Surfactant Protein D: A Therapeutic Target for Allergic Airway Diseases

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Introduction

Allergic airway diseases are multifactorial and influenced by genetic, immune and environmental components (Allinne et al. 2019; Polverino et al. 2018). These diseases are growing challenges to global health (Pawankar 2014). The pattern of pulmonary inflammation such as rhinorrhoea, airway hyperresponsiveness and airway obstruction are exhibited as clinical features in asthma and allergic rhinitis (Jeffery and Haahtela 2006). Allergic airway disease is largely established by the overexpression of IgE generated in response to allergens that are innocuous to non-allergic individuals (Kratzer and Pickl 2016; Voskamp et al. 2020).

Peripheral blood mononuclear cells such as Dendritic cells (DCs), T and B lymphocytes, and granulocytes like mast cells and eosinophils, are critical in allergic reactions through the secretion of an array of mediators with airway constrictive and pro-inflammatory consequences (Figs. 1 and 2) (Méndez-Enríquez and Hallgren 2019). Immune hyperresponsiveness toward specific environmental allergens can lead to airway remodelling and pulmonary tissue damage (Palm et al. 2012; Kuruvilla et al. 2019). The current novel therapeutic regimens for airway allergic diseases, apart from allergen- immunotherapy, are mainly biologics that block allergic mediators such as cytokines and cellular receptors, such as Omalizumab, Dupilumab, mepolizumab, and Benralizumab (Staubach et al. 2018; Hellings et al.

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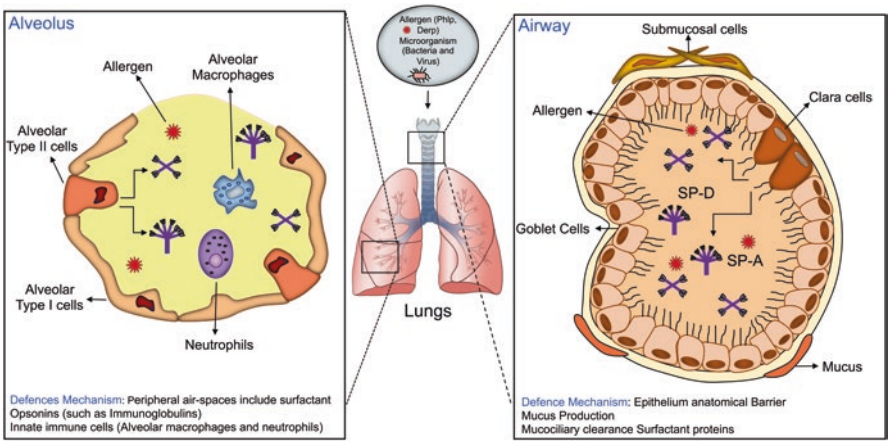

Fig. 1 Lungs are constantly challenged with Allergens and microorganisms leading to the production of several defense mechanisms. This includes formation of anatomical epithelium barrier, mucus production and mucociliary clearance surfactant protein. In airway surfaces Clara cells stimulate SP-A and SP-D production after allergen exposure. Small particles might reach to the alveolar gas-exchange region of the lungs. Defense mechanisms get activated and peripheral airspace starts secreting surfactants, other opsonins and innate immune cells, i.e., macrophages and neutrophils

