Introduction

Air harbours enormous number of pathogens such as viruses, bacteria, fungi etc. Many of these pathogens can cause acute infections that are effectively cleared by the host immune system whereas some are able to establish persistent infection. The innate immune system constitutes the first line of host defence against these pathogens, where pulmonary surfactant proteins are considered to play important role in innate immunity in airways.

Pulmonary surfactant is a complex mixture of lipids (90%) and proteins (10%) that forms a thin film at the air-water interface of the alveoli reducing the surface tension at the alveolar interface, thus preventing alveolar collapse (Kishore et al. 2005). Of four surfactant proteins (SPs) (SP-A, SP-B, SP-C and SP-D), SP-A and SP-D belong to the collectin (collagen-containing C-type lectin) family. SP-A and SP-D can bind and agglutinate a wide range of microbial pathogens, and modulate host defence strategies for effective clearance of pathogens and regulating inflammatory processes of the lung.

SP-A and SP-D are hydrophilic proteins characterized by four domains consisting of: (1) N-terminal, cysteine-rich non-collagenous domain, which cross links monomeric subunits and helps in disulphide bond dependent oligomerization; (2) triple-helical Collagenous domain, which is involved in multimerising subunits, activation of immune system, binding site for the putative collectin receptors, Calreticulin/CD91; (3) trimerizing α-helical coiled-coil neck region, which is the...
nucleation point for refolding and (4) C-terminal C-type lectin domain or carbohydrate recognition domain (CRD), which binds to a range of carbohydrate, phospholipids and other self and nonself ligands. Each monomeric subunit can further assemble to yield multimers up to dodecamers in the case of SP-D. SP-A has a tulip-like appearance while SP-D can be visualised as its minimal cruciform structure under the electron microscopy (Fig. 1) (Crouch 1998; Nayak et al. 2012).

This chapter provides an overview of the various ligands on the pathogens that are recognised by SP-A and SP-D, and the effector mechanisms that are triggered by such recognition processes, which is aimed at clearing or restraining the invading pathogens at the mucosal surfaces at pulmonary as well as extrapulmonary sites.

**Fig. 1** SP-A and SP-D structure: The primary structure consists of four region N-terminal cysteine-rich region, long collagenous region, α-helical coiled neck region, and C-terminal carbohydrate recognition domain (CRD). This primary structure forms a trimer which can acquire bouquet-like structure assembled from six trimers in the case of SP-A. In case of SP-D, four trimeric units oligomerise to form cruciform dodecamer and also higher-order multimeric structures (fuzzy ball)
Protective Effects of SP-A and SP-D Against Viral Pathogens

Innate immune recognition of viruses is crucial for limiting several viral infections and its related pathogenesis. SP-A and SP-D act as soluble pattern recognition receptors (PRRs) in recognizing viral surface molecules and activating immune cells to facilitate the clearance of viral pathogens (Fig. 2).

**Influenza A Virus**

Influenza A virus (IAV) is associated with acute respiratory illness and represents an ongoing threat to human and animal health leading to substantial morbidity and mortality. Various Influenza pandemics were caused by H1NI (Spanish Flu) in 1981,

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**Fig. 2** SP-A and SP-D engage with range of pathogens, including (a) Viruses (Influenza A virus, Human Immunodeficiency virus-1, Herpes Simplex Virus, Respiratory syncytial virus, Human papilloma virus, SARS coronavirus, Rotavirus, Ebola) are shown here (b) Fungi viz. Aspergillus, Candida, Histoplasma, Cryptococcus and Coccidioides (d) Bacteria viz., Streptococcus E. Coli, Mycobacteria, Pseudomonas, K. Pneumonia, Staphylococcus, and (e) Parasites viz. P carinii and N. brasiliensis. Here octademamer of SP-A molecule and fuzzy ball multimeric SP-D molecule has been shown (c)
H2N2 (Asian Flu) in 1957, H3N2 (Hong Kong Flu) in 1986, and A(H1N1)pdm09 (Swine Flu) in 2009. (Taubenberger and Morens 2009; Tripathi et al. 2015; Hsieh et al. 2018a, b). The worst pandemic recorded was in 1918 killing up to 50 million people worldwide (Johnson and Mueller 2002), approximately 675,000 deaths in the US alone (Taubenberger and Morens 2006).

Most IAV subtypes possess two membrane-bound surface glycoproteins expressing N-linked oligosaccharides, Hemagglutinin (HA) and the neuraminidase (NA). HA attaches the virus to the cell with attaching terminal sialic acid residues on glycoproteins or glycolipids to initiate the infectious cycle, whereas NA cleaves terminal sialic acids to release virions (Kosik and Yewdell 2019). There are 16 HA and 9 NA in different subtypes of IAV circulating in humans and animals. When a subtype with a new HA or NA variant appears in the human population by genetic reassortment, it usually causes a pandemic because there is no pre-existing immunity against the new virus. HA and NA can contain mixture of branched structures terminating in the sugar mannose, complex branched structures terminating in galactose and/or N-acetyl-galactosamine (GalNAc) or even hybrid-type oligosaccharides (Basak et al. 1981; Ward and Dopheide 1981). Oligosaccharides attached to the globular head of the glycoprotein display considerable variations in number as well as location. These viruses have undergone antigenic drift possibly through addition of glycans to the HA (Sun et al. 2011; Abe et al. 2004). The numbers of N-linked glycosylation sites on the head of HA increases after their emergence in the human population in case of pandemic and seasonal H1N1 and H3N2 episodes (Tate et al. 2014).

Innate immunity plays an important role in mounting initial response against IAV infection. N-linked glycans present on the surface of IAV, are detected by soluble humoral factors of the innate immune system mounting anti-IAV activities against virions and virus-infected cells (Tate et al. 2014). SP-A and SP-D contribute to initial protection against IAV; SP-D seems to be the most potent due to its specific mode of binding to viral carbohydrates (Hartshorn et al. 1994). SP-A inhibits IAV by binding to HA in a calcium-dependent manner through its sialyted carbohydrates present in the lectin domain, and thus, is classified as γ-inhibitor (Benne et al. 1995; Hartshorn et al. 1997a, b). However, SP-D-mediated inhibition is via binding to high-mannose oligosaccharides on HA and is calcium-dependent, thus it is recognised as β-type inhibitor of IAV (Hartshorn et al. 1993a, b; White et al. 2004). SP-A exhibits greater hemagglutination activity against IAV subtypes with reduced number of glycosylation on HA molecule (Hartshorn et al. 1997a, b). Glycosylation of HA at N165 (glycosylation position at 165 amino acid residue) was found to be important for the neutralization of IAV by SP-D (Reading et al. 1997).

