Chapter 4
Collectins: Innate Immune Pattern Recognition Molecules

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Abstract Collectins are collagen-containing C-type (calcium-dependent) lectins which are important pathogen pattern recognising innate immune molecules. Their primary structure is characterised by an N-terminal, triple-helical collagenous region made up of Gly-X-Y repeats, an α-helical coiled-coil trimerising neck region, and a C-terminal C-type lectin or carbohydrate recognition domain (CRD). Further oligomerisation of this primary structure can give rise to more complex and multimeric structures that can be seen under electron microscope. Collectins can be found in serum as well as in a range of tissues at the mucosal surfaces. Mannanbinding lectin can activate the complement system while other members of the collectin family are extremely versatile in recognising a diverse range of pathogens via their CRDs and bring about effector functions designed at the clearance of invading pathogens. These mechanisms include opsonisation, enhancement of phagocytosis, triggering superoxidative burst and nitric oxide production. Collectins can also potentiate the adaptive immune response via antigen presenting cells such as macrophages and dendritic cells through modulation of cytokines and chemokines, thus they can act as a link between innate and adaptive immunity. This chapter describes the structure-function relationships of collectins, their diverse functions, and their interaction with viruses, bacteria, fungi and parasites.

Keywords Collectins · Pathogens · Innate immunity · Phagocytes · Receptors

4.1 Introduction

Collectins (collagen-containing C-type lectins) are soluble mammalian C-type lectins, which represent an important group of pattern-recognition molecules and serve multiple functions in the innate immune system. The term “collectin” was first
used by Malhotra et al. (1992). They are known to mediate pathogen recognition through calcium-dependent carbohydrate recognition domains (CRDs). The following nine collectins have been identified to date: mannan-binding lectin (MBL), three bovine serum collectins, conglutinin, CL-43 and CL-46, lung surfactant proteins SP-A and SP-D, and more recently discovered collectins including, collectin kidney 1 (CL-K1, also called CL-11), collectin liver 1 (CL-L1, also called CL-10) and collectin placenta 1 (CL-P1 also called CL-12). The overall functions of collectins include microbial aggregation and neutralisation, opsonisation, complement activation, and modulation of inflammatory responses.

### 4.2 Structure of Collectins

Collectins are oligomers of trimeric subunits. For most collectins, the subunits are homotrimers (made up of three identical polypeptides) but heterotrimers can be found for SP-A, which is made up of highly homologous SPA-1 and SPA-2 polypeptides. Heterotrimers can also form in the case of CL-10 and CL-11 (Fig. 4.1). The subunit of each collectin is composed of (i) a short N-terminal (7-28 amino acid residues) cysteine-rich domain, involved in multimerisation (by disulphide bridging); (ii) a collagen-like domain composed of Gly-X-Y triplets repeats, where X and Y represent any amino acids; (iii) a short segment which can form coiled-coil helices, and (iv)

![Fig. 4.1](image)

**Fig. 4.1** Molecular structural representation and biological functions of human collectins. Collectins are shown as monomeric subunits, followed by trimeric subunits, composed of an N-terminal domain, collagen-like region, α-helical coiled-coil neck region and C-terminal carbohydrate recognition domain (CRD). Biological functions of each domain are also briefly described.
Fig. 4.2 Three-dimensional structures of trimeric human SP-A (a), SP-D (b), and MBL (c). Representations of the trimeric “head” of collectins. These structures represent the ‘neck’, and the CRDs of three polypeptides which make up the trimeric subunit. The helix interacts with a neighbouring carbohydrate recognition domains (Kishore et al. 2006; Skjoedt et al. 2012).

the C-terminal globular C-type lectin domain, also called the CRD (carbohydrate recognition domain) (Uemura et al. 2006) (Fig. 4.1).

The triple-helical collagen region provides significant rigidity and stability to the molecule (Colley and Baenziger 1987). Another structural feature of the collagen-like domain of collectins is that it can be O-glycosylated (Colley and Baenziger 1987). Both MBL and SP-A show an interruption of the Gly-X-Y triplet repeats, which introduces a bend in the otherwise straight triple helix. This enables the fully assembled multi-subunit structure to angle away from the central core, producing a structure resembling a bouquet of flowers (Fig. 4.2) (Voss et al. 1991). Several distinct functions of the collagen domain of collectins have been reported. The collagen domains of SP-A and MBL are involved in receptor-mediated properties. A GEKGEK specific motif found within the collagen domain of MBL is suggested to bind C1q receptor (Arora et al. 2001), and mediates the enhancement of phagocytosis through C1qR (Arora et al. 2001). A similar motif is within the collagen domain of SP-A (White et al. 1985), which is also involved in the interaction with C1q receptor (Malhotra et al. 1992; Malhotra et al. 1990), and mediates phagocytosis of Staphylococcus aureus by monocytes (Geertsma et al. 1994). Furthermore, the collagen
domain of MBL is shown to bind MBL-associated serum proteases, MASP1, 2 and 3, which mediate complement activation via the lectin pathway (Thiel et al. 1997; Tan et al. 1996). Additionally, the positively charged collagen region found in the membrane bound CL-P1 is involved in the uptake of oxidised LDL particles (Ohtani et al. 2001).