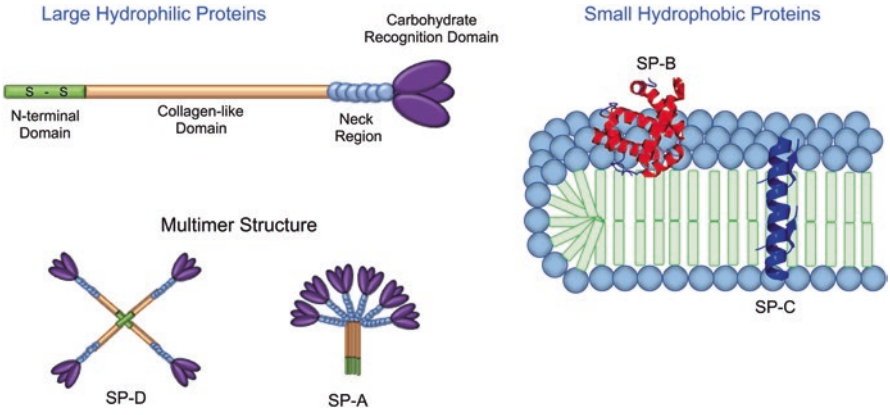

Fig. 2 (**a**) hydrophilic surfactant proteins SP-A and SP-D are multimeric proteins where single subunit monomer contains lectin domain (CRD), neck region and a collagen like domain. (**b**) Trimeric subunits come together to form oligomeric structure form through non-covalent bond to forms octamers (18 monomers) for SP-A, and dodecamers (12 monomers) for SP-D (**c**)

2017; Trischler et al. 2017; Fitzgerald et al. 2016). However, concerns have been raised about long-term side effects, prediction of treatment responses, the ability of these agents to promote tolerance induction, and the high financial cost (Breiteneder et al. 2019). Therefore, novel inhibitors of allergen-specific IgE and Th2 cytokines are much needed as an alternative therapeutic modality with lower costs and a

broader scope of application. Studies have shown the pivotal role of surfactant protein D (SP-D) in modulating immune hyperresponsiveness in the lung; this infers its importance to be considered an alternative therapeutic candidate in hindering pulmonary allergic reactions (Schleh et al. 2012; Sorensen 2018; Carreto-Binaghi and Taylor 2016; Winkler and Hohlfeld 2013). This chapter will highlight the immunomodulatory effects of SP-D in type I mediated hypersensitivity focusing on its impact on immune cells that fuel allergic airway reactions.

Surfactant Protein D: Molecular Structure and Function

Initial purification and characterization of SP-D in the late 80s and early 90s paved the way for the determination of the structure and the immune functions of SP-D (Persson et al. 1989; Possmayer 1988; Malhotra et al. 1990, 1992). SP-D protein is a member of collectin family of innate carbohydrate pattern recognition molecules; it is calcium-dependent C-type lectin, and has multimeric structure (Holmskov et al. 1994). It is synthesised by airway epithelium, mainly type II pneumocytes and non-ciliated Clara cells (Crouch et al. 1992). It is hydrophilic with 43 kDa molecular weight; its monomer structure is composed of four regions: a short N-terminal region attached to a collagen-like domain, followed by an α-helical coiled-coil neck region, and C-type lectin or carbohydrate recognition domain (CRD) (Fig. 3) (Håkansson et al. 1999). The collagen region can form triple-helical structures, and by virtue of trimerizing capability of neck region, the C-terminal CRD region forms

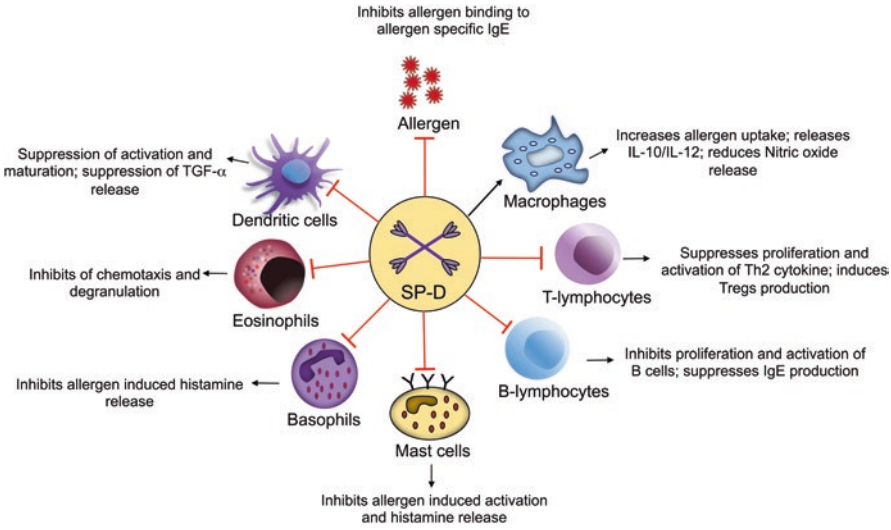

Fig. 3 Overview of the immunological functions of surfactant protein D and its interaction with other immune cells involved in allergic airway inflammation