SP-A and SP-D show effectiveness in dealing with infectivity in a cooperative manner; SP-A, which is largely surfactant-associated (lipid associated) acts primarily at the surfactant interface, while SP-D, being largely a soluble (pulmonary secrections) molecule shows its potency in the fluid phase of airways (Hartshorn et al. 1994). The Ca²⁺-dependent binding of SP-A to IAV strain A/X31 takes place through NA (Malhotra et al. 1994). Additionally, SP-A acts as an opsonin for the phagocytosis of IAV by alveolar macrophages. This opsonisation capability of SP-A was
due to its sialic acid residues, thus helping in the removal of virus (Benne et al. 1997). SP-D does not seem to act as an opsonin for the phagocytosis of IAV (Benne et al. 1997) but strongly neutralises and aggregates viral particles by binding to high mannose oligosaccharide residues near the sialic acid binding sites of HA, thus, inhibiting the attachment of IAV to host cells. These inhibitory effects are mediated by the calcium-dependent carbohydrate-binding property of SP-D on viral HA and NA (White et al. 2004). SP-D also has the ability to bind high mannose type II glycans on some IAVs (Qi et al. 2011).

Aggregation of IAV by surfactant proteins is an important neutralization mechanism that prevents viral particles from infecting target host cells, in addition to enhancing virion phagocytosis by macrophages to clear IAV more efficiently. The extended cruciform structure of SP-D helps in bridging interactions with multiple viral particles, leading to the formation of large viral aggregates (Brown-Augsburger et al. 1996). Aggregation of viral particles by SP-D possibly reduces the count of infectious viral particle and subsequently enhances clearance by mucociliary and phagocytic mechanisms. This viral aggregation by SP-D enhanced neutrophil binding of IAV and associated respiratory burst response against them (Hartshorn et al. 1994) (Fig. 3).

IAV infection can induce impaired responsiveness leading to dysfunction in respiratory burst, degranulation and intracellular bacterial killing by phagocytic cells, thereby increasing host’s susceptibility to bacterial superinfections which is

Fig. 3 Biological activities of SP-A and SP-D: Alveolar type-II cells in lungs secrete SP-A and SP-D which can bind, agglutinate and neutralize wide range of microbial pathogens including viruses, bacteria, fungus and parasites. SP-A (bouquet-like structure) and SP-D (cruciform structure) are capable of modulating host defence strategies for effective clearance of pathogens by cytokine production and ROS generation by effector cells such as macrophages (Mφs), dendritic cells (DC), neutrophils, natural killer cells (NK) and lymphocytes. Both SP-A and SP-D are capable of enhancing opsonization, phagocytosis and eventually intracellular killing by innate immune cells such as alveolar macrophages (Mφs) and dendritic cells (DC). This helps in clearing or restraining the invading pathogens at the mucosal surfaces at pulmonary as well as extrapulmonary sites.
an important cause of morbidity and mortality during IAV epidemics (Kilbourne 1987). Hartshorn et al. have reported the protective effect of SP-D against bacterial superinfection in vivo, which was possibly due to opsonisation of the virus with SP-D (Hartshorn et al. 1994). SP-D strongly increased neutrophil respiratory burst response towards IAV in vitro, thus, demonstrating a proinflammatory response (White et al. 2005). In an experiment involving pre-incubation of neutrophils with SP-D, the H$_2$O$_2$ response to IAV was found to be reduced, whereas by preincubating IAV with dodecameric SP-D, H$_2$O$_2$ response to the virus increased quite strongly. This suggests that during preincubation with SP-D, possibly the inhibitory receptors of neutrophils were occupied by SP-D and thus, prevented the virus to bind with neutrophils. Thus, depending on whether SP-D is first incubated with IAV or neutrophils, SP-D can either increase or reduce respiratory burst responses of neutrophils upon exposure to IAV. Similarly, preincubation of IAV with SP-A increased neutrophil uptake of IAV and stimulated H$_2$O$_2$ generation. However, SP-A and SP-D together caused a reduction in H$_2$O$_2$ responses compared with SP-D alone (White et al. 2005). Human neutrophil peptides (HNPs) were subsequently found to bind SP-D and modify its interactions with IAV. Though HNPs were found not to inhibit HA activity of IAV but strongly interfered with neutralizing activity of SP-D by directly binding to its CRD. This binding of SP-D to HNP was not affected by the degree of multimerization of SP-D and was not calcium dependent (Hartshorn et al. 2006).

SP-D binding to pandemic IAV subtype (pH1N1) can modulate its replication in the lower respiratory tract (Hawgood et al. 2004). This was assessed by comparing chimeric IAV with HA segment of 1918 (H1N1), 1957 (H2N2), 1968 (H3N2) or 2009 (H1N1) with seasonal IAVs. HA of pandemic viruses showed lower binding for SP-D, whereas HA of seasonal influenza strain exhibited strong in vitro binding to SP-D with little lung pathology in the infected mice (Qi et al. 2011). The pandemic strains derived from zoonotic sources have fewer N-linked glycosylation sites (Bush et al. 1999; Hensley et al. 2009; Kash et al. 2006), which probably explains less SP-D binding, and hence, significant pathology in the lower respiratory tract. H1 and H3 subtypes that causes seasonal epidemics express more glycans on the head of their HA, bind SP-D efficiently, causing effective viral inhibition. The level of CCL2 and CSF3 chemokine expression were found to be lower with high SP-D binding activity thus exhibiting little lung pathology in infected mice (Qi et al. 2011; Hsieh et al. 2018a, b).

Human H1-containing IAV has two or more glycosylation sites, suggesting that the host specificity of IAV may also depend on the characteristics of HA glycosylation (Inkster et al. 1993). In a experiment where susceptibility of different H1N1 viruses (including strains of A(H1N1) pdm) were assessed towards the anti-viral activities of human SP-D, it was found that seasonal H1N1 viruses demonstrated variations in their sensitivity towards SP-D as the number and location of N-glycosylation sites on HA varied, whereas most A(H1N1) pdm viruses carried a single N-glycosylation site (Asn104) on the head of HA and found resistant to the antiviral activities of SP-D (Job et al. 2010). Thus, γ-inhibitors like SP-A may respond better in combating against strains that are resistant to SP-D (Stevens et al. 2018).
Glycosylation on the HA appears to increase over time in strains that establish themselves in the human population (White et al. 2004). Interestingly, a recent study has shown that the anti-viral activity of isolated lectin domains of SP-D can markedly increase for seasonal strains of IAV by modifying specific residues around the saccharide binding pocket. The combined change of D325A (aspartic acid 325) along with R343V (arginine 343) in the neck and CRD regions of human SP-D showed neutralizing activity similar to full length SP-D dodecamers for seasonal IAV (Hartshorn et al. 2010; Crouch et al. 2011). At the same time, mutated versions of SP-D (D325A + R343V mutant neck and CRD; in the mutant neck and CRD region the penultimate mannose in the chain binds in the lectin site) showed enhanced binding to the reduced number of mannosylated glycans present on the HA of these strains, and thus, were able to inhibit pandemic IAV (Hsieh et al. 2018a, b). Pigs are considered to be important intermediates in the emergence of new IAV strains due to reassortment of viral genes derived from human, avian, or porcine influenza viruses. Hemagglutination inhibition activity by Porcine SP-D was found to be related to the terminal sialic acids (SAs) present on the N-linked oligosaccharide in the CRD region. The SA-mediated interaction of SP-D can be observed only in pigs as they have unique glycosylation profile of SP-D compared to ducks and swine viruses where there are no conserved glycosylation sites at the tip of their HA (Van Eijk et al. 2003). The carbohydrates of porcine SP-D is uniquely sialated with α (2,6)-linked SA, in contrast to SP-A, which contains both α (2,3)- and α (2,6)-linked SAs on its N-linked carbohydrate as confirmed through lectin staining and by cleavage with linkage-specific sialidases (Van Eijk et al. 2004). Thus, an N-linked CRD glycosylation provides interactions with the SA-binding site of IAV and an enhanced interaction with IAV glycans were favoured by tripeptide loop (presence of a unique tripeptide extension of the long loop in the CRD of SP-D, referred to as “326 GSS”) at the lectin-binding site. N-glycosylated neck-CRD fragment of porcine SP-D (RpNCRD) unlike the human analogue RhNCRD, demonstrated potent neutralizing activity against pandemic A/Aichi/68 (H3N2) (Van Eijk et al. 2018).