The cysteine residues found within the N-terminal domain (7-28 amino acids) form disulphide bonds between monomers, thereby, stabilising trimeric subunits as well as a larger multimers. It was believed that at least two cysteine residues are required at the N-terminal domain for the formation of multimers of trimeric subunits (Brown-Augsburger et al. 1996; McCormack et al. 1999; McCormack et al. 1997a, b). However, in the case of CL-43, it is secreted as a single trimeric subunit, despite having two cysteine residues (Rothmann et al. 1997; Lim et al. 1994a, b). Therefore, other factors contribute to oligomerisation of trimeric subunits, in addition to the of N-terminal cysteine residues.

The C-terminal region contains a coiled-coil trimerizing neck region (residues 112-130 in human MBL) (Fig. 4.1), and the CRD (residues 134-245 in human MBL) which folds up into an independent globular carbohydrate-binding structure for each polypeptide chain. Each subunit is held together covalently through disulphide bonds, or non-covalently structured into oligomers of up to six subunits. C-type CRDs are connected to the collagen-like domain through the ‘neck’ region (24-28 amino acid residues) (Hoppe and Reid 1994). Furthermore, the neck region is involved in aligning the collagen chains.

### 4.2.1 Ligand Specificity of Collectins

A broad carbohydrate specificity is required by collectins in order to recognise and bind a large repertoire of (pathogen-associated molecular patterns) PAMPs. Such broad specificity is achieved by an open and flexible trough-like binding pocket found within the CRDs. The selection of ligands by this site depends on the positioning of vicinal hydroxyl groups of sugars, which form coordination bonds with a ligated calcium ion, hydrogen bonds and a polar Van der Waals contact (Ng et al. 1996). Ligand specificity of collectins is divided into two main sub-classes (mannose-binding or galactose-binding type), which is based on a three amino acid residue motif found in the Ca++ ion binding site. The sequence 185-Glu-Pro-Asn is associated with binding of mannose-like sugars, while the sequence 185-Gln-Pro-Asp is associated with binding galactose-like sugars. The molecular differences based on which CRDs discriminate between mannose and galactose-type ligands depend on the orientation of C3 and C4 vicinal hydroxyl groups presented on monosaccharides. Mannose-specific CRDs bind ligands in which hydroxyl groups at the C3 and C4 positions are in an equatorial orientation (mannose, glucose, glucosamine), while in galactose these vicinal hydroxyls are in an axial orientation (Drickamer and Taylor 2015). Inhibition studies using monosaccharides have shown that most likely, all the
above described collectins, except CL-P1, prefer mannose ligands over galactose (Ohtani et al. 2001; Holmskov et al. 1994).

However, a wider range of binding specificity has been reported for MBL and lung surfactant proteins SP-A and SP-D, as these collectins are also capable of binding to nucleic acids (Nadesalingam et al. 2003), phospholipids (Sano et al. 1999), as well as non-glucosylated proteins.

Fucose, a hexose deoxy sugar is bound by mannose-specific CRDs in a different manner as it has equatorial hydroxyl groups placed on its C2 and C3 position of the sugar ring, not the C3 and C4 (Weis et al. 1991a, b; Ng et al. 1996; Iobst and Drickamer 1994). Computational docking studies have demonstrated that α-D-glucose docks into the CRD of SP-D via vicinal equatorial hydroxyl groups on the 2- and 3- position of its sugar ring (Allen et al. 2001a, b). Although MBL affinity is reported to be very low for monosaccharide galactose, MBL crystallographic studies demonstrate that galactose is ligated in the MBL binding region via coordination bonds with hydroxyl groups placed at C1 and C2 position of the sugar ring (Ng et al. 1996). In addition to galactose and mannose, binding of collectins to a range of sugars has also been studied (Holmskov et al. 1994); they exhibit preferences for certain sugar residues over others. For instance, despite SP-D being structurally similar to conglutinin, it displays a greater affinity for maltose, a glucose disaccharide, which is a weak ligand for conglutinin. SP-D is suggested to have a lower affinity for GlcNAc, which is the best ligand for conglutinin. Moreover, binding of CL-43 to sugars is closely related to MBL, although the structure of CL-43 is closer to SP-D and conglutinin (Lu et al. 2002).

The sugar-binding specificity of CL-11/CL-K1 has been investigated (Venkatraman Girija et al. 2015). It has a larger recognition interface than MBL, and recognises predominantly mannose-rich structures, interacting with two sugar residues at a glycan terminal, rather than a single sugar.

