ARTÍCULO DE REVISIÓN

Gac Méd Caracas 2024;132(Supl 1):S152-S159
DOI: 10.47307/GMC.2024.132.s1.20

A systematic review of the role of surfactants in bronchial asthma: Implications for pathogenesis and treatment of the disease

Una revisión sistemática del papel de los surfactantes en el asma bronquial: implicaciones para la patogénesis y el tratamiento de la enfermedad

Imetkul Ismailov[1], Nihal Kılınç[2], Bhupendra Kumar Magarde[3], Mohd Musheer[4], Shakil Ahmad[5]

SUMMARY

The study aims to examine existing literature and highlight the significance of surfactants as a factor in pathogenesis and a potential therapeutic target in bronchial asthma. A systematic search is conducted in Scopus, Web of Science, and PubMed/Medline, utilizing specific keywords related to surfactants and bronchial asthma. The findings demonstrate that surfactants, a unique mixture of lipids and proteins, play a crucial role in the mechanisms of innate and adaptive immunity in the lungs. They act as a mechanical barrier, modulate inflammatory responses, and interact with pathogens. Changes in surfactant composition and levels have been associated with various lung diseases, including bronchial asthma. Deficiency or dysregulation of surfactants may contribute to the development and severity of the disease. The findings suggest that optimizing surfactant function or utilizing exogenous surfactant therapy may have potential benefits in managing bronchial asthma.

Keywords: *Surfactants, bronchial asthma, pathogenesis, immunomodulation, pathophysiology.*

RESUMEN

El propósito del estudio es examinar la literatura existente y resaltar la importancia de los tensoactivos como un factor en la patogénesis y un objetivo terapéutico potencial en el asma bronquial. Se realiza una búsqueda sistemática en Scopus, Web of Science y PubMed / Medline, utilizando palabras clave específicas relacionadas con surfactantes y asma bronquial. Los hallazgos demuestran que los tensoactivos, que son una mezcla única de lípidos y proteínas, desempeñan un papel crucial en los mecanismos de inmunidad innata y adaptativa en los pulmones. Actúan como una barrera mecánica,

DOI: https://doi.org/10.47307/GMC.2024.132.s1.20

ORCID: 0000-0003-2670-3954[1]
ORCID: 0000-0002-9731-0560[2]
ORCID: 0009-0008-9995-5048[3]
ORCID: 0009-0006-6650-2881[4]
ORCID: 0009-0006-4096-9934[5]

[1]Pathology, Basic and Clinical Pharmacology Department, Osh State University, Osh, Kyrgyzstan

Recibido: 1 de octubre 2023
Aceptado: 2 de diciembre 2023

[2]Medical Pathology Department, *Çanakkale* Onsekiz Martakkale Onsekiz Mart University, *Çanakkale*, Turkey
[3]Osh State University, Osh, Kyrgyzstan
[4]Osh State University, Osh, Kyrgyzstan
[5]Osh State University, Osh, Kyrgyzstan

Isabek Gulamov, E-mail: is.t.gulamov@gmail.com

modulan las respuestas inflamatorias e interactúan con los patógenos. Los cambios en la composición y los niveles de tensoactivo se han asociado con diversas enfermedades pulmonares, incluido el asma bronquial. La deficiencia o desregulación de tensoactivos puede contribuir al desarrollo y la gravedad de la enfermedad. Los hallazgos sugieren que la optimización de la función del surfactante o la utilización de terapia con surfactante exógeno pueden tener beneficios potenciales en el manejo del asma bronquial.

Palabras clave: *Surfactantes, asma bronquial, patogénesis, inmunomodulación, fisiopatología.*

INTRODUCTION

Bronchial asthma (BA) (J45) is one of the most prevalent chronic diseases, which defines its importance for public health primarily in developed countries (1,2). BA is estimated to affect more than 300 million people worldwide (3), is diagnosed in both children and adults, and is much more common in urban populations and high-income countries (4-6).

