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SP-A and SP-D in host defense against fungal infections and allergies

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1. ABSTRACT

Innate immunity mediated by pattern recognition proteins is relevant in the host defense against fungi. SP-A and SP-D are two such proteins belonging to the class of collagen domain containing C-type lectins, or collectins. They bind to the sugar moieties present on the cell walls of various fungi in a dose dependent manner via their carbohydrate recognition domain (CRD). SP-A and SP-D directly interact with alveolar macrophages, neutrophils, lymphocytes. We review these roles of SP-A and SP-D against various clinically relevant fungal pathogens and fungal allergens. SP-A and SP-D gene deficient mice showed increased susceptibility/ resistance to various fungal infections. Patients of fungal infections and allergies are reported with alterations in the serum or lung lavage levels of SP-A and SP-D. There are studies associating the gene polymorphisms in SP-A and SP-D with alterations in their levels or functions or susceptibility of the host to fungal diseases. In view of the protective role of SP-D in murine models of *Aspergillus fumigatus* infections and allergies, therapeutic use of SP-D could be explored further.

2. INNATE IMMUNE DEFENSE AGAINST FUNGAL INFECTIONS: SP-A AND SP-D

Opportunistic fungal infections create therapeutic challenges, particularly in high risk immune-compromised patients with AIDS, cancer, those with congenital immunodeficiency and those undergoing transplantation. Invasive mycoses patients despite empirical treatments show higher mortality and morbidity rates due to toxic side effects of and growing resistance to the antifungal drugs. A detailed understanding of the nature and function of the immune system in fungal infections is, therefore, highly essential to develop novel strategies in drug and immunotherapy.

Host defense against pathogenic fungi comprises of innate immune response involving neutrophils, monocytes, macrophages, dendritic cells and lymphocytes and pattern recognition molecules such as toll-like receptors, mannose receptor, collectins etc. The innate and adaptive immune responses are intimately linked and controlled by sets of molecules and receptors that act to generate the most effective form of immunity for protection

SP-A and SP-D in fungal infections and allergies soluble Pattern Recognition Receptors (PRRs)

Mechanism	Effect
Microbiostatic	SP-A and SP-D increase the lag time of fungal growth and inhibit hyphal and pseudohyphal outgrowth. They inhibit fungal entry into host tissue.
Aggregation/ Agglutination	SP-A and SP-D bind to the surface glycoproteins and crosslink pathogens.
Opsonization	The binding of SP-A and SP-D on the surface of fungus enhances the respiratory burst and pathogen uptake by macrophage and neutrophils.
Innaten Immune Modulation	Control of inflammation, Recognition and clearance of apoptotic and necrotic cells, Modulation of maturation and antigen presentation by dendritic cells
Adaptive immune modulation	SP-A and SP-D bind allergens, which has the effect of inhibiting IgE binding, reduces B and T lymphocyte proliferation, suppresses histamine release from basophils and mast cells, and directs the polarization of T cells towards Th1; modulate the maturation of dendritic cells. SP-A binds C1q, blocking its binding to C1r and C1s, reducing complement mediated damage
Chemotaxis	The chemotactic domains (for phagocytes) can be localized to CRD for SP-D and collagen tail for SP-A.

Table 2. SP-A and SP-D binds to a variety of fungi

	SP-A	SP-D
Opportunistic fungal pathogens:		
Cryptococcus neoformans	√	√
Aspergillus fumigatus	√	√
Pneumocystis carinii	√	+/-
Primary fungal pathogens:		
Histoplasma capsulatum	√	√
Blastomyces dermatitidis	√	√
Coccidiodes posadasii	√	√

against the pathogen. Currently there is considerable interest in innate immune molecules active against fungi that may have specific targets or may be multifunctional in their mechanism of action. Pattern Recognition Receptors (PRRs) are innate immune molecules that bind common essential constituents of pathogens such as LPS, peptidoglycan, lipoteichoic acid of bacteria, DNA or RNA of viruses, and fungal glucans (1). These broad-spectrum PRRs are thought to be a first line of defense, involved in controlling pathogen number and minimizing tissue damage caused by the inflammatory response, while allowing time for activation and modulation of the adaptive immune response. Numerous PRRs have been studied and one family of predominantly soluble PRRs are collectins, which bind carbohydrate and lipid structures that are found on pathogens. These oligomeric molecules are characterized by the presence of a C-terminal Ca^{2+} dependent C-type lectin domain containing collagen. At present nine mammalian collectins have been described namely collectin liver-1 (CL-L1), collectin placenta-1 (the only membrane-bound collectin), collectin kidney-1 (CL-K1), collectin of 43 kD (CL-43), collectin of 46 kD (CL-46), conglutinin, mannan-binding lectin (MBL), surfactant protein A (SP-A) and surfactant protein D (SP-D).