In 1957 pandemic, a novel H2N2 subtype was formed when H2 virus re-assorted with the circulating H1N1. Thus, considering the fact that a low pathogenicity avian influenza virus (LPAIV) subtype can re-assort leading to emergence of new pandemic, activities of two recombinant human SP-D forms against LPAIV strains (H2N1, H5N1, H6N1, H11N9) were assessed. It was found that these avian IAV strains, containing H2, H5, H6 and H11 were not susceptible to lung SP-D activity due to presence of predominantly complex glycans at the key glycosylation sites (Parsons et al. 2020).

A recombinant form of human SP-D (rfhSP-D), containing homotrimeric neck and CRD regions was used to test if rfhSP-D interfered with the ability of pH1N1 and H3N2 IAV subtypes to infection lung epithelial cell line (A549). rfhSP-D could inhibit IAV entry, down-regulate viral replication (M1) and associated pro-inflammatory response. mRNA levels of TNF-α, IFN-α, IFN-β and IL-6 were downregulated during the initial stage of IAV infection with rfhSP-D (Al-Ahdal et al. 2018). However, in similar assays, a recombinant fragment of human SP-A Biological Activities of SP-A and SP-D Against Extracellular and Intracellular Pathogens
composed of trimeric neck and CRD (rfhSP-A) enhanced the infection, as evident from enhanced viral replication (higher expression of M1 genes) as well as increased expression of TNF-α, IL-12, IL-6 and IFN-α (Al-Qahtani et al. 2019). Interestingly full length native SP-A was able to downregulate the expression of M1 genes, suggesting that a complete SP-A molecule is required for protection against IAV (Al-Qahtani et al. 2019). These two studies highlighted that SP-A and SP-D are quite distinct in their ability to negate IAV infection. SP-A seems to require its intact structure including collagen region as opposed to SP-D where rfhSP-D was found to be a self-sufficient entity in dealing with IAV infection.

**Human Immunodeficiency Virus-1 (HIV-1)**

HIV-1, which is responsible for acquired immunodeficiency syndrome (AIDS), remains a leading cause of global morbidity. SP-A and SP-D can be found at various mucosal locations such as lungs, oral cavities, gastro-intestinal tract, genitourinary tract as we all as in ovar, vagina and cervix etc. (Tino and Wright 1996; Madsen et al. 2000; Leth-Larsen et al. 2004; Nayak et al. 2012; Madhukaran et al. 2016); all are also important sites for HIV-1 transmission. Thus, the role of SP-A and SP-D in HIV-1 pathogenesis and transmission has been examined.

The glycosylated HIV-1 envelope protein, gp120, plays an important role in pathogenesis of AIDS. SP-D binds gp120 in a calcium-dependent manner; native dodecameric SP-D binds HIV-1 gp120 more strongly than native trimeric SP-D (Meschi et al. 2005a, b). SP-D possibly binds to the centre of the oligomerized gp120 molecule via glycans located in the V3 loop (Madsen et al. 2013). SP-D can agglutinate both gp120 and intact inactivated HIV Bal particles in the presence of calcium (Madsen et al. 2013). SP-A also binds with HIV-1 gp120 via high mannose oligosaccharides efficiently neutralize both R5 and X4 strains of HIV (Gaiha et al. 2008). Both SP-A and SP-D could inhibit infection of CD4+ T cells by two different strains of HIV-1, BaL and IIIB (Gaiha et al. 2008; Madsen et al. 2013). SP-D enhanced binding to HIV-1 to immature monocyte-derived dendritic cells as well as transfer from DCs to T cells *in vitro* (Madsen et al. 2013).

Bronchoalveolar lavage of HIV-1-infected individuals showed increase level of SP-A, which was found to enhance the attachment of *Mtb* to alveolar macrophages. This possibly explains the increased risk of tuberculosis during HIV-1 infection (Downing et al. 1995). The ability of native human SP-D and rfhSP-D to bind gp120 was assessed in addition to viral inhibition in three different targets, Jurkat T cells, U937 monocytic cells and PBMCs. Both native SP-D and rfhSP-D inhibited HIV-1 entry efficiently and blocked CD4 and gp120 interaction. rfhSP-D also significantly suppressed HIV-1 induced cytokine storm and phosphorylation of kinases p38, AKT and Erk1/2 in HIV-1 induced immune activation *in vitro* suggesting the potential use of rfhSP-D for immunotherapy against viral infection (Pandit et al. 2014). Mucosal biocompatibility of rfhSP-D has been assessed *ex vivo* where it showed inhibition in HIV-1 transfer across the vaginal tissues and downregulation of NF-κB.
and mTOR transcripts while the expression of tight junctions and cytoskeleton genes were upheld (Pandit et al. 2019).

A direct protein-protein interaction between rhSP-D and dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) through their C-type lectin domains has been observed (Dodagatta-Marri et al. 2017). SP-D and DC-SIGN showed competitive binding behaviour towards immobilized HIV-1 gp120, possibly suggesting SP-D and gp120 may occupy same sites on DC-SIGN as revealed through in silico analysis. rhSP-D also inhibited cis-transfer of DC-SIGN-bound HIV-1 to T cells in culture.