Globally, BA affects 11.7 % of children aged 6 to 7 and 14.1 % of children aged 13 to 14 (6,7). In the national study Epidemiology of Allergic Diseases in Poland (ECAP), allergy symptoms were found in 40 % of children aged 6-7 and 43 % of children aged 13-14, and BA in 4.4 and 6.5 %, respectively (7). A survey of schoolchildren aged 13-16 revealed that BA prevalence was 9.7 % (8).

Severe forms of BA in children provoke delayed consequences for health in adulthood. Analysis of longitudinal studies suggests that childhood BA predisposes to the development of chronic obstructive pulmonary disease in adults (5,9). Optimization of BA treatment in children, including its severe forms, would reduce the likelihood of the described adverse health effects (10,11).

The condition of patients with severe BA is challenging to control despite the daily use of high doses of inhaled corticosteroids and additional treatment, which may encompass oral medications (12), allergy management (13), biologic therapies for refractory cases (14), and lifestyle adjustments to minimize triggers (5,15).

Some experts believe BA to be not a separate nosologic unit, most likely, but a heterogeneous category of pathologic conditions. The pathogenesis of asthma involves various immune cells (mast cells, eosinophils, neutrophils, innate lymphoid cells), structural elements of lung tissue (epithelial cells, vessels, nerves), as well as cytokines/mediators released during inflammatory processes (10,15,16).

The complexity of BA pathogenesis and the instability of response to treatment further emphasize the need for continued research to clarify the pathogenesis and search for new therapeutic targets in this disease. A promising direction in the study of BA pathogenesis is analyzing the role of surfactants, changes in the state of which are considered an aspect of the pathogenesis and diagnosis of the disease, as well as a potential therapeutic target (17-19). To date, the positive effect of surfactants has been established in several diseases and pathological conditions of the respiratory system, which is believed to be due to their protective properties (20,21).

The research goal in the present paper is to analyze scientific findings on the role of surfactants as a factor in pathogenesis and a therapeutic target in BA.

METHODS

Criteria for the search and selection of literature

A systematic review of the role of surfactants in BA employed the following specific criteria for the search and selection of relevant literature:

Studies focused on investigating the role of surfactants in BA.

Research articles exploring the pathogenesis, diagnosis, or therapeutic targets related to surfactants in BA.

Search strategy

To identify relevant literature, a systematic search was conducted using various electronic databases, including Scopus, Web of Science, and PubMed/Medline. The search strategy involved the utilization of specific keywords and terms

related to BA and surfactants. The keywords were selected based on their relevance and significance within the Medical Subject Headers (MeSH) terminology.

The search strategy included combinations of keywords such as "surfactant", "lung surfactant", "bronchial asthma", "asthma pathogenesis", and "asthma treatment." The Boolean operators (e.g., AND, OR) were employed to refine the search and capture articles that addressed the intersection of surfactants and BA.

Surfactants: general information on structure and function

Pulmonary surfactants are a unique mixture of lipids and proteins that create a layer between tissue fluid and inhaled air over the entire surface of pulmonary alveoli (18,21,22). Initially, surfactants were assumed to perform a purely physical (biomechanical) function. However, recent studies have shown that they play an important role in innate and acquired lung immunity mechanisms because of their immunomodulatory properties. In addition, surfactants are involved in the pathogenesis of various lung diseases, particularly acute respiratory distress syndrome (RDS), idiopathic pulmonary fibrosis, and pneumonia (23,24).

Studies have confirmed the potential role of surfactants in the pathophysiologic mechanisms of BA development and progression. Respiratory epithelium is considered one of the critical regulators of initiating and maintaining the immune response because these cells are in direct contact with environmental factors (15,25). As a first-line barrier, the respiratory epithelium not only expresses antigen pattern recognition receptors but also secretes a wide range of bioactive substances with different functions, including enzymes, mucins, surfactants, and cytokines (26).

It has been established that changes in the amount of surfactant in the fluid obtained by bronchoalveolar lavage are associated with various lung diseases, including BA. The significant role of surfactant changes in the amount and composition of developing eosinophilic asthma has also been confirmed (15).