SP-A and SP-D are the two best studied collectins. Apart from their homeostatic role in the regulation of lung surfactant, they are effective secretory molecules, employing a variety of mechanisms to kill, or reduce the infectivity of different pathogens. Initially these include bacteriostatic and fungistatic mechanisms, agglutination of bacteria, fungus and viral particles, opsonization, enhancement of phagocytosis and modulating the adaptive response (2) (Table 1). In the lungs, SP-A and SP-D are synthesized by alveolar type II cells and non-ciliated bronchial epithelial cells (Clara cells) of the terminal bronchioles and conducting airways (3-5). SP-D levels in surfactant lining of the alveolar epithelia are very low (~10-fold) than that of SP-A. There are several evidences that suggest extra-pulmonary existence of these collectins. They have been detected in the serous glands of proximal human trachea, in the endocytic compartment of macrophages, and human inner ear. Low levels of material antigenically similar to SP-D are found in normal human serum, and animal studies indicate the presence of SP-D, or SP-D-like proteins, in gastric mucosa, skin, mucosal lining of female and male genital tract, lacrymal, and salivary glands. Their presence in tear and saliva and epithelial lining appears to suggest that SP-A and SP-D are general scavenging defense molecules in body secretions with a plausible role in modulation of mucosal immunity (6).

This review will discuss the role of lung surfactant proteins A and D in host defense against fungal pathogens and allergens.

3. STRUCTURE OF SP-A AND SP-D

The primary structure of SP-A and SP-D comprises of 4 regions; a cysteine-containing N-terminus that is linked to a triple-helical collagen region composed of repeating Gly-X-Y triplets followed by an α-helical coiled coil neck region and a globular structure at the C-terminal comprising a C-type lectin or carbohydrate recognition domain (CRD). This primary structure trimerises to form a structural unit, which, then either hexamerises to form bouquet-shaped SP-A or tetramerises to form cruciform shaped SP-D. The C-type CRDs are spaced in a trimeric orientation at the end of triple-helical collagen region. The CRD region binds to pathogens due to its carbohydrate pattern-recognition properties, whereas, the collagen region interacts with putative receptors present on the immune cells in order to bring about effector functions.

Functional SP-A has a hexameric structure wherein six subunits, each with 105 kDa, associate to yield a molecule of 630 kDa. The overall shape of SP-A is very similar to that of the serum complement protein C1q, with both the molecules appearing in the electron microscope as a bouquet-like structure with 6 globular heads linked by collagen-like strands to a fibril-like central core. The mature forms of SP-A are composed of 248 amino acids (aa), which include: an N-terminal segment (7 aa), a collagen-like region (73 aa), the neck region (34 aa), and a CRD domain (123 aa). Similarly, functional SP-D is composed of oligomers of subunits of 130-kDa each subunit that associate to yield a molecule of 520-kDa (6, 7). The degree of subunit oligomerization affects the recognition of and binding strength to the carbohydrate ligands on the surfaces of pathogens (8).

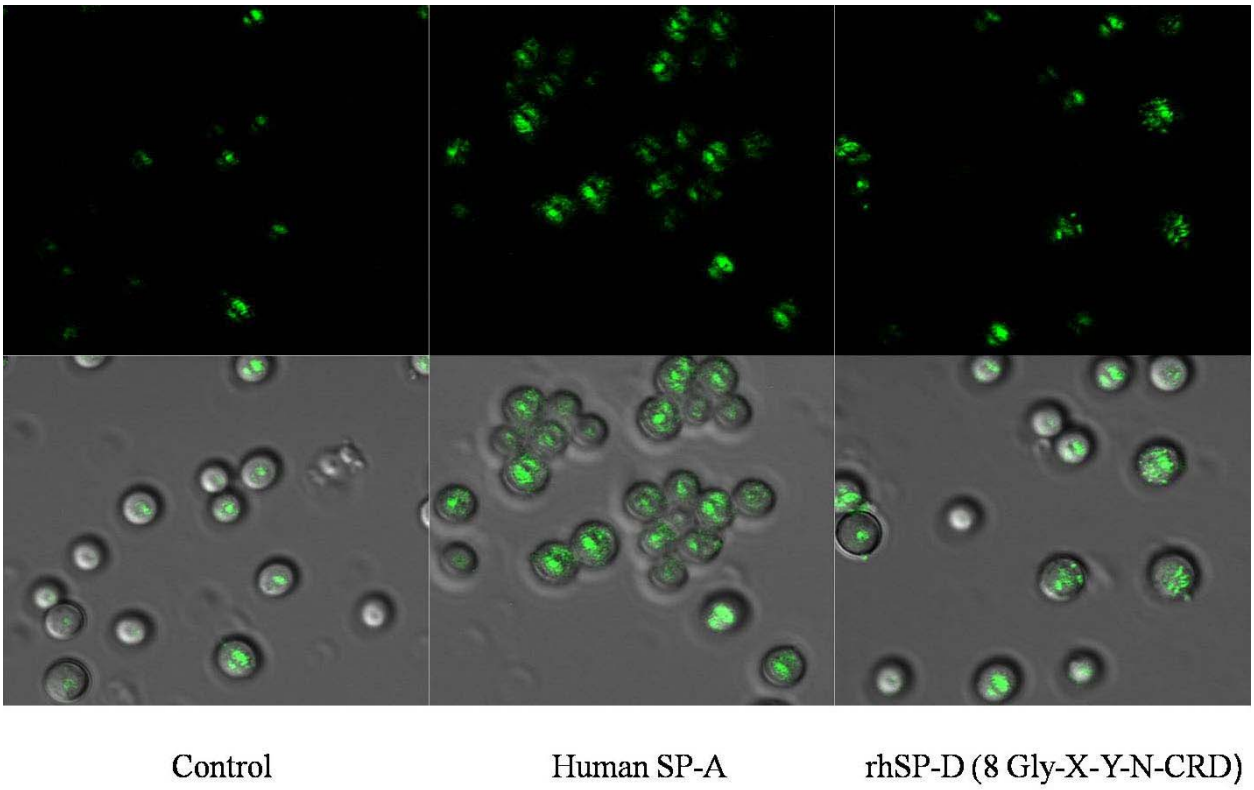

Figure 1. SP-D and SP-A binding to *Aspergillus* conidia.