**Herpes Simplex Viruses (HSV)**

Herpes viruses are large family of DNA viruses, which are known to cause lytic infection in permissive cells. HSV have co-evolved with human for million years; these viruses can establish a latent infection and persist in humans for the lifetime. Pathogenic effects occur when the host acquires genetic defects in the immune responses or if the viral load becomes too high (Kurt-Jones et al. 2017). Herpes simplex virus type 1 (HSV-1) is a typical human-restricted pathogen with higher frequencies in developing countries (Su et al. 2016) and is responsible for causing a lifelong latent infection in neurons; it can get reactivated causing lytic infection mostly in epithelial or mucosal cells (Nicoll et al. 2012; Roizman and Whitley 2013). Herpesvirus, compared to other enveloped viruses, needs the combined effort of multiple glycoproteins and multiple host receptors to infect, depending on the cell type (Watson et al. 2019). SP-A binds HSV-1 infected Hep-2 cells which can be inhibited by heparin, but not by mannose polysaccharide. Heparin could also dissociate cell bound SP-A, suggesting the role of polyanionic oligosaccharide in SP-A-HSV-1 interaction (van Iwaarden et al. 1992). SP-A has been shown to act as an opsonin in the phagocytosis of HSV-1 by alveolar macrophages, suggesting its important anti-viral properties (van Iwaarden et al. 1990).

**Respiratory Syncytial Virus (RSV)**

Respiratory syncytial virus (RSV) is a major respiratory pathogen in infants and young children. RSV causes an upper respiratory tract infection that may progress to acute bronchiolitis or interstitial pneumonia (LeVine et al. 1999a, b). Almost every child suffers from a mild upper respiratory tract infection by RSV but morbidity and mortality are related to lower respiratory tract involvement only (Griese 2002). Heavily glycosylated G-protein present in the RSV envelope aids in attachment with the host cells. This G protein contains several sites for N-linked glycosylation and almost 30% of its amino acids are serine and threonine residues (Griese 2002).
The potential role of SP-A in RSV infection has been examined via SP-A-deficient (SP-A−/−) mice. SP-A−/− mice had increased numbers of RSV plaque-forming units in their lungs than in SP-A+/+ wild type mice. Infiltration of neutrophils and proinflammatory cytokines such as -TNF-α and IL-6 were also enhanced in lungs of SP-A−/− than in SP-A+/+ mice after RSV administration. Thus, SP-A played important role in pulmonary clearance of RSV in vivo which was associated with an enhanced respiratory burst by the alveolar macrophage (LeVine et al. 1999a, b). Daily levels of surfactant proteins in bronchoalveolar lavage (BAL) fluid from ventilated infants with RSV infection and in a ventilated surgical patients (control) were investigated; concentrations of SP-A and SP-D per ml of BAL fluid were found to be significantly reduced in children with RSV infection, suggesting that the reduction of surfactant proteins may contribute to the respiratory failure in RSV patients (Kerr and Patron 1999).

G protein from RSV (human, A2 strain) interacts with both native and rhSP-D via the CRD region of SP-D. rhSP-D was able to inhibit viral replication in the lungs (Hickling et al. 1999). The binding of SP-A to RSV G-protein was found to be inhibitable by both EDTA and mannan, suggesting the involvement of carbohydrate moiety of the G-protein interacting through the carbohydrate recognition domain of the SP-A (Hickling et al. 2001).

**Human Papillomavirus (HPV)**

HPV is the most common viral infection of the reproductive tract. Most HPV infections get cleared by cell-mediated immunity within a year, but sometimes, it can result in persistent infection with an increased probability of progression into invasive cancers (Stanley 2010). In an attempt to assess the impact of SP-A during the early events of sexual HPV transmission, a study was conducted in wildtype C57BL/6 mice. SP-A-mediated opsonization of HPV16-PsVs (pseudovirions) and significantly increased HPV16-PsVs uptake by eosinophils, neutrophils, monocytes, and macrophages in the female reproductive tract (Ujma et al. 2019).

**SARS Coronavirus (SARS CoV)**

Severe acute respiratory syndrome (SARS) outbreak in 2003 attributed to pulmonary infection with a novel coronavirus (SARS-CoV) infecting more than 8000 individuals and caused approximately 10% mortality (LeDuc and Barry 2004). SARS-CoV infects human hosts through the respiratory system and it interplays with the host innate immune system in the lung alveoli. The spike protein (S-protein) that interacts with the host and shows high degree of glycosylation was found to interact with SP-D (Leth-Larsen et al. 2007). The effect of S-protein binding to macrophages and DCs was also investigated. Plasma SP-D levels were significantly
elevated in SARS-type pneumonia (Wu et al. 2009). SP-A and SP-D were found to bind with HCoV-229E (a common non-SARS human CoV) and pre-treatment of HCoV-229E with SP-A or SP-D inhibited viral infection of 16HBE, bronchial epithelial cells. SP-D showed better effectiveness in inhibiting infection of 16HBE cells whereas SP-A was found more effective at inhibiting infection of alveolar macrophages (Funk et al. 2012).

**Other Viruses**

Vaccinia virus that is principally transmitted between humans by aerosol droplets, interacts with SP-D directly through A27 viral protein which lacked glycosylation. When challenged with the virus, SP-D−/− mice incurred greater mortality compared to SP-D+/+ wild type mice, suggesting SP-D participating in host defense (Perino et al. 2013).

Ebola virus binds human as well as porcine SP-D through its glycoprotein. This interaction enhanced pseudoviral infection in pulmonary cells (A549) suggesting the possible role of SP-D in enhancing viral spread (Favier et al. 2018). In case of pulmonary infection mediated by adenovirus, SP-A showed enhancement in viral clearance inhibiting lung inflammation (Harrod et al. 1999).

Rotaviruses are non-enveloped viruses having a glycoprotein VP7 which forms the smooth surface of the virion from where VP4, an outer capsid protein, protrudes as spikes. Bovine SP-D was able to bind with VP7 glycoprotein of rotavirus strain NCDV and displayed neutralizing activity that was dependent upon glycosylation of VP7 (Reading et al. 1997).

**Bacterial Pathogens**

Despite the fast-acting intracellular signalling mechanisms induced by PRRs, microbial pathogens have evolved countermeasures to thwart innate immunity in order to survive and proliferate in the host. It is now clear that evolution has selected a conserved set of anti-microbial peptides as well as Pattern Recognition Receptors (PRRs) that initiate signals as a first line of defence against invading pathogens. If a bacterial pathogen is able to successfully evade destruction by anti-microbial peptides, most host organisms have evolved a second line of defence centred on microbial recognition of PAMPs by PRRs and the subsequent production of cell-intrinsic immune mechanisms and/or recruitment of immune cells. In response to these challenges, many bacterial pathogens have modified the molecular structure of their PAMPs, thereby avoiding immune detection through stealth and evasion. For example, lipopolysaccharide (LPS) is a ubiquitous component of Gram-negative bacteria cell wall, and is composed of diverse O-antigen side chains that are anchored to the outer leaflet of the bacterial envelope by Lipid A. Importantly, Lipid A is directly
recognized by the mammalian TLR4-MD2-CD14 PRR complex to activate innate immune signalling pathways.