Surfactants comprise about 90 % lipids and 10 % proteins, which alveolar epithelial cells (pneumocytes) synthesize. These cells have many endoplasmic reticulum and lamellar bodies, specialized organelles that accumulate surfactant. Lipids and proteins are mixed, transported, secreted, and recirculated in the alveolar space (27). Surfactants also include the so-called highly dynamic molecules that enable frequent compression and stretching of the surfaces that the surfactants cover (28).

There are two types of surfactant-specific proteins: hydrophilic (surfactant protein (SP)-A and SP-D) and hydrophobic (SP-B, SP-C). Hydrophilic surfactants play an important role by helping to reduce surface tension in the alveoli, whereas hydrophobic surfactants are involved in immune defense mechanisms in the alveolar space (29,30). SP-A and SP-D belong to a subgroup of mammalian lectins called «collectins» or «C-type lectins.» These lectins consist of oligomers with carbohydrate recognition domains at the C-terminus and collagen-like domains at the N-terminus. Recently, two novel surfactant proteins, SP-G and SP-H, have been identified in the lungs (29).

SP-B and SP-C are small proteins encoded by separate genes on the 2nd and 8th chromosome, respectively (30). SP-A and SP-D are structurally related multimeric proteins encoded by a multigene family located on the 10th chromosome next to other members of the collectin family (31). Secreted SP-A is an octadecamer with six trimeric subunits, and secreted SP-D is a dodecamer with four trimeric subunits. Although the degree of multimerization of surfactants varies in different animal species and even in individual representatives of the same species, all collectins form multimers, which increases their affinity for pathogens and immune cells (32). Among collections, SP-D has the most extensive and flexible collagen domain interacting with various pathogens.

Role of surfactants in immunomodulation

Normal immune system functioning implies an adequate response to pathogenic molecules with no response to harmless substances. Innate immunity provides the defense of the

host organism at the initial stages of infection, after which the adaptive immune response is activated (33). SP-A and SP-D have been found to play an important role in maintaining immune balance (34). Increased expression of SP-A and SP-D is associated with a lower frequency and severity of allergic reactions. In contrast, surfactant deficiency enhances allergic immune responses, indicating these molecules' potential role in preventing BA development (18). It is believed that the most important role in the pathogenesis of BA is played precisely by SP-A and SP-D (35).

Pulmonary surfactants implement and regulate lung defense mechanisms, acting as a mechanical barrier to various environmental factors by removing pathogens and modulating inflammatory responses. Lipid homeostasis is effectively regulated under physiological conditions. Still, their metabolism can be disturbed by oxidation, proteolytic degradation, and inhibition of surfactants, leading to the development of respiratory diseases and respiratory failure, which is correlated with an increased mortality rate (34).

Deficiency of surfactants (especially SP-D) is a factor in the activation of type II airway inflammation in BA due to the activation of immune cells (primarily eosinophils and lymphocytes) and impaired regulation of the interaction between immune cells and epithelium (15).

Role of surfactants in the pathogenesis of BA and obstructive lung diseases

SP-A and SP-D function as pattern-recognition receptors and bind to viruses, bacteria, and fungi, facilitating their phagocytosis. The association between viral infections and exacerbations of BA is now considered proven (36). Human rhinovirus, respiratory syncytial virus, and influenza A virus are the primary pathogens associated with the risk of development or exacerbation of BA (37,38). The severity of such aggravations primarily results from the absence of etiotropic antiviral therapy.

Surfactants facilitate more efficient and rapid viral clearance due to the functioning of the carbohydrate-recognizing domain (CRD) (39). Recently, it has been shown that some coronavirus strains can exacerbate BA, with the coronavirus glycoprotein being recognized explicitly by SP-D (40).

Bacterial infections also increase the likelihood of asthma exacerbation. Such pathogens as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are risk factors for a more severe course of respiratory diseases and exacerbations of BA (41). SP-A and SP-D bind to *S. pneumoniae* cell wall components (including lipoteichoic acid and peptidoglycan) through the CRD. These surfactants were shown to play an important part in implementing the innate immune response during H—influenzae infections (42).