4.. INTERACTIONS WITH FUNGAL PATHOGENS

The role of SP-A and SP-D during bacterial and viral infections is well established. However, less is known about its possible roles during invasive fungal infections. Collectins bind mannose and glucose residues, which are part of most microbial ligands, more avidly than galactose, fructose, and sialic acid, which are common components of glycoproteins of higher eukaryotes. SP-A and SP-D both are known to recognize and induce immune responses against clinically relevant fungal pathogens, such as *Aspergillus fumigatus*, *Blastomyces dermatitidis, Candida albicans*, *Coccidiodes immitis and Coccidiodes posadasii, Cryptococcus neoformans*, *Histoplasma capsulatum, Pneumocystis carinii* (Table 2). Collectively, these fungi are by far the most prominent and lethal fungal pathogens worldwide. Here, we discuss the interaction and role of SP-A and SP-D in host defense against specific fungal pathogens.

4.1 OPPORTUNISTIC FUNGAL PATHOGENS

4.1.1. *Aspergillus fumigatus*

Aspergillus fumigatus is a ubiquitous airborne fungal pathogen. There are two severe forms of the disease namely, Allergic bronchopulmonary aspergillosis (ABPA), a hypersensitivity disease that occurs frequently in patients with asthma or cystic fibrosis and Invasive pulmonary aspergillosis (IPA), a fatal disease affecting highly immunocompromised patients. Invasive pulmonary aspergillosis is rapidly progressive, often fatal, and is characterized by tissue destruction associated with abundant hyphae in necrotic tissue. Between these two severe forms of the disease, there are various sub-acute and chronic forms of pulmonary aspergillosis, such as sub-acute invasive also called chronic necrotizing (CNPA), chronic cavitary, chronic fibrosing and simple aspergilloma (9).

Macrophages and neutrophils play a pivotal role in containing the infection as macrophages phagocytose the fungal conidia and neutrophils destruct the hyphae. Impairment of these functions in the host leads to increased susceptibility to *A. fumigatus*. Recognition of conidia by macrophages occurs after shedding of the hydrophobin layer during swelling and germination. Both conidia and hyphae are trapped in neutrophil extracellular trap (NETs) which prevents the systemic spreading of the fungus in the host. However, *A. fumigatus* interferes with the innate immune mechanisms, with both the complement activation and defense mechanisms of phagocytes, thereby evading at least in part the host defense.

SP-A and SP-D have been shown to be protective against invasive aspergillosis. Both these collectins bind and agglutinate *A. fumigatus* conidia, and this interaction enhances phagocytosis and killing of germinating conidia by alveolar macrophages and neutrophils (10). We confirmed the binding of SP-A and SP-D at the surface of non-germinating conidia by confocal microscopy (Figure 1). SP-D binding to *A. fumigatus* hyphae is reported to be

calcineurin-sensitive, as calcineurin is known to play an important role in regulating production of key cell wall binding partners, such as 1, 3-beta-D-glucan (11).

Madan *et al.*, showed protective effects of intranasal administration of SP-A, SP-D, and recombinant human SP-D (rhSP-D) in the immunosuppressed murine model of invasive pulmonary aspergillosis (IPA) challenged intranasally with *A. fumigatus* conidia. Mice treated with, Amphotericin B (AmB), a known antifungal drug, SP-D, and rhSP-D showed a survival rate of 80, 60, and 80%, respectively, compared with 100% mortality in the untreated group. However, SP-A treatment did not have a significant effect on mortality. This highlighted a more important anti-fungal role for SP-D. Treatment of IPA mice with various doses of SP-D or rhSP-D showed lower Colony Forming Units (CFU) counts in the lung tissues and dramatically reduced fungal hyphae, consistent with raised levels of TNF-γ and IFN- γ in the bronchoalveolar lavage fluid (BALF) of treated mice (12). In a later study, Singh *et.al* showed that rhSP-D provided dose dependent therapeutic protection against fatal challenge with *A. fumigatus* conidia. SP-D mediated protective mechanisms include suppression in levels of pathogenic Th2 cytokines (IL-4 and IL-5), enhanced local production of protective Th1 cytokines, TNF- α and IFN-γ, and that of protective C-C chemokine, MIP-1 α (13).

Madan *et al.*, in their recent study, examined the susceptibility of immunosuppressed SP-A knockout or SP-D knockout mice to *A. fumigatus* conidia. *A. fumigatus*-challenged SP-A-/- (SP-A (-/-) IPA) mice showed less mortality (40%) than the WT-IPA mice (100%). On administration of SP-A to these SP-A (-/-) IPA, their mortality increased to 60% and levels of TNF-α and ratio of IFN- γ to IL-4 decreased significantly. The SP-D (-/-) IPA mice (57.14%) showed similar mortality as WT-IPA mice (60%). However, the SP-D (-/-) IPA mice (42.86% mortality on day 2) died earlier than the WT-IPA mice (20% mortality on day 2), showed a higher hyphal density and tissue injury in lungs. Treatment with SP-D or rhSP-D reduced the mortality to 50% and 33%, respectively, concomitant with higher IFN- γ to IL-4 ratios in treated SP-D -/- mice, compared to untreated control group. This study indicated that SP-D -/- mice are more susceptible to IPA, while, SP-A gene deficient mice acquire resistance to IPA confirming the observations in wild type invasive aspergillosis model (14).