a trimeric structure. This subunit can further oligomerise due to N-terminal region cross-linking to yield dodecamers. The homotrimeric CRD region mediates binding to various ligands on pathogens/allergens that exhibiting carbohydrate and charge patterns, whereas the collagen region binds to putative receptors on effectors cells such as macrophages (Kishore et al. 2006). SP-D multimerization is required for enhancing CRD binding affinity of to its ligands (Wright 2005). Interestingly, in the late 90s, a functional recombinant fragment of human SP-D (rfhSP-D) comprised of trimeric CRD and α-helical coiled neck region was expressed in E. coli and subsequently characterised for potential therapeutic applications via *in vitro*, *in vivo* and *ex vivo* allergic models (Kishore et al. 1996, 2006; Wang et al. 1996).

Surfactant Protein D: Immunomodulatory Mechanisms in Allergic Airway Inflammatory Events

The idea of immunomodulation by SP-D in allergy stems from the observations by Wang et al. who showed that SP-D (purified from human lung lavage) as well as rfhSP-D can bind to house dust mite extracts (*Dermatophagoides pteronyssinus; Der p*) and purified native *Der P1* in a calcium- and carbohydrate-dependent manner, thus, inhibiting *Der p*- IgE complex formation *in vitro* (Wang et al. 1996). Likewise, SP-D and rfhSP-D bound to *Aspergillus fumigatus* allergens and reduced histamine release from sensitised basophils derived from allergic bronchopulmonary aspergillosis (ABPA) patients (Madan et al. 1997). These findings suggested that SP-D binding to allergens can suppress early phase of inducing allergic airway reactions.

Protection by SP-D Against Allergic Eosinophilia

Infiltration of lung tissues with eosinophils is a sign of allergic airway inflammation ((Felton et al. 2014). This process involves eosinophilic differentiation and migration from the bone marrow to the lungs as a result of Th2 derived cytokines, particularly IL-13 and IL-5 (Esnault and Kelly 2016). Activation of eosinophils gives rise to the release of pro-inflammatory cytokines and cytotoxic proteins, including eosinophilic peroxidase (EPO), major basic protein (MBP) and reactive oxygen species (Acharya and Ackerman 2014). This leads to more destruction in the airway tissues and increases the tone of inflammatory allergic events (Yousefi et al. 2018).

SP-D has been shown to bind to eosinophils via its CRD and CD32 and block chemotaxis release and degranulation of Eosinophil Cationic peptide (Von Bredow et al. 2006). In addition, Madan et al. have demonstrated that SP-D and rfhSP-D reduced eosinophilia, allergen-specific IgE and IL-2, IL-4, and IL-5 levels in

pulmonary hypersensitivity murine models induced by *A. fumigatus* allergens (Madan et al. 2001). Similarly, Singh et al. found that rfhSP-D significantly reduced specific IgE, Il-4 and IL-5 levels, and peripheral eosinophilia in pulmonary mice models triggered by *Der p* (Singh et al. 2003). Furthermore, a study by Mahajan et al. demonstrated *ex vivo* that rfhSP-D increased apoptosis of activated eosinophils derived from allergic patients, without affecting eosinophils from healthy donors (Mahajan et al. 2008). Additionally, *A. fumigatus* allergen sensitized mice treated with SP-D (or rfhSP-D) showed a reduction in eosinophilia and eotaxin level, and consequently lower airway hyperresponsiveness (Erpenbeck et al. 2006). Thus, SP-D has a crucial role in regulating eosinophilia in allergic airway inflammation.