**Gram Positive Bacteria**

There are several Gram-positive bacteria which can cause respiratory distress in adults leading to pulmonary inflammation, like *Staphylococcus aureus* and *Streptococcus pneumonia* (Ewig and Torres 1999; Goel et al. 1999). Pneumococci are one of the leading causes of septicemia, meningitis, and lower respiratory tract infections in humans, where *S. pneumoniae* produces two hemolysins contributing to the pathogenicity (Navarre and Schneewind 1999). Group A streptococci are responsible for pharyngitis, impetigo, rheumatic fever, and acute glomerulonephritis, whereas Group B streptococci can cause neonatal sepsis and meningitis in developed countries (Navarre and Schneewind 1999).

The cell wall of Gram-positive bacteria is composed of a peptidoglycan (PepG) macromolecule that is attached with several other accessory molecules such as teichoic acids, teichuronic acids, polyphosphates, or carbohydrates. About 40% weight of the bacterial cell wall comprises of multiple layers of cross-linked PepG (Shockman and Barrett 1983). PepG and lipoteichoic acid (LTA) are capable of inducing inflammatory response and can also initiate septic shock (De Kimpe et al. 1995). SP-A was found to bind with a wide range of Gram-positive bacteria such as *Staphylococcus aureus* (van Iwaarden et al. 1990; Kuan et al. 1992a, b; Greertsma et al. 1994; McNeely and Coonrod 1994a, b; Manz-Keinke et al. 1992), Group A *Streptococcus* (Ohmer-Schröck et al. 1995), Group B *Streptococcus* (LeVine et al. 1997, 1999a, b), *Streptococcus pneumonia* (Kuronuma et al. 2004; Sano et al. 2007) mostly either with the PepG or with LTA via CDRs and also enhanced uptake by phagocytosis. SP-D could bind with *Bacillus subtilis*, *Staphylococcus aureus*, Group B *Streptococcus* and *Streptococcus pneumonia* (van de Wetering et al. 2001; Hartshorn et al. 1998; Shepherd 2002; Jounblat et al. 2004). Hartshorn et al. (1998) have shown that SP-A and SP-D both were able to increase calcium-dependent uptake of *Streptococcus pneumoniae*, and *Staphylococcus aureus* by neutrophils. The aggregation capability was influenced by the degree of multimerization of SP-D (Hartshorn et al. 1998). The N-terminal and/or collagen domains of SP-D contribute to the enhanced bacterial binding and aggregating activities since multimeric structure was found to be important for SP-D efficacy (Hartshorn et al. 2002). rfhSP-D (consisting of the head and neck regions of the native molecule) could bind with several strains of *Streptococcus pneumoniae* where the strength of binding varied between different capsular serotypes, but was not able to enhance killing of pneumococci by human neutrophils (Jounblat et al. 2004).

SP-A gene-deficient (SP-A<sup>−/−</sup>) mice showed increased susceptibility to airway challenge of group B streptococci, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* (LeVine et al. 1997, 1998, 1999a, b). Although SP-A binds to both *Staphylococcus aureus* and enhances its phagocytosis by monocytes, it fails to
stimulate intracellular killing and production of reactive oxygen intermediates (Greertsma et al. 1994). SP-A can also enhance scavenger receptor A (SR-A)-mediated uptake of *Streptococcus pneumoniae* (Kuronuma et al. 2004). It can also bind di-saturated phosphatidylglycerol of *Mycoplasma pneumoniae* and inhibit its bacterial growth in vitro (Piboonpocanun et al. 2005).

**Gram-Negative Bacteria**

Gram-negative bacteria contain lipopolysaccharide (LPS), a cell wall-resident PAMPs, which allows PRR-containing phagocytes to recognize bacterial invasion and mount innate immune responses. LPS consists of a hydrophobic membrane anchor portion (lipid A) of relatively conserved core oligosaccharide coupled to a distal polysaccharide (O-antigen) that extends from the bacterial surface (Raetz and Whitfield 2002). O-specific chain consists of up to 50 repeating oligosaccharide units of 2–8 monosaccharide components which differs between strains. *Haemophilus influenzae*, for example, contains O-antigen structures that closely resemble human glycosphingolipids due to the presence of N-acetylenuraminic acid or L-fucose (Moran et al. 1996). Lipid A portion is responsible for the immunostimulatory activity of LPS (Matsuura 2013).

SP-A and SP-D bind LPS of Gram-negative bacteria and enhance their phagocytosis by alveolar macrophages (Pikaar et al. 1995). Lipid A moiety of smooth strains of Gram-negative bacteria contains O-antigen whereas the rough strains lack the O-antigen (Van Iwaarden et al. 1994). Binding of SP-A to LPS of *E. coli* appears dependent on Ca²⁺ but it is not affected by mannan and heparin, or by deglycosylation of the SP-A. SP-A associates via the lipid A moiety of rough LPS, but not with smooth LPS (Van Iwaarden et al. 1994). Lectin blot analysis demonstrated specific binding of SP-D to LPS from several strains of enteric Gram-negative bacteria including *E. coli*. SP-D can agglutinate *E. coli* in a calcium- and carbohydrate-dependent manner (Kuan et al. 1992a, b).

*Klebsiella pneumoniae* is an anaerobic, Gram-negative bacterium indigenous to the oral cavity and intestinal tract; however, it often causes severe respiratory and urinary tract infections. *K. pneumoniae* strains of the K2 capsular serotype are usually highly virulent in mice; the capsule is recognized by mannose receptor (MR) present on macrophages (Kabha et al. 1995). SP-A acts as an opsonin and enhances phagocytosis of K21a (low virulent, capsule containing Man α1 Man sequences) serotypes of *K. pneumoniae* by alveolar macrophages via MR (but not of K2) (Kabha et al. 1997).

The binding of native human SP-D purified from lung lavage as well as a recombinant fragment of human SP-D (rhhSP-D) composed of trimeric neck and CRD regions, to bind LPS from various Gram-negative bacteria (*E. coli, K. pneumoniae* and *Ps. aeruginosa*) has been examined by Kishore et al. (1996a, b). rhSP-D was able to bind to the LPS similar to native SP-D (Kishore et al. 1996a, b). SP-A is also able to aggregate *Hemophilus influenza* type A and induce phagocytosis by
macrophages (McNeely and Coonrod 1994a, b). SP-A brings about NO-mediated killing of *M. pulmonis* by alveolar macrophage (Hickman-Davis et al. 1998). In addition, SP-A deficiency modifies surfactant aggregate content and lowers the inhibition resistance of LA surfactant *in vitro* compared with experiments involving congenic normal mice (uninfected B6 SP-A<sup>−/−</sup> versus B6 mice) (Hickman-Davis et al. 2007). Bacteriostatic effect of SP-A on *Mycoplasma pneumoniae* was found to be mediated by binding to its surface disaturated phosphatidylglycerols (Ledford et al. 2009).

**Mycobacteria**

Mycobacteria range from environmental, non-pathogenic species, to opportunistic pathogens that can infect immuno-compromised hosts (Saelens et al. 2019). Mycobacterium genus includes strict pathogens, potential or opportunistic pathogens, and non-pathogenic, saprophytic species. These are the causative organisms for most important diseases including tuberculosis (TB), leprosy, Buruli ulcer, and pulmonary non-tuberculous mycobacterial (NTM) disease (Forbes et al. 2018).