SP-A and SP-D are believed to recognize most Gram-negative bacteria by their lipopolysaccharide. It has been demonstrated that surfactants can interact with *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Staphylococcus aureus* (36).

The relationship between sensitization to fungi and the severity of BA has been corroborated by skin tests for hypersensitivity to *Alternaria tenuis, Cladosporium cladosporoides, Helminthosorium maydis,* and *Epicoccum nigrum*. In addition, allergic bronchopulmonary aspergillosis due to the colonization of the respiratory tract by *Aspergillus fumigatus* may occur in BA patients in the presence of susceptibility (43).

SP-A and SP-D bind to *A. fumigatus*, increasing phagocytosis by alveolar macrophages and neutrophils. SP-D has also been shown to inhibit the adhesion of *A. fumigatus* to the epithelial surface (44).

As new data become available, the role of surfactants in the modulation of immune responses is becoming increasingly clear. Eosinophilia in blood or sputum is usually found in a more severe course of BA with less effective therapy and a less favorable prognosis (45).

SP-A suppresses the production of interleukin (IL)-8 by eosinophils (46). There are various assumptions regarding the function of eosinophils; recent studies have confirmed the important role of eosinophil extracellular traps (EETs) in developing type II inflammation in severe eosinophilic asthma (36). Eosinophil granule

proteins (an eosinophil-derived neurotoxin) abundantly present in EETs may be one of the factors responsible for the severity of the course of BA and lung function impairment (47). SP-D directly binds to the membrane of eosinophils, preventing the formation of EETs. This process depends on the concentration of SP-D and the presence of carbohydrates (48).

The critical role of SP-D in BA (negative regulatory feedback) was confirmed in a study that found that in patients with aspirin-induced exacerbation of respiratory disease, SP-D deficiency causes activation of eosinophil-mediated inflammation and promotes airway remodeling (15).

The proliferation and activation of lymphocytes play a decisive role in the induction of the adaptive immune response in BA. T-lymphocytes release IL-5, which induces the differentiation, recruitment, activation, and functional activity of eosinophils (49), while the activity of lymphocytes is suppressed by SP-A and SP-D (50).

Surfactants have also been found to inhibit the ability of lymphocytes to produce Interleukin-2 (IL-2) (51), a key cytokine involved in the induction of the allergic response. A significant increase in IL-13 concentration has been found to occur with SP-A or SP-D deficiency, resulting in the hyperplasia of goblet cells, localized hyperactivity phenomena, and tissue remodeling (52). In addition, SP-A and SP-D dose-dependently inhibit the proliferation of lymphocytes in response to dust mite allergens (53).

Potential therapeutic uses of surfactants

Surfactant replacement therapy is a relatively new approach to treating patients with surfactant deficiency. The first attempt to use exogenous surfactant in RDS in premature infants was made in the 1960s, achieving a decrease in mortality, the incidence of air leak syndrome, and the risk of chronic lung disease (53). In addition, surfactant therapy has been effective in neonatal pneumonia, children with acute lung injury (ALI), and acute RDS (ARDS). In contrast, surfactant therapy in adults with ALI or ARDS has not been proven effective in this cohort (54).

The lack of effect in adults may be attributed to the inability of surfactants to significantly affect the mechanisms underlying the pathogenesis of ALI and ARDS in these categories of patients. Several studies on surfactant therapy for ARDS in neonates have since been conducted, but the efficacy of surfactants in asthma has not been evaluated. It is assumed that the development of surfactants as drugs may become the basis for a promising method for treating asthma in children but not in adults.

It has been proposed to employ biological (bovine and porcine) and synthetic (protein-free) surfactants. Biological surfactants have several limitations, including the risk of adverse events, high cost, and the instability of the product's properties. The limitations of biological surfactants have created the need to develop synthetic surfactants free of the above disadvantages. Thus, a 3rd generation surfactant (CHF5633) was developed, which has shown promising results in evaluating the efficacy of RDS therapy (55,56).