Allergen Uptake and Antigen Presentation Modulation

SP-D can effectively bind to allergens and enhance the uptake of allergens by alveolar macrophages, an important step in modulating the allergic airway inflammation ((Haczku 2008). Alveolar macrophages and Dendritic cells (DCs) play a crucial role in allergic pulmonary inflammation driven by T lymphocytes (Moser and Murphy 2000; Novak et al. 2004; Desch et al. 2013). DCs are accountable for inducing activation and differentiation of T lymphocyte in allergic airway reactions (Matzinger 1994). SP-D has been shown to bind to immature DCs in a carbohydrate and calcium-dependent manner (Brinker et al. 2001). Hansen et al. showed that SP-D can attenuate antigen presentation by DCs in the lung (Hansen et al. 2007). Additionally, SP-D interferes with DC maturation and TNF-α secretion in the pulmonary mice model (Hortobágyi et al. 2008). Therefore, SP-D may alter the allergen-antigen presentation by DCs to T lymphocytes which inhibits the intensification of airway allergic events (Fig. 4).

Alveolar macrophages have a crucial role in maintaining mucosal immune tolerance in the lung (Macaubas et al. 2003). Liu et al. have examined the role of SP-D on activated alveolar macrophages during allergic pulmonary inflammation in Derp-sensitised mice where it worked via blocking Nitric Oxide (NO) and TNF-α productions (Liu et al. 2005). Additionally, elevated expression of allergen-induced TLR4 in AMs of SP-D null mice has been reported (Schaub et al. 2004). These results indicated that SP-D can suppress inflammatory mediators in alveolar macrophages in allergic airway inflammation. Consistent with these observations, SP-D treatment in an allergic murine model increased levels of IL-10, IL-12, and IFN-γ in bronchoalveolar lavage fluid and reduced goblet cell hyperplasia. When alveolar macrophages were cultured in the presence of SP-D and allergen together, heightened levels of IL-10, IL-12, and IFN-γ were produced, suggesting alveolar macrophages being a target for SP-D actions against the development of airway hyperreactivity and inflammation (Takeda et al. 2003).