**Mycobacterium tuberculosis**

Tuberculosis caused by *Mycobacterium tuberculosis* (*Mtb*) is an ancient disease which co-evolved compatibly with humans. TB has now emerged as a major global health concern affecting almost one third of global population (Ferluga et al. 2020). Alveolar macrophages are the initial sites of infection with *Mtb* and innate immune arm in the lungs plays an important role in controlling the inhaled pathogen. SP-A enhances phagocytosis of the virulent *Mtb* Erdman strain by alveolar macrophages (Gaynor et al. 1995). SP-A shows high affinity binding to attenuated *Mtb* strain (H37Ra) with a $K_d$ value of $1.9 \times 10^{-9}$ M in a calcium dependent manner and also enhances adherence of bacilli to mouse alveolar macrophages (Pasula et al. 1997). Deglycosylated SP-A exhibits minimal binding to *Mtb* (Pasula et al. 1997) and does not enhance the adherence of *Mtb* to monocytes (Gaynor et al. 1995), indicating the importance of sugar moieties during the interaction. In spite of SP-A being helpful in aggregation and phagocytosis of *Mtb*, SP-A appears to suppress reactive nitrogen intermediate production, a likely mechanism through which *Mtb* possibly counter-acts the cytotoxic response of alveolar macrophages (Pasula et al. 1999). Sidobre et al. (2000) have identified mycobacterial lipoglycans as putative ligands for human SP-A, which requires both the terminal mannose residues and the aglycone moiety for optimal binding. In addition, lipomannan and mannosylated lipoarabinomannan (ManLAM) are also SP-A ligands (Sidobre et al. 2002). Cell surface molecule, Apa (alanine- proline-rich antigenic) glycoprotein, was found to be another potential adhesion molecule on *Mtb* that can interact with human SP-A (Ragas et al. 2006).
SP-D has also been shown to bind and agglutinate virulent \textit{Mtb} Erdman strain and reduce uptake of bacilli by human macrophages (Ferguson et al. 1999; Ferguson and Schlesinger 2000). This binding of SP-D to \textit{Mtb} is calcium- and sugar-dependent. SP-D shows minimal binding to the avirulent \textit{M. smegmatis}. Lipoarabinomannan (LAM) is a major surface lipoglycan of \textit{Mtb} (Schlesinger et al. 1994) and the binding of SP-D to Erdman lipoarabinomannan seems to be mediated by the terminal mannosyl oligosaccharides (Ferguson et al. 1999).

The collagen region of SP-D seems to be required for enhanced binding to \textit{Mtb} and is essential for agglutination (Ferguson et al. 2002). Dodecameric SP-D, but not rfhSP-D, causes agglutination of \textit{Mtb}, confirming that the multivalent nature of SP-D is essential for agglutination. SP-D binds and masks the terminal mannose caps of Man LAM of \textit{Mtb}. It is also capable of limiting the intracellular growth of bacilli inside the macrophages by enhancing phagosome-lysosome fusion (Ferguson et al. 2006).

During inhalation, respiratory pathogens are exposed to shear forces as they travel to the terminal airways. Interaction of SP-A and SP-D with virulent (H37Rv) and attenuated (H37Ra) \textit{Mtb} strains has thus been investigated under shear conditions to mimic the dynamic lung microenvironment (Hall-Stoodley et al. 2006). SP-A binds both strains well nearly 4–5 times better under shear conditions, compared to static conditions and BSA control (Hall-Stoodley et al. 2006). Covalently surface-immobilised SP-D binds virulent \textit{Mtb} and \textit{Mtb} ManLAM-coated beads feebly and agglutinates bacilli poorly, compared to when \textit{Mtb} is pre-incubated with soluble SP-D, which causes efficient bacterial agglutination, highlighting the importance of SP-D conformation in its biological functioning (Hall-Stoodley et al. 2006). In a study to examine the effect of SP-A on MR expression on human monocyte-derived macrophages, SP-A was found to specifically regulate surface expression of functional MR, without altering complement receptor (CR) expression. Monocyte-derived macrophages cultured on an SP-A substrate demonstrated enhanced pinocytosis of mannose BSA and phagocytosis of \textit{Mtb} lipoarabinomannan-coated microspheres (Beharka et al. 2002). Antibodies against the SP-A-binding neck domain (\(\alpha\)-SP-R210n) also inhibited \textit{Mtb} induced proliferation of lymphocytes and secretion of IFN-\(\gamma\) and TNF-\(\alpha\) is possibly through enhanced production of IL-10 and TGF-\(\beta\)1 (Samten et al. 2008).

\textit{Mycobacterium avium}

Nontuberculous mycobacteria (NTM) such as \textit{Mycobacterium avium} are slowly growing pathogens in natural and artificial environments. NTM may result in colonization, infection, and causing diseases that can be detected in the respiratory and gastrointestinal tracts or on the skin of healthy individuals (Griffith et al. 2007; Brown-Elliott et al. 2012; Forbes et al. 2018). \textit{M. avium} complex (MAC) includes two species, \textit{M. avium} and \textit{M. intracellularare}. Pulmonary infection caused by the MAC can occur in immunocompetent hosts; disseminated infections usually occur in people living with HIV-1. The most common presentations of MAC lung...
Infections in immunocompetent hosts are TB-like apical fibrocavitary disease or interstitial nodular infiltrates and bronchiectasis (Griffith et al. 2007; Brown-Elliott et al. 2012). SP-A and SP-D bind *M. avium* in a calcium-dependent and independent manner, respectively (Kudo et al. 2004). The mutated form of SP-A (E195Q, R197D) show decreased binding to *M. avium* but can still stimulate phagocytosis similar to wild-type SP-A. SP-A and SP-D could enhance MR-mediated phagocytosis of *M. avium* by macrophages (Kudo et al. 2004). SP-D can agglutinate *M. avium*, involving CRD region (Ariki et al. 2011). The binding of SP-A strongly inhibits the growth of *M. avium* in culture. SP-D binds *M. Avium* surface in clusters whereas SP-A almost covers the entire bacterial surface as observed under scanning electron microscopy (Ariki et al. 2011). SP-A suppresses NO production by *M. avium*-stimulated alveolar macrophages through inhibition of TNF-α production (Hussain et al. 2003).

*Mycobacterium bovis* BCG

The live, attenuated BCG strain of *M. bovis* is used for TB vaccination. The effects of functional (in exon, non-synonymous) polymorphisms of SP-D on the interaction between SP-D and *M. bovis* BCG have been investigated by Hsieh et al. (Hsieh et al. 2018a, b). It appears that residue 11 Met (92T) is likely to cause susceptibility to TB as in comparison to SP-D 92C (amino acid residue 16, Threonine). SP-D 92T (amino acid residue 16, Methionine) which exhibits reduction in binding to *M. bovis* BCG, inhibiting phagocytosis and aggregation, and inhibition of intracellular growth (Hsieh et al. 2018a, b). SP-A enhances BCG-induced inducible NO synthase protein level, and subsequent production of TNF-α and NO in rat macrophages (Weikert et al. 2000).

