nevertheless, the development of pharmaceutical surfactants may provide a promising therapeutic approach to asthma treatment in children, but not in adults.

To date, animal-derived (from bovine or porcine origin) and synthetic surfactants (protein-free) are available. However, natural surfactants have some limitations such as costs, biological risk, and inconsistent production. Therefore, a need of synthetic surfactants, which improve immunological concerns and give consistent response, has emerged. Recently, a third-generation surfactant (CHF5633) yielded promising results for RDS therapy [72, 73], suggesting synthetic surfactants have better efficacy. In addition to commercially available surfactants, other factors affecting endogenous or exogenous surfactant production have been identified. In

particular, antenatal corticosteroid treatment showed beneficial effects on inducing surfactant production by maturation of alveolar epithelial cells [74]. Moreover, nintedanib treatment has been revealed to modulate surfactant production [75]. Although nintedanib was neither first developed to enhance surfactant production nor intended to be used for asthma management, this medication may extend further approaches to surfactant replacement therapy, especially in patients with severe eosinophilic asthma who suffer from frequent respiratory infections and asthma exacerbations. Further investigations are required to find safe and effective ways for applying surfactants as correct targets in patients with asthma.

Surfactant treatment has some clinical issues and limitations. First, surfactants are commonly administered by an endotracheal/oropharyngeal tube or a nebulizer; however, the tube for using surfactants can damage of patient airways [74]. Positive pressure by a ventilator can also induce interstitial lung injury. Secondly, there remains a risk of immune responses to animal-derived proteins or treatment-related infections [67]. Thirdly, harvest of natural surfactants from bovine or porcine lungs is difficult to scale. Nevertheless, surfactant therapy may be expected as an advanced treatment for various lung diseases when such limitations are solved.

Conclusions

Pulmonary surfactants play an important role in the first defense mechanism of the lungs constantly exposed to environmental factors, as they act as a barrier by removing pathogens and by modulating inflammatory responses. Surfactant (especially SP-D) imbalance is responsible for enhancing type 2 airway inflammation in asthma as immune cell activation (especially, eosinophils, and lymphocytes) and impaired regulation of immune cell–epithelium interactions. Therapeutic interventions improve surfactant homeostasis by stimulating the endogenous surfactant production or by exogenous surfactant supplementation, which may have a potential benefit in asthmatic patients with eosinophilia, although further studies are needed to explore the possibility of surfactants as a targeted therapy.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

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