4.1.2. *Candida albicans*

The opportunistic fungi *Candida albicans* normally colonizes the mucosal surfaces of humans. *C. albicans* germinate in the respiratory tract upon entering the lung via inhaled air, by dissemination into the lungs via the bloodstream, or via aspiration. Their incidence in the alveolar compartment is a serious threat for mechanically ventilated and immunocompromised patients. In these patients, *C. albicans* alters its cell morphology from yeast to hyphae which enables the fungus to penetrate host tissues. This dimorphic growth is considered an important virulence factor. Despite a high incidence of *Candida* colonization in airways, pathological involvement of the respiratory tract is rare in the immunocompetent host. Therefore, the lung requires an efficient defense mechanism to protect itself from invasion by *C. albicans* (15).

Very little is known about the interactions of *C. albicans* and collectins. SP-A does not seem to serve as an opsonin for the phagocytosis of *C. albicans* by alveolar macrophage and strongly inhibited IL-1, IL-8, MIP-1 and MCP-1 production upon *C. albicans* challenge to alveolar macrophages. The study suggested that SP-A shields macrophages from interacting with *C. albicans* ligands (16, 17). SP-D binds *C. albicans*, resulting in agglutination of the pathogen. Binding was calcium dependent and was inhibited by competing sugars maltose or mannose. Interaction of SP-D with *C. albicans* profoundly inhibited fungal growth, hyphal production and phagocytosis of *C. albicans* by alveolar macrophages (15).

4.1.3. *Cryptococcus neoformans*

Cryptococcus neoformans is a basidiomycete yeast-like fungus with a predilection for the respiratory and nervous systems. In healthy individuals, infection is mild, self-limiting, and restricted to the lung. However, in immunocompromised individuals, particularly those with AIDS, this opportunistic fungus causes life-threatening infections. Although meningitis is the predominant clinical presentation, the primary site of infection is the lung. As only particles smaller than 2 μm in diameter can reach the alveoli, it is believed that infection starts with inhalation of basidiospores or desiccated forms of *C. neoformans*, which are small and weakly encapsulated. Without treatment, cryptococcosis easily disseminates throughout the body in the immunocompromised host, causing the most severe problems in the central nervous system.

SP-D is known to agglutinate and phagocytose acapsular *C. neoformans* (18). SP-D also binds to capsular and hypocapsular *C. neoformans* however, with lower affinity than that of acapsular. Capsular components GXM (glucuronxylomannan) and MP1 (mannoprotein 1) are the binding partners for SP-D (19).

Geunes-Boyer *et al.*, showed that SP-D binding to cap59Delta mutant cells (hypocapsular strain of *C. neoformans*) was six-fold greater than binding to wild-type encapsulated strain H99. It also enhanced the phagocytosis of cap59Delta cells by four-fold *in vitro*. Intranasal inoculation of mice with labeled cap59Delta or H99 cells, resulted in a greater number of phagocytosed *C. neoformans* cells in the lung sections of wild-type mice than in SP-D-/- mice, confirming that SP-D enhances the phagocytosis of *C. neoformans*. However, they suggested that *C. neoformans* may use SP-D as a vehicle to gain access to specific intracellular compartments where it can grow and divide in intracellular vesicles (20).

Like SP-D, SP-A also agglutinates acapsular *C. neoformans.* However, this binding does not result in phagocytosis by macrophages (21) and hence, does not enhance its uptake. The susceptibility of SP-A -/- mice to

C. neoformans infection is similar to that of wild-type mice (20).

4.1.4. *Pneumocystis carinii*

Pneumocystis carinii pneumonia (PCP) remains the most significant cause of morbidity and mortality in HIV-infected patients, as well as an important life-threatening opportunistic infection in other immunocompromised patients with defects in cell-mediated immunity. From numerous reports, it is known that there are several complex interactions between host and pathogen that develop during PCP. Upon entry into the upper airways, *P. carinii* forms a proteinaceous foamy exudate that includes lipids and surfactant proteins, which can restrict respiration and lead to pneumonia.

SP-A and SP-D bind to *P. carinii* via the surface glycoprotein gp120 (also known as gpA or gp95), a mannose- and glucose- rich glycoprotein expressed on cysts and trophozoites (22). In addition to interaction of these collectins with gpA, β-1, 3glucan core and 1, 6- and 1, 4-β- linked glucose have also been implicated in the interactions of SP-D with *Pneumocystis* (19). It is likely that the characteristic cyst aggregates observed in lung biopsies of patients with *P carinii* infection are contributed by the collectins.

SP-D aids attachment of *P carinii* to alveolar macrophage (AM), but does not seem to increase its uptake. Whereas, SP-A reduces *P. carinii* binding to AM and hence, its phagocytosis. However, this may potentiate its binding to alveolar epithelium (23-25).