Fungi

Fungal pathogens can cause life-threatening infections in immunocompetent as well as immunocompromised individuals. *Aspergillus fumigatus* and *Candida albicans* yeasts can cause opportunistic infections during immune suppression, as observed in patients receiving treatment against AIDS (Kauffman and Carver 1990). Furthermore, fungal infections are often persistent and not easy to treat as it is difficult to target them without affecting host cells.
**Aspergillus fumigatus**

*Aspergillus fumigatus* is a ubiquitous airborne fungus, which is responsible for allergic bronchopulmonary aspergillosis (in immunocompetent individuals), invasive pulmonary aspergillosis (affecting highly immunocompromised subjects) and a range of sub-acute and chronic forms of pulmonary aspergillosis (Madan and Kishore 2020).

Madan et al. have conducted *in vitro* and *in vivo* experiments to establish the protective role of SP-A and SP-D against allergic and invasive aspergillosis (Madan et al. 1997a, b). SP-A and SP-D bound and agglutinated *A. fumigatus* conidia and enhanced its uptake and killing by alveolar macrophages and neutrophils (Madan et al. 1997a). In another study where culture filtrate allergens and various purified glycosylated and non-glycosylated allergens of *A. fumigatus* were assessed, both SP-A and SP-D could bind to allergens and purified glycosylated allergens in a carbohydrate-specific and calcium-dependent manner but were unable to bind with the deglycosylated allergens (Madan et al. 1997b), suggesting that the binding was mediated through their CRD region with the carbohydrate residues on the allergen. Both the surfactants were also able to inhibit *A. fumigatus* allergen-induced histamine that was released from the basophils of allergic patients (Madan et al. 2001). Rat BAL fluid containing SP-D has been shown to inhibit binding of conidia to the extracellular matrix proteins and A549 lung epithelial cells (Yang et al. 2000). Reduction in the conidia binding was observed with pre-treatment of epithelial cells and extracellular matrix proteins with SP-D (Ordonez et al. 2019).

SP-D shows reduced binding to *kre6* yeast mutant (cell wall comprising about 50% less β(1→6)-glucan than the wild type) compared to the wild type, confirming that β(1→6)-glucan is a fungal ligand for SP-D (Allen et al. 2001). SP-D has been found to bind with *A. fumigatus* dormant conidial surface melanin pigment and galactomannan (GM) as well as galactosaminogalactan (GAG), two cell-wall polysaccharides. SP-D showed calcium-dependent binding with GM and GAG recognised by its CRD region, whereas SP-D binding was calcium-independent for melanin requiring collagen region (Wong et al. 2018). Human monocyte-derived macrophages (MDMs) show efficient phagocytosis towards SP-D-opsonised conidia and could subsequently induce the production of pro-inflammatory cytokines. MDMs cultured with SP-D-opsonized conidia produced significantly higher TNF-α, IL-6 and IL-8 than the control groups, unstimulated MDMs and when co-cultured with un-opsonized conidia (Wong et al. 2018).

Murine models of ABPA, when intranasally treated with SP-A and SP-D, demonstrated reduction in *A. fumigatus*-specific IgE and IgG levels, peripheral and pulmonary eosinophilia, and Th2 cytokine response (Madan et al. 2001). However, SP-D (and rfhSP-D) was considerably more effective in ameliorating the allergic features compared to SP-A. SP-D−/− gene deficient mice exhibited intrinsic hyper eosinophilia and showed several-fold increase in the levels of IL-13 and IL-5 and reduction in the IFN-γ to IL-4 ratio following *A. fumigatus* allergen challenge. Intranasal administration of SP-D or rfhSP-D downregulated pulmonary
eosinophilia and specific IgG and IgE antibodies in ABPA murine models (Madan et al. 2005a). Reduction in the bronchial hyper-responsiveness, bronchial eosinophilia and in Th-2 cytokines due to exogenous SP-D treatment were found possibly due to reduction in eotaxin level in the lungs (Erpenbeck et al. 2006).

In a murine model of invasive pulmonary aspergillosis, treatment with SP-D or rfhSP-D reduced the mortality by about 85% compared to untreated groups (Madan et al. 2010), concomitant with higher production of TNF-α, IFN-γ and MIP-1α (Singh et al. 2009). SP-Δ−/− mice challenged intranasally with wildtype conidia or melanin ghosts (hollow melanin spheres) displayed reduction in pro-inflammatory cytokines in the lung compared with wildtype mice. SP-D was found to bind with melanin present on the dormant A. fumigatus conidial surface, facilitating conidial phagocytosis and also inhibiting ROS quenching capacity of melanin (Wong et al. 2018).

**Candida albicans**

*Candida albicans* is a commensal opportunistic fungus present on the skin and in mucosal tissues that causes candidiasis during immunosuppressive conditions. SP-D was found to bind to *C. albicans* yeast which was inhibited in the presence of EDTA and mannan (Ordonez et al. 2019). Incubation of *C. albicans* with SP-D results in the inhibition of hyphal outgrowth as well as phagocytosis by alveolar macrophages (van Rozendaal et al. 2000). *C. albicans* infection of a human airway epithelial cell line, Calu3, increased synthesis of IL-8 and IL-6 significantly and infection decreased by neutrophils in the presence of SP-D; SP-D had no significant effect on the *C. albicans*-induced oxidative burst (Ordonez et al. 2019).

**Histoplasma capsulatum**

*Histoplasma capsulatum* is a dimorphic fungal pathogen; its inhalation results in a flu-like illness in most cases. However, but some instances, it can cause more serious pneumonitis or a chronic cavitary pulmonary infection (Deepe 1999). SP-A and SP-D treatment results in increased yeast permeability, and enhanced entry into pulmonary macrophages. However, SP-A and SP-D do not seem to inhibit the growth of macrophage-internalized *H. capsulatum* (McCormack et al. 2003).
Cryptococcus neoformans

*Cryptococcus neoformans* is a soil-dwelling organism that obtains its nutrition from digesting material in the environment and secretes a range of enzymes to degrade host molecules (Almeida et al. 2015). This fungal pathogen primarily affects immunocompromised individuals through inhalation of spores and may spread to the central nervous system causing life-threatening meningitis and is relatively common in AIDS patients.

SP-A and SP-D bind acapsular *C. neoformans* in a calcium-dependent manner (Schelenz et al. 1995). SP-D binds quite efficiently the acapsular form (but not the capsular form) and aggregates them. Assembly of glucuronoxylomannan (GXM) in the capsule probably lowers the affinity for SP-D in the capsular form preventing aggregation (van de Wetering et al. 2004). The binding ligand for SP-D are GXM and mannoprotein 1 (MP1) components of the cryptococcal capsular components (van de Wetering et al. 2004).