The obtained evidence indicates that synthetic surfactants are potentially more effective than biological ones. In addition to developing commercially available surfactants, one of the research directions may also be the study of factors influencing the endogenous or exogenous production of these biologically active substances (58). Antenatal corticosteroid therapy can induce the production of surfactants by activating the maturation of alveolar epithelial cells.

Nintedanib is a drug capable of modulating surfactant production (58). Although it was initially developed for a different purpose and was not intended for the treatment of BA, its administration could potentially provide a new approach to surfactant replacement therapy, especially in patients with severe eosinophilic asthma suffering from frequent respiratory infections and exacerbations of BA (58).

Surfactant therapy is fraught with several unresolved clinical problems and limitations. Surfactants are usually administered through an endotracheal/laryngeal tube or nebulizer, which can cause mechanical damage to the airway. Positive pressure during artificial ventilation can cause interstitial lung injury. Furthermore,

there is a continuing risk of immune response to animal proteins and infectious complications from therapy with biological surfactants (53,54). Nevertheless, if these limitations are overcome, surfactant therapy is expected to become an advanced method for treating various lung diseases in the future.

CONCLUSION

BA is a chronic respiratory disease with both immediate and long-term adverse effects, including death and irreversible disability. The clinical and socioeconomic significance of BA is relatively high. The importance of the problem is due to the increasing prevalence of the disease and respiratory symptoms and the need to assess the impact of various factors in the development and progression of these pathologic conditions. Recently, surfactants have been considered one of the most important factors in BA pathogenesis. However, there is no clear consensus on their pathogenetic significance and the possibility of their use in treating BA. Since the treatment of BA in children remains an urgent clinical task, further research into the pathophysiology of the disease and the search for more effective methods of its treatment are needed. This research will make it possible to achieve a significant improvement in the health status of patients and, in turn, reduce the associated social costs, as well as improve the quality of life of patients suffering from BA.

The primary limitation that persists throughout this review is the scarcity of clinical data and trials evaluating the practical implementation of surfactant-based therapies in BA patients. While the *in vitro* and animal studies discussed in this review offer valuable mechanistic insights, translating these findings into clinically effective treatments for BA remains uncertain. To bridge the gap between theoretical promise and clinical reality, rigorous clinical trials involving pediatric and adult BA patients are imperative. These trials should explore surfactant-based therapies' safety, efficacy, dosing regimens, and long-term outcomes.

The evidence obtained so far points to the prospect of developing methods for the therapeutic use of surfactants to achieve two goals: preventing and treating exacerbations of the disease and suppressing type II airway inflammation. Further research is needed to find safe and effective methods for using surfactants and associated therapeutic targets in patients with BA.

REFERENCES

1. Abramson MJ, Guo Y. Indoor endotoxin exposure and ambient air pollutants affect asthma outcomes. Am J Respir Crit Care Med. 2019;200(6):652-654.
2. Khreis H, Cirach M, Mueller N, de Hoogh K, Hoek G, Nieuwenhuijsen MJ, et al. Outdoor air pollution and the burden of childhood asthma across Europe. Eur Respir J. 2019;54:1802194.
3. Nelson RK, Bush A, Stokes J, Nair P, Akuthota P. Eosinophilic asthma. J Allergy Clin Immunol: In Practice. 2020;8(2):465-473.
4. Agache I, Miller R, Gern JE, Hellings PW, Jutel M, Muraro A, et al. They are emerging concepts and challenges in implementing the exposome paradigm in allergic diseases and asthma: A Practall document. Allergy. 2019;74(3):449-463.
5. Jansson SA, Backman H, Andersson M, Telg G, Lindberg A, Stridsman C, et al. Severe asthma is related to high societal costs and decreased health-related quality of life. Respir Med. 2020;162:105860.
6. Mallol J, Cranol J, von Mutis E, Odhiambo J, Keil U, Stewart A; ISAAC Phase Three Study Group. The international study of asthma and allergies in childhood (ISAAC) phase three: A global synthesis. Allergologia et Immunopathologia. 2013;41(2):73-85.
7. Samoliński B, Raciborski F, Lipiec A, Tomaszewska A, Krzych-Fałta E, Samel-Kowalik P, et al. Epidemiologia chorób alergicznych w Polsce (ECAP). Alergologia Polska - Polish J Allergol. 2014;1:10-18.
8. Wypych-Ślusarska A, Czech E, Kasznia-Kocot J, Słowiński J, Niewiadomska E, Skrzypek M, et al. Health inequalities among students of lower secondary school in Bytom, Poland. Ann Agric Environm Med. 2018;25: 4-8.
9. Tai A, Tran H, Roberts M, Clarke N, Wilson J, Robertson CF. The association between childhood asthma and adult chronic obstructive pulmonary disease. Thorax. 2014;69(9):805-810.
10. Annesi-Maesano I, Forastiere F, Balmes J, Garcia E, Harkema J, Holgate S, et al. The clear and persistent impact of air pollution on chronic respiratory diseases: A call for interventions. Eur Respir J. 2021;57(3):2002981.