SP-A and SP-D contribute to the clustering of *P. carinii in vivo* by interacting with gpA. SP-A-/- CD4-depleted mice showed a greater lung burden, an increase in numbers of alveolar macrophage, inflammation and lung injury, whereas, SP-D-/- CD4-depleted mice showed a more rapid onset in disease, with increased lung burden and inflammation. These mice exhibited an enhanced susceptibility to *P. carinii* despite increased infiltration of inflammatory cells and modified production of oxidative species during the infection. Higher oxides which are involved in pathogen killing, were reduced in the lungs of the SP-A-/- mice, while the higher levels of all oxidative species in the lungs of the SP-D-/- animals was thought to increase lung injury. These models also highlighted the interdependence of SP-A and SP-D. A reduction in the post-infection level of SP-D in the lungs of the SP-A-/- mice was thought to be due to the lower IL-4 and IL-5 levels, while the SP-D-/- mice had a 40-50% decrease in SP-A-/- levels at baseline. These observations emphasize the difficulty in separating the effects of these two proteins during *P. carinii* infection, while demonstrating that they are involved in its clearance during the early stage of infection by modifying the inflammatory response, and later, regulating the adaptive immune response (26, 27)

However, in another study, hypobaric hypoxia weakened rats showed significantly impaired levels of SP-A and SP-D, and did not favour growth of *P. carinii.* It is plausible that there may be other factors in these rats that are strengthening the host defense against *P. carinii* infection despite impaired levels of collectins (28).

4.2. PRIMARY FUNGAL PATHOGENS

4.2.1. *Blastomyces dermatitidis*

Blastomycosis is a pulmonary disease contracted by inhalation of airborne conidia or mycelial fragments of the dimorphic fungus *Blastomyces dermatitidis*, which promptly converts to its parasitic form, yeasts. Various infections includes asymptomatic disease, acute or chronic pneumonia, and disseminated disease with granuloma formation and suppuration, especially in immunodeficient patients, who are at higher risk for developing widely disseminated blastomycosis (29).

The production of TNF-α by the alveolar macrophages is important in promoting host defense against *B. dermatitidis.* It is reported that β-1,3 glucan on the yeast stimulates TNF-α production by the macrophages, and TNF-α production is strongly inhibited in the presence of SP-A and SP-D. BALF from SP-D knockout mice did not interfere with *B. dermatitidis* cell stimulation of alveolar macrophage for TNF-α production. If BALF from SP-A knockout mice or pure SP-D was added to BALF from SP-D knockout mice, the mixture interfered with *B. dermatitidis* cell stimulation of alveolar macrophage TNF-α production. The data suggested that SP-D in BALF binds β-glucan on *B. dermatitidis*, blocking BAM access to β-glucan, thereby inhibiting TNF-α production and may reduce inflammation and tissue destruction but could also promote disease (30).

4.2.2. *Coccidiodes immitis and Coccidiodes posadasii*

Coccidioidomycosis or Valley Fever is a fungal disease caused by highly virulent, soil-fungus caused by *Coccidioides immitis* or *posadasiie.* It is the most virulent fungal pathogen enlisted in Select Agent list and poses a risk for bioterrorism (31). Primary infection in the lungs is initiated by inhalation of air-borne arthroconidia that converts into endosporulating spherule in the lung. Clinical manifestations of the disease range from pulmonary infection to a more severe fatal mycosis involving extra-pulmonary tissues in 1–10% of the infected people. However, very little is known regarding the role of innate immune response against *Coccidioides*.

Both SP-A and SP-D bind to Coccidiodal antigens. However, binding of SP-A and SP-D to endospores, a form likely to be encountered early in infection, is not yet studied. In BALF samples of *C. posadasii* infected mice, the concentrations of SP-A and SP-D were 38% and 4% of those in lavage fluid samples of non-infected control mice, respectively. This indicates that *C. posadasii* infection perturbs the pulmonary SP-A and SP-D, potentially enabling the disease progression and promoting fungal dissemination (32)

4.2.3. *Histoplasma capsulatum*

Histoplasma capsulatum is a dimorphic fungal pathogen that usually results in a self-limited flu-like illness that is associated with inflammatory pulmonary infiltrates

and can cause a more serious pneumonitis or a chronic cavitary pulmonary infection. The organism can also act as an opportunistic pathogen and can cause progressive, disseminated disease in immunosuppressed patients.

SP-A and SP-D exert potent, macrophage-independent fungicidal activity against the yeast phase of *Histoplasma*. Incubation with the surfactant proteins caused a marked decrement in viability. This alteration was associated with a calcium-dependent, collectin-mediated increase in the permeability of the *Histoplasma* cell wall. Hence, the direct antimicrobial properties of SP-A and SP-D appear to play a physiologically relevant role in innate immune defense against *Histoplasma*. SP-A and SP-D inhibit the biosynthetic capacity of *Histoplasma*. The collectin-mediated reduction in protein synthesis by *Histoplasma* was associated with the loss of the capacity to replicate, consistent with cell death. The *Histoplasma* inoculum size did not affect the fungicidal properties of the collectins. SP-A and SP-D modulate the growth and viability of *H. capsulatum* in the presence and absence of alveolar macrophages. SP-A gene deficient mice showed a higher fungal burden in the lungs than wild-type. However, both SP-A and SP-D failed to inhibit the growth of yeast that had been internalized by macrophages (33).