Interestingly, SP-D seems to facilitate infection of pathogenic fungus *C. neoformans in vitro and in vivo* (Geunes-Boyer et al. 2009a, b, c, 2012). SP-D bind and protects *C. neoformans* cells from macrophage induced H2O2-induced oxidative stress (Geunes-Boyer et al. 2012). *C. neoformans* infection appears to be facilitated by the presence of endogenous SP-D in wild-type mice influencing fungal burden in the lungs and faster dissemination to the CNS than in SP-D−/− mice (Geunes-Boyer et al. 2009a, b, c). SP-D−/− mice seem resistant to fungal infection; however, exogenous SP-D treatment renders mice susceptible (Geunes-Boyer et al. 2012). SP-D increases susceptibility to *C. neoformans* infection by augmenting *C. neoformans*-driven pulmonary IL-5 and eosinophil infiltration in lungs (Geunes-Boyer et al. 2012).

In an experiment where SP-A and SP-D double knock-out mice, humanized SP-D transgenic (hTG SP-D), and wild-type (WT) mice were treated with or without p38 inhibitor prior to intratracheal injection with *C. neoformans*, p38 MAPK phosphorylation level was found significantly higher in double knock-out mice than in the WT mice. This level came to normal following phosphorylated p38 (p-p38) inhibitor treatment in the double knock-out mice. Transgenic SP-D expression in the hTG SP-D mice also showed decrease in p38 level and showed enhanced in vivo phagocytic activity of *C. neoformans*. Thus, lack of SP-A and SP-D seems to influence higher phosphorylated p38 leading to enhanced phagocytic activity of the alveolar macrophages (Abdel-Razek et al. 2016).

Other Fungi

*Coccidioides posadasii* is a highly virulent soil fungus that causes coccidioidomycosis (Valley fever) in many arid regions of the Americas (Kollath et al. 2019). Both SP-A and SP-D bind to Coccidioidal antigens but no significant changes were
observed in the amounts of SP-A and SP-D in BALF after 5 days of intranasal challenge with *C. posadasii* (Awasthi et al. 2004).

*S. cerevisiae*, an ubiquitous ascomycetous yeast, is a common colonizer of mucusal surfaces and part of the normal flora of the gastrointestinal tract, the respiratory tract, and the vagina (Salonen et al. 2000). Fungemia the most important clinical syndrome caused by *S. cerevisiae* and has also been described in immunosuppressed patients. It can also cause pneumonia, empyema, liver abscess peritonitis, vaginitis, esophagitis, urinary tract infection, cellulitis etc. (Munoz et al. 2005). SP-D was found to bind and aggregate *S. cerevisiae*, which was further being inhibited by EDTA (Allen et al. 2001).

**Parasite**

**Pneumocystis carinii**

*Pneumocystis carinii*, an extracellular protozoan capable of causing diffused pneumonia in immunocompromised hosts, is a major infection in patients with AIDS. The infection presents as non-productive cough, shortness of breath, fever and bilateral interstitial infiltrates. Pneumocystosis-related surfactant changes have been reported in both humans and corticosteroid-treated experimental models (Aliouat et al. 1998; Prevost et al. 1997). SP-A was found to bind *P. carinii*; its level markedly increased in the infected pneumonia patients with AIDS in lower respiratory tracts (Phelps and Rose 1991; Zimmerman et al. 1992).

O’Riordan et al. reported SP-D as a major component of the alveolar exudates that typify *P. carinji* pneumonia and is capable of binding to the surface of *P. Carinji* organisms through saccharide-mediated interactions with gpA present on the surface of the organism (O’Riordan et al. 1995). With increasing concentrations of calcium SP-D binding to gpA was enhanced, whereas manganese and magnesium cations had negligible effect. SP-D exhibited maximum binding at pH 7.4, whereas inhibited significantly at pH 4. SP-D interactions with *P. Carinii* gpA was found to be facilitated by dodecameric and higher order forms of SP-D (Vuk-Pavlovic et al. 2001).

*P. carinii* pneumonia was also found to be associated with raised levels of alveolar SP-D where synthesis and secretion of SP-D increased with acute injury and epithelial activation (Atochina et al. 2003). The transgenic mouse model with over-expression of SP-D (SP-D OE) was used to understand the role of SP-D in the pathogenesis, where the transgenic mice showed about 30–50 fold greater SP-D level than the wild-type. The SP-D OE animals showed significant higher levels of TNF-α and macrophage inflammatory protein-2 in BLF throughout the period of infection. And as both the SP-D OE and WT were deficient of CD4 lymphocytes, the study suggests that SP-D possibly facilitates the development of *Pneumocystis* infection in an immunosuppressed mouse model (Vuk-Pavlovic et al. 2006).
*Nippostrongylus brasiliensis*

*Nippostrongylus brasiliensis* is a natural parasite of rat, closely related to human hookworm and is primarily used as an important model for studying host’s parasite immune response. Thawer et al showed that with *N. brasiliensis* infection, SP-D concentrations increased in the lung. rfhSP-D could bind to L4 parasites to enhance their killing by alveolar macrophages. *N. Brasiliensis* infection of SP-D−/− mice resulted in profound impairment of host innate immunity and ability to resolve infection (Thawer et al. 2016). With prior treatment of rfhSP-D, the number of IL-13 producing type 2 innate lymphoid cells (ILC2) was enhanced and increased production of the type 2 cytokines IL-4 and IL-13 (Thawer et al. 2016).

**Perspectives**

It is clear that SP-A and SP-D have important roles to play in recognising a wide range of pathogens and clearing them via various mechanisms detailed in this chapter. A number of target ligands are already known; few other are yet to be discovered. The two surfactant proteins also modulate adaptive immune response, thus acting as a pro-active link between innate and adaptive immunity. There are several receptor candidates for collagen regions; however, in most cases, it is the CRD region that binds to the pathogen surface. The knock-out mice have given sufficient information about the pathogen susceptibility. However, the SP-D−/− mice yields lung phenotypes that are already leaky, dysregulated and inflammatory. This can cause a significant bias in the pathogen challenge model. A number of gene polymorphisms and alteration in the SP-A and SP-D protein levels have been noted in a range of pathological conditions; however, they are yet to become a clinically robust biomarker. The properties of rfhSP-D remain intriguing and elusive since presence of collagen region, and oligomeric state of SP-D, has been reported to be paramount in its efficiency. However, the recombinant fragment composed of neck and CRD region of human SP-D seems to have potent therapeutic effects in vitro, in vivo and ex vivo.

As it is evident from the literature review, studies about the effects of SP-A and SP-D on various pathogens are limited in some cases. Thus, there is a greater need to have a concerted effort in pursuing studies with emerging pathogens. A number of parasitic diseases need to be looked at in terms of the roles these two mucosal proteins can play outside lungs.
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