11. Khreis H, Kelly C, Tate J, Parslow R, Lucas K, Nieuwenhuijsen M. Exposure to traffic-related air pollution and risk of development of childhood asthma: A systematic review and meta-analysis. Environm Internat. 2017;100:1-31.
12. Shivashankar M, Dhandayuthapani M. A study of inhalation drugs in asthma management in northern parts of Tamilnadu. Materials Today: Proceedings. 2019;15:268-272.
13. Busse W W, Castro M, Casale T B. Asthma management in adults. J Allergy Clin Immunol: In Practice. 2023;11(1):21-33.
14. Mümmler C, Milger K. Biologics for severe asthma and beyond. Pharmacol Therap. 2023;252:108551.
15. Choi Y, Lee DH, Lee JH, Shin YS, Kim SH, Park HS. Immunomodulatory function of surfactant protein D in eosinophilic asthma. Allergy. 2019;74(1):192-195.
16. Hirahara K, Shinoda K, Morimoto Y, Kiuchi M, Aoki A, Kumagai J, et al. Immune cell-epithelial/mesenchymal interaction contributing to allergic airway inflammation associated pathology. Frontiers Immunol. 2019;10:570.
17. Nefzi M, Wahabi I, Hadj Fredj S, Othmani R, Dabboubi R, Boussetta K, et al. Association analysis of the surfactant protein-C gene to childhood asthma. J Asthma. 2022;59(1):1-11.
18. Blanco O, Ramírez W, Lugones Y, Díaz E, Morejón A, Rodríguez VS, et al. Protective effects of Surfacen® in allergen-induced asthma mice model. Internat Immunopharmacol. 2022;102:108391.
19. Feo-Lucas L, Godio C, Minguito de la Escalera M, Alvarez-Ladrón N, Villarrubia LH, Vega-Pérez A, et al. Airway allergy causes alveolar macrophage death, profound alveolar disorganization, and surfactant dysfunction. Frontiers Immunol. 2023;14:1125984.
20. Belov GV, Arbuzov AA, Brimkulov NN. Otsenka sostoianiia surfaktantnoi sistemy legkikh. (Assessment of the state of the lung surfactant system). Bishkek. 2005;104.
21. Kalmatov RK, Dzhumaeva LM, Belov GV, Shakhmatova AK. Surfaktant slizistykh kak indikator vozdeistvii vneshnei sredy na organism (Mucosa surfactant as an indicator of environmental exposures on the organism). Meditsina Kyrgyzstana. 2009;3:43-47.
22. Nayak A, Dodagatta-Marri E, Tsolaki AG, Kishore U. An insight into the diverse roles of surfactant proteins, SP-A and SP-D in innate and adaptive immunity. Frontiers Immunol. 2012;3:131-135.
23. Achakulwisut P, Brauer M, Hystad P, Anenberg SC. Global, national, and urban burdens of paediatric asthma incidence attributable to ambient NO_2 pollution: Estimates from global datasets. Lancet Planet Health. 2019;3(4): e166–e178.