5. INTERACTION WITH FUNGAL ALLERGENS

Fungi mainly from ascomycota and basidiomycota, have long been recognized as an important source of allergens in patients with atopic disease and have been known to cause a broad panel of human disorders. Fungal spores and/or mycelial cells cause type I and type III allergy leading to a spectrum of allergic diseases, including allergic bronchopulmonary mycoses, allergic sinusitis, hypersensitivity pneumonitis, atopic dermatitis and allergic asthma. Sensitization to molds has been reported in up to 80% of asthmatic patients. About 150 individual fungal allergens from approximately 80 mold genera have been identified in the last 20 years (34). SP-A and SP-D are known to interact *in vitro* with pollen and mite allergens and their interaction has resulted in reduced IgE binding and histamine release. With respect to fungal allergens and fungal allergic disease, the role of SP-A and SP-D in host defense has only been explored in the fungus, *Aspergillus fumigatus*.

A. fumigatus is known to cause both IgE-mediated and non IgE-mediated hypersensitivity in immunocompetent patients, leading to development of allergic bronchopulmonary aspergillosis (ABPA). ABPA is clinically characterized by episodic bronchial obstruction, positive immediate skin reactivity, elevated *A. fumigatus*-specific IgG and *A. fumigatus*-specific IgE antibodies in serum, peripheral and pulmonary eosinophilia, central bronchiectasis, and expectoration of brown plugs or flecks (35). Other important features of ABPA are activated Th2 cells and asthma, and patients may develop localized pulmonary fibrosis at later stages of the disease. The murine model resembles the human disease immunologically, exhibiting high levels of specific IgG and IgE, peripheral blood and pulmonary eosinophilia, and a Th2 cytokine response (36).

SP-A and SP-D both bind via their CRD region to allergenic extracts derived from *A. fumigatus* and this binding resulted in inhibition of specific IgE binding to allergens, and allergen-induced histamine release from sensitized basophils (37, 38).

In vivo therapeutic trials of SP-A, SP-D, and rhSP-D in murine models of *A. fumigatus* induced pulmonary hypersensitivity have shown interesting results. Intranasal administration using 3 doses on consecutive days significantly lowered eosinophilia and specific IgG and IgE antibody levels in the mice. This therapeutic effect persisted up to 4 days in the SP-A-treated ABPA mice and up to 16 days in the SP-D- or rhSP-D-treated ABPA mice. Lung sections of the ABPA mice exhibited extensive infiltration of lymphocytes and eosinophils, which were considerably reduced following treatment with SP-D or rhSP-D. The levels of IL-2, IL-4, and IL-5 were decreased, while IFN-γ levels increased in supernatants of the cultured spleen cells, suggesting a shift in the cytokine profile from pathogenic Th2 to protective Th1 response. This suggests that SP-A and SP-D appear to suppress the Th2 responses, probably via their ability to modulate functions of antigen-presenting cells, such as macrophages and dendritic cells, which may eventually lead to an induction of IL-12-dependent Th1 responses (39-42).

It is evident from the studies that SP-D knockout mice are more susceptible than wild-type mice whereas, SP-A knockout mice were found to be nearly resistant to *A. fumigatus* sensitization. Intranasal treatment with SP-D or rhSP-D rescued the *A. fumigatus* sensitized SP-D-/- mice, while SP-A treated *A. fumigatus* sensitized SP-A-/- mice show several fold elevated levels of IL-13 and IL-5, resulting in increased pulmonary eosinophilia and damaged lung tissue. This suggests differential mechanisms involved in SP-A and SP-D mediated resistance to allergen challenge. Hypereosinophilia exhibited by both SP-A-/- and SP-D-/- mice, probably due to significantly raised levels of IL-5 and IL-13 in these mice, suggests that SP-A and SP-D may have a role in regulating eosinophil infiltration in allergic hypersensitivity and asthma that is not limited to *A. fumigatus* induced allergic diseases (43).

Some more studies have demonstrated a protective role of SP-D in fungal allergies. Haczku *et al.*, showed that there was a 9-fold increase in SP-D protein levels in the *A. fumigatus* sensitized mice. The increased levels of SP-D showed a significant positive correlation with serum IgE ($r = 0.85$, $P < 0.001$) (44). Atochina *et al.*, reported that C57BL/6 mice have attenuated airway hyper-responsiveness in comparison to Balb/c mice. *A. fumigatus* challenge of sensitized C57BL/6 mice induced a markedly increased SP-D protein expression in the SA surfactant fraction (1,894 +/- 170% of naïve controls) that was 1.5 fold greater than the increase in Balb/c mice (1,234 +/- 121% $p < 0.01$). Further, sensitized and exposed C57BL/6 mice had significantly lower IL-4 and IL-5 in the BAL fluid than that of Balb/c mice ($p < 0.05$). The study suggested that elevated SP-D levels could be responsible for attenuation of *A. fumigatus* induced hyperresponsiveness in C57Bl/6 mice (45). Cao *et al*, 2004,