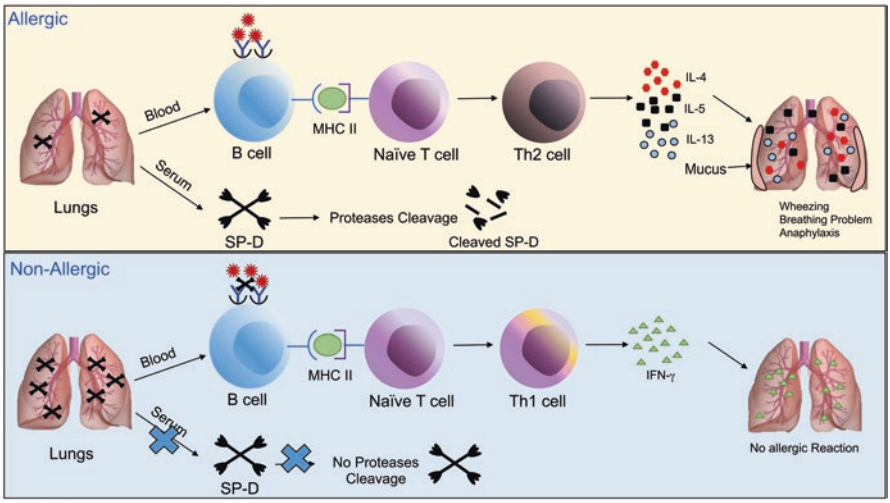

Fig. 4 Role of SP-D in healthy and allergic lungs

Modulation of Lymphocytes Mechanisms in Allergic Pulmonary Reactions

Inhalation of allergens in atopic patients induce inflammatory events involving mainly allergen-specific IgE and degranulation of mast cell and eosinophils; these events are orchestrated by B and T lymphocytes including IL-4, IL-5, and IL-13. Asthmatic patients have a high population of activated pulmonary T lymphocytes ($CD4^+$) characterised by elevated $CD25^+$ and $CD69^+$ expression (Corrigan et al. 1993). Genetically manipulated mice with Th2 cytokines deficiency have shown an absence of pulmonary allergic reaction features (Hamelmann et al. 2000). Thus, SP-D null mice show persistent activation of T lymphocytes in the lung in response to exogenous antigens (Fisher et al. 2002).

SP-D inhibits T lymphocyte proliferation in response to antigenic and mitogenic activation (Borron et al. 1998; Vass et al. 2004). SP-D has been shown ex vivo to inhibit histamine release and lymphocyte proliferation in asthmatic patients induced by phytohemagglutinin (PHA) and Der p (Wang et al. 1998). Moreover, high level of CTLA4 (a negative regulator of T-lymphocytes) has been reported in the presence of SP-D *in vitro* and *in vivo* (Lin et al. 2010). These results underline the potential role SP-D in regulate T-lymphocyte activation and proliferation expression in airway allergy.

B cells appear to be convenient target for SP-D in allergic inflammation. B lymphocytes play a crucial role in allergic airway inflammation (Ghosh et al. 2012), via production of allergen-specific IgE and secretion of IL-4, which induces Th2 differentiation (De Vooght et al. 2013; Harris et al. 2000). B lymphocyte null mice treated with cockroach allergens show low levels of Th2 cytokines (Lindell et al.

2008). In addition, allergen presentation by B lymphocytes results in T cell expansion, Th2 polarization and more allergen-specific IgE synthesis (Linton et al. 2003; Crawford et al. 2006). B lymphocytes are also involved in eosinophilic pulmonary inflammation (Drake et al. 2015).

Recently, an *ex vivo* study by Qaseem et al. using allergic rhinitis patients' samples revealed that rfhSP-D suppressed basophil and B, and T lymphocytes activations. rfhSP-D bound to B lymphocytes in a calcium- and carbohydrate-dependent manner through the CRD region. Furthermore, rfhSP-D hindered allergen-IgE complexes from binding to CD23 (FcεRII). rfhSP-D also blocked IgE synthesis by B cells despite the presence of IL-4, IL-21, and CD40L (Qaseem et al. 2017). These results put together the immune functions of SP-D in modulating granulocytes and lymphocytes in airway allergic reactions. CD23 is low affinity receptor for IgE mainly on B lymphocytes which is involved in allergen-specific IgE upregulation though the interaction with CD21 (complement receptor 2) (Conrad et al. 2007). The study of Qaseem et al. revealed SP-D reduced CD23 expression on B cells.

Surfactant Protein D Expression in Allergic Airway Diseases

SP-D levels are elevated in nasal tissue of patients with chronic rhinosinusitis (Ooi et al. 2007). High serum levels of SP-D have reported in allergic patients following allergen challenge (Koopmans et al. 2004). In addition, asthmatic patients showed high SP-D levels in the bronchial alveolar lavage fluid as compared with non-asthmatic controls (Cheng et al. 2000). Murine models with acute lung allergic reactions show high levels of SP-D in the pulmonary tract (Wang and Reid 2007). Thus, SP-D may serve as a biomarker for the severity of allergic immune response (Hartl and Griese 2006).

Significance and Future Direction

Research in unravelling various mechanisms of protective effects of SP-D against airway allergic diseases has highlighted the therapeutic potential of rfhSP-D. This small fragment of human SP-D seems to bind allergens, inhibit IgE-allergen interaction, suppress basophil activation, modify allergen presentation, suppress proliferation of allergen-stimulated B and T lymphocytes, induce Th2 to Th1 polarisation, and suppress IgE synthesis by primed B cells. The data so far in the field clearly point towards logical clinical trials.

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