24. Han S, Mallampalli RK. The role of surfactant in lung disease and host defense against pulmonary infections. Ann Am Thorac Soc. 2015;12(5):765-774.
25. Belov GV, Kalmatov RK, Dzhumadilova DSh, Brimkulov NN, Akhmetova MI. Surfaktantaia sistema legkikh v usloviiakh gornogo klimata (Lung surfactant system in mountain climate). Meditsina Kyrgyzstana. 2011;7:48-51.
26. Whitsett JA, Alenghat T. Respiratory epithelial cells orchestrate pulmonary innate immunity. Nature Immunol. 2015;16(1):27-35.
27. Lopez-Rodriguez E, Gay-Jordi G, Mucci A, Lachmann N, Serrano-Mollar A. Lung surfactant metabolism: Early in life, early in disease and target in cell therapy. Cell and Tissue Research. 2017;367(3):721-735.
28. Haller T, Dietl P, Pfaller K, Frick M, Mair N, Paulmichl M, et al. Fusion pore expansion is a slow, discontinuous, and Ca^{2+}-dependent process regulating secretion from alveolar type II cells. J Cell Biol. 2001;155(2):279-289.
29. Vieira F, Kung JW, Bhatti F. Structure, genetics and function of the pulmonary associated surfactant proteins A and D: The extrapulmonary role of these C type lectins. Annals of Anatomy - Anatomischer Anzeiger. 2017;211:184-201.
30. Weaver TE. Synthesis, processing, and secretion of surfactant proteins B and C. Biochimica et Biophysica Acta. Molecular Basis of Disease. 1998;1408(2-3):173-179.
31. Nogee LM. Genetic causes of surfactant protein abnormalities. Current Opinion in Pediatrics. 2019;31(3):330-339.
32. Crouch E, Wright JR. Surfactant proteins A and D and pulmonary host defense. Ann Rev Physiol. 2001;63:521-524.
33. Iwasaki A, Medzhitov R. Control of adaptive immunity by the innate immune system. Natural Immunol. 2015;16(4):343-353.
34. Finn PW, Bigby TD. Innate immunity and asthma. Proceedings Am Thorac Soc. 2009;6(3):260-265.
35. Schicht M, Rausch F, Finotto S, Mathews M, Mattil A, Schubert M, et al. SFTA3, a novel protein of the lung: Three-dimensional structure, characterisation and immune activation. Eur Respir J. 2014;44(2):447-456.
36. Choi Y, Jang J, Park HS. Pulmonary surfactants: A new therapeutic target in asthma. Current Allergy and Asthma Reports. 2020;20(11):70.
37. Oliver BG, Robinson P, Peters M, Black J. Viral infections and asthma: an inflammatory interface? Eur Respir J. 2014;44(6):1666-1681.
38. Kim CK, Callaway Z, Gern JE. Viral infections and associated factors that promote acute exacerbations of asthma. Allergy, Asthma Immunol. 2018;10(1):12-17.