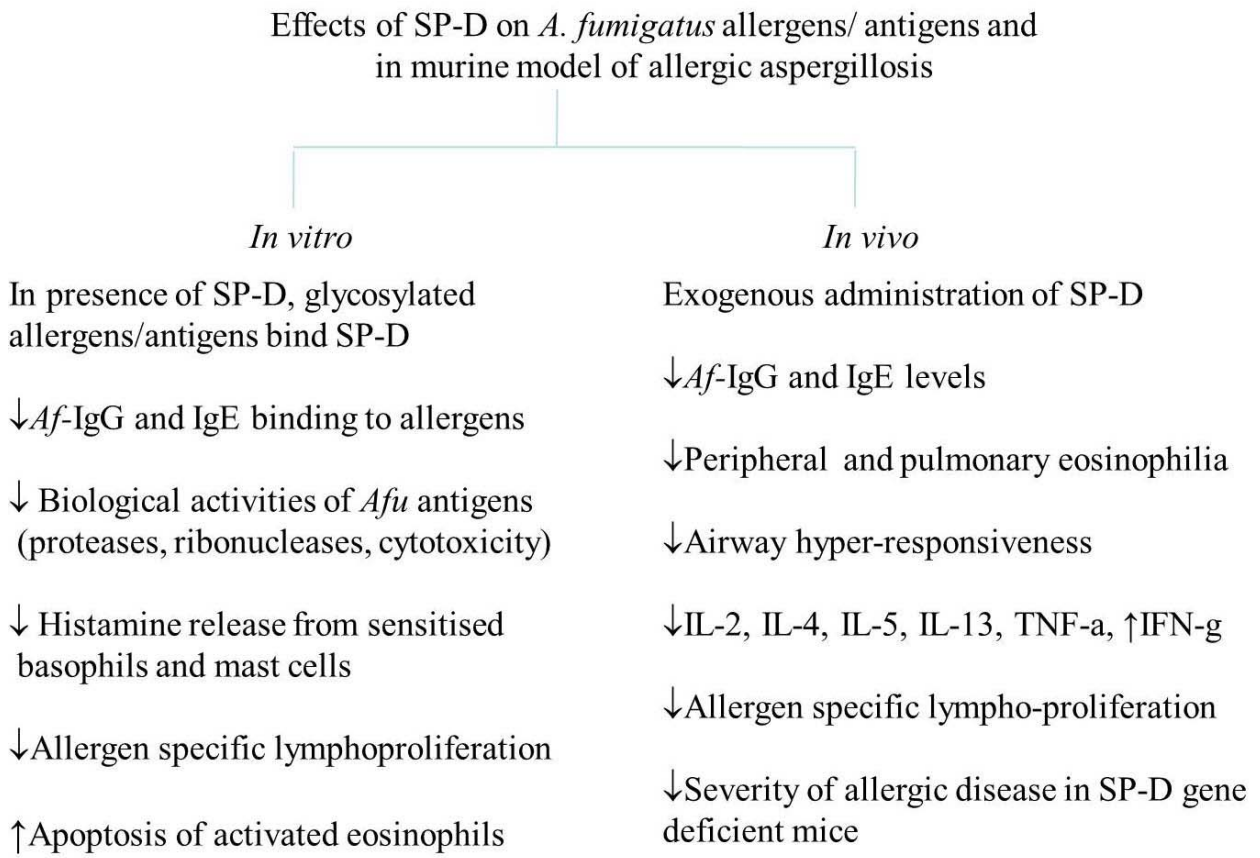

Figure 2. Effect of SP-D on *A. fumigatus* allergens/antigens and in murine model of allergic aspergillosis

showed that IL-4 selectively upregulates SP-D expression, and it may act at the level of mRNA in isolated pulmonary epithelial cells (46). Haczku *et al.,* 2006, demonstrated that mice sensitized and challenged with either *Aspergillus fumigatus* have increased SP-D levels in their lung. Administration of IL-4 and IL-13, the two Th2 type of cytokines relevant in the pathogenesis of *Aspergillus* induced allergy, increased SP-D mRNA and protein levels in the lung. STAT-6-deficient mice as well as IL-4/IL-13 double knockout mice failed to increase SP-D production upon allergen challenge. Interestingly, addition of rSP-D significantly inhibited Af-driven Th2 cell activation *in vitro* whereas mice lacking SP-D had increased numbers of CD4(+) cells with elevated IL-13 and thymus- and activation-regulated chemokine levels in the lung and showed exaggerated production of IgE and IgG1 following allergic sensitization (47). Hortobagyi *et al.,* 2008, showed SP-D mediated inhibition of TNF-alpha in murine models of *Aspergillus fumigatus* mediated allergic sensitization. Allergen-induced increase of SP-D in the airways coincided with resolution of TNF-alpha release and cell influx. SP-D-deficient mice had constitutively high numbers of alveolar mononuclear cells expressing TNF-alpha, MHC class II, CD86, and CD11b, characteristics of proinflammatory, myeloid dendritic cells that were significantly suppressed in presence of recombinant SP-D in the marrow-derived dendritic cell cultures (48).

The collectins appear to offer resistance to allergen challenge by interfering with allergen-IgE interaction, mast cell/basophil degranulation, cellular infiltration, and helper T cell polarization. They also modify the cytokine and chemokine profiles during inflammation due to infection, allergen challenge, or apoptotic and necrotic cells. The mechanisms underlying the role of SP-A and SP-D in host defense against *A. fumigatus* mediated allergies are summarized in (Figure 2). Since IgE cross-linking, histamine release, lymphocyte proliferation, persistent activated eosinophilia and antigen presentation are central steps in the development of allergic asthma, the possibility of using exogenous SP-A and SPD (or their recombinant fragments) as therapy for allergic disorders merits further investigation (2).

6. LEVELS OF SP-A AND SP-D DURING INFECTIONS AND ALLERGY

SP-A and SP-D are constitutively expressed in lungs and at various mucosal surfaces as first line of defense against any infection. Alterations in the levels of SP-A and SP-D have been reported in asthma, and pulmonary infections caused by *P. carinii* during AIDS (49).

Abnormal levels of SP-A and SP-D in the BALF have been reported in hypersensitivity lung diseases (50).

Asthmatics show increased amounts of SP-A and SP-D in BALF compared with those in controls, and serum SP-D levels for two allergic patients have been shown to decrease following corticosteroid therapy (51). Recently, serum SP-D level has been reported to be significantly higher in allergic patients than in controls (mean serum SP-D concentration: 62.7 ng/ml in allergic patients vs. 49.5 ng/ml in non-allergic controls). In addition, baseline serum SP-D appeared to be an independent predictor for the magnitude of the late asthmatic response after allergen challenge (52).

SP-A and SP-D also appear in the circulation in specific infections. High serum concentrations of SP-A in usual interstitial pneumonia compared with non-specific interstitial pneumonia is a good diagnostic marker. *P. carinii* pneumonia is associated with raised levels of alveolar SP-A and SP-D, probably as a result of increased expression and accumulation of these collectins. The synthesis and secretion of both collectins increase with acute injury and epithelial activation (53). It could be attributed to type II cell hyperplasia and/or greater synthesis of these collectins, combined with a breakdown of epithelial barrier due to lung injury, fibrosis, and exaggerated inflammation.

Detection of SP-A and SP-D in sera may be a useful and non-invasive new diagnostic tool for a range of infections. The successive monitoring of serum levels of SP-A and/or SP-D may predict disease activity. However, it is presently unclear if these alterations are a cause or consequence of the disease. Also, the mechanisms by which SP-A and SP-D increase in patients sera are unclear.

7. POLYMORPHISMS IN GENES ENCODING SP-A AND SP-D

Significant roles of both SP-A and SP-D in host defense against fungal pathogens have led to studies to identify polymorphisms in genes encoding SP-A or SP-D in humans and its correlation with increased susceptibility to infections. The genes encoding SP-A and SP-D are located on chromosome 10q22–q23. Functional SP-A is encoded by two highly homologous genes that are referred to as *SP-A1* and *SP-A2*, whereas the SP-D is expressed by a single gene (8). It is likely that certain polymorphisms in *SP-A* and *SP-D* may result in the production of proteins with impaired function(s), which in turn increases the likelihood for infection by fungal pathogens.

Several single-nucleotide polymorphisms (SNPs) are present in the *SP-A1*, *SP-A2*, and *SP-D*. The *SP-A* locus has been shown to be sufficiently polymorphic among various populations. Two exonic (SP-A2 G1649C and SP-A2 A1660G) and two intronic (SP-A2 T1492C and SPA1 C1416T) polymorphisms in the collagen region of *SP-A2* and *SP-A1* showed significant association with allergic bronchopulmonary aspergillosis (ABPA) patients. The patients carrying either one or both of GCT and AGG alleles of *SP-A2* had markedly higher eosinophilia, total IgE antibodies and lower FEV1 (the clinical markers of ABPA). A significantly higher frequency of AGA allele (A1660G) of *SP-A2* was observed in ABPA patients in comparison to controls. This polymorphism when existing along with a non-redundant polymorphism, SP-A2 G1649C (Ala91-Pro) resulted in a stronger association with ABPA (A1660G and G1649C) (54).

In another study in caucasian population, Vaid *et al*, 2007, observed significant association of CC genotype at position 1649 of *SP-A2* with chronic cavitary pulmonary aspergillosis (CCPA) ($x2=7.94$; $pcorr < 0.05$) but not with ABPA patients. SNPs analysed in *SP-A1* did not differ between cases and controls. The authors suggested that distinct alleles and genotypes of *SP-A2* may contribute to differential susceptibility of the host to CCPA or ABPA (55).

Genetic studies have highlighted allelic variations that can influence the quantity and mutlimericity of SP-D produced in the serum. These changes have differential effects on binding. Individuals with the Thr/Thr(11)-encoding genotype had significantly lower SP-D serum levels with predominantly the monomeric form of SP-D than individuals with the Met/Met(11) genotype with higher oligomeric forms. SP-D from the high m.w. peak bound preferentially to intact influenza A virus and Gram-positive and Gram-negative bacteria, whereas, the monomeric species preferentially bound to isolated LPS (56). However, there has been no study correlating *SP-D* polymorphisms with susceptibility to fungal infections.

8. PERSPECTIVES AND CONCLUSIONS

It is established beyond doubt that SP-A and SP-D have important roles in host defense against fungal infections and allergies. The studies so far have focused on respiratory fungal pathogens. Extrapulmonary presence of SP-A and SP-D in digestive tract mucosa, reproductive tract mucosa, and most importantly skin, which is a major target of fungal pathogens, emphasizes that these proteins may also be useful in other fungal infections. A recombinant form of SP-D has clearly shown therapeutic efficacy in animal models of both allergic and invasive aspergillosis. Such studies are very much needed for other fungal diseases. Further, with respect to application of this knowledge for the benefit of patients of aspergillosis, clinical trials testing the therapeutic efficacy of recombinant SP-D are the need of the hour.

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