39. Wang J, Li P, Yu Y, Fu Y, Jiang H, Lu M, et al. Pulmonary surfactant-biomimetic nanoparticles potentiate heterosubtypic influenza immunity. Science. 2020;367(6480):367.
40. Tan KS, Lim RL, Liu J, Ong HH, Tan VJ, Lim HF, et al. Respiratory viral infections in exacerbation of chronic airway inflammatory diseases: Novel mechanisms and insights from the upper airway epithelium. Frontiers Cell Develop Biol. 2020;8:99.
41. Kloepfer KM, Lee WM, Pappas TE, Kang TJ, Vrtis RF, Evans MD, et al. Detection of pathogenic bacteria during rhinovirus infection is associated with increased respiratory symptoms and asthma exacerbations. J Allergy Clin Immunol. 2014;133(5):1301-1307.
42. Ujma S, Horsnell WG, Katz AA, Clark HW, Schäfer G. Nonpulmonary immune functions of surfactant proteins A and D. J Innate Immunity. 2017;9(1):3-11.
43. Knutsen AP, Slavin RG. Allergic bronchopulmonary aspergillosis in asthma and cystic fibrosis. Clin Developm Immunol. 2011;2011:843763.
44. Ordonez SR, van Eijk M, Escobar Salazar N, de Cock H, Veldhuizen EJA, Haagsman HP. Antifungal activities of surfactant protein D in an environment closely mimicking the lung lining. Molec Immunol. 2019;105:260-269.
45. Licari A, Manti S, Castagnoli R, Marseglia A, Foiadelli T, Brambilla I, et al. Immunomodulation in pediatric asthma. Frontiers Pediat. 2019;7:289.
46. Schleich FN, Chevremont A, Paulus V, Henket M, Manise M, Seidel L, et al. Importance of concomitant local and systemic eosinophilia in uncontrolled asthma. Eur Respir J. 2014;44(1):97-100.
47. Lee Y, Lee JH, Yang EM, Kwon E, Jung CG, Kim SC, et al. Serum levels of eosinophil-derived neurotoxin: A biomarker for asthma severity in adult asthmatics. Allergy, Asthma Immunol Res. 2019;11(3):394-405.
48. Yousefi S, Sharma SK, Stojkov D, Germic N, Aeschlimann S, Ge MQ, et al. Oxidative damage of SP-D abolishes control of eosinophil extracellular DNA trap formation. J Leukocyte Biol. 2018;104(1):205-214.
49. Pelaia C, Paoletti G, Puggioni F, Racca F, Pelaia G, Canonica GW, et al. Interleukin-5 in the pathophysiology of severe asthma. Frontiers Physiol. 2019;10:1514.
50. Pastva AM, Wright JR, Williams KL. Immunomodulatory roles of surfactant proteins A and D: Implications in lung disease. Proceedings Am Thorac Soc. 2007;4(3):252-257.
51. Borron PJ, Crouch EC, Lewis JF, Wright JR, Possmayer F, Fraher LJ. Recombinant rat surfactant-associated protein D inhibits human T lymphocyte proliferation and IL-2 production. J Immunol. 1998;161(9):4599-4603.
52. Francisco D, Wang Y, Conway M, Hurbon AN, Dy ABC, Addison KJ, et al. Surfactant protein-A protects against IL-13-induced inflammation in asthma. J Immunol. 2020;204(10):2829-2839.
53. Hentschel R, Bohlin K, van Kaam A, Fuchs H, Danhaive O. Surfactant replacement therapy: From biological basis to current clinical practice. Pediatric Research. 2020;88(2):176-183.
54. Raghavendran K, Willson D, Notter RH. Surfactant therapy for acute lung injury and acute respiratory distress syndrome. Critical Care Clin. 2011;27(3):525-559.
55. Sweet DG, Turner MA, Stranak Z, Plavka R, Clarke P, Stenson BJ, et al. A first-in-human clinical study of a new SP-B and SP-C enriched synthetic surfactant (CHF5633) in preterm babies with respiratory syndrome. Archives of Disease in Childhood. Fetal and Neonatal Edition. 2017;102(6):497-503.
56. Madsen J, Panchal MH, Mackay RA, Echaide M, Koster G, Aquino G, et al. Metabolism of a synthetic compared with a natural therapeutic pulmonary surfactant in adult mice. J Lipid Research. 2018;59(10):1880-1892.
57. Cecchi L, D'Amato G, Annesi-Maesano I. External exposome and allergic respiratory and skin diseases. J Allergy Clin Immunol. 2018;141(3):846-857.
58. Kamio K, Usuki J, Azuma A, Matsuda K, Ishii T, Inomata M, et al. Nintedanib modulates surfactant protein-D expression in A549 human lung epithelial cells via the c-Jun N-terminal kinase-activator protein-1 pathway. Pulmonary Pharmacol Therap. 2015;32:29-36