### 4.3 Biosynthesis and Localisation of Collectins

Human MBL is synthesised by hepatocytes and secreted into the blood stream (Sastry et al. 1991; Ezekowitz et al. 1988; Hansen et al. 2000). Initially, MBL was isolated from the liver of the rabbit, rat and chicken, where expression levels were detected in the soluble cytosol, rather than on the cell surface. Two forms of MBL (MBL-A and MBL-C) were detected in rodents (Hansen et al. 2000; Drickamer et al. 1986), rabbits (Kawasaki et al. 1978; Kozutsumi et al. 1980) and rhesus monkeys (Mogues et al. 1996). However, only one form of MBL is present in humans and chimpanzees (Mogues et al. 1996). Although the liver is the main production site of MBL-A and MBL-C in mice, mRNA expression of MBL was also detected in various tissues (Table 4.1) (Shushimita et al. 2015). Substantial expression levels of MBL-A and MBL-C were reported in kidney and intestine (Table 4.1). Detection of MBL proteins in the small intestine suggests that MBL may have similar roles to secretory IgA (Reichhardt et al. 2012).
| Collectins | Tissues of origin | Tissues of presentation | Remarks |
|------------|-------------------|-------------------------|---------|
| MBL        | Liver and small intestine | Serum | Two different variants of MBL (A and C) have been identified in animals, while only one variant is found in humans and chimpanzee. |
| Conglutinin, CL-43 and CL-46 | Bovine liver | Serum | These bovine collectins plays an important role in the first line of defense against rumen microbes without eliciting general inflammatory response |
| SP-A and SP-D | Clara cells, intestinal mucosa, thymus, prostrate gland, Eustachian tube, paranasal sinuses, middle ear, synovium | Alveolar space, mucosal surfaces, semen | Extrapulmonary expression of SP-A is limited to a few organs, while SP-D expression has been detected in many non-pulmonary mucosal tissues |
| CL-P1 | Placenta, and vascular endothelial cells | Endothelial cells | CL-P1 is the only membrane bound collectin with an intracellular domain. It is suggested to play many roles which differ from those of soluble collectins |
| CL-K1 | | Serum | Different from all other collectins, but seems to have functions phylogenetically similar to CL-L1 |

The collectins SP-A and SP-D are primarily detected in the alveolar space of the lungs, and synthesised by alveolar type-II cells (Table 4.1) (Voorhout et al. 1992, Nayak et al. 2012), and nonciliated bronchial epithelial cells, also known as Clara cells (Voorhout et al. 1992; Crouch et al. 1992). Although the lung is the main
Table 4.1 (continued)

| Collectins | Tissues of origin | Tissues of presentation | Remarks |
|------------|-------------------|-------------------------|---------|
| CL-L1      | Liver and hepatocyte | Ubiquitous             | Immunoblot analyses using human liver demonstrated that CL-L1 was distributed to the cytoplasm. It is also involved in embryonic development |

site of SP-A and SP-D synthesis, presence of SP-D has also been reported at extrapulmonary sites. SP-D expression has been shown immunohistochemically in human trachea, brain, heart, kidneys, testis, salivary gland, placenta, prostate, small intestine, and pancreas (Table 4.1). A low expression level has been detected in spleen, uterus, adrenal gland and mammary glands (Fisher and Mason 1995; Madsen et al. 2000; Herías et al. 2007). Furthermore, immunoreactivity of SP-D has also been shown in the epithelial cells of both small and large ducts of the parotid gland, lacrimal and sweat glands, epithelial cells of intra-hepatic bile ducts and gall bladder, as well as esophagus, exocrine pancreatic ducts, and in the urinary tract (Madsen et al. 2000; Bräuer et al. 2007). In the case of SP-A, low levels are detected in small intestines from human and rat (Table 4.1) (Lin et al. 2001, van Iwaarden et al. 1990). In addition to its presence in the murine uterus, very low SP-A expression is found in human prostate, amniotic fluid, thymus and salivary gland (Madsen et al. 2003). SP-A and SP-D have also been localised in the fetal membranes, and choriodecidual layer of the late pregnancy uterus (Miyamura et al. 1994). As a result of pulmonary microbial infection, the protein levels of both SP-A and SP-D have been reported to increase in the alveolar compartment (Atochina et al. 2001). Thus, the level of SP-D increases in response to allergen-induced eosinophilia (Kasper et al. 2002), suggesting that both SP-A and SP-D may function as acute phase reactants within the lungs. Furthermore, hypoxia results in an increased concentration of both SP-A and SP-D in the alveolar compartment (White et al. 2001).

Conglutinin, CL-46 and CL-43 are serum collectins identified in bovidae and synthesised in the liver (Hansen et al. 2002). These collectins provide a first line of defense against microbial pathogens. CL-L1 mRNA was detected in the liver, and studies using Northern blot analysis have suggested that low levels occur in the placenta. Although most collectins are secreted, CL-L1 was found in the cytosol of hepatocytes, which may suggest its interaction with intracellular ligands (Ohtani et al. 1999). The presence of CL-P1 was reported in vascular endothelial cells (Table 4.1); CL-P1 is suggested to be membrane bound, and it contains an intracellular domain (Ohtani et al. 2001). Expression of MBL, SP-A and SP-D at the mucosal surfaces suggest the innate immune roles of these collectins against invading pathogens. During
Helicobacter pylori infection, an increased level of SP-D has been detected, suggesting the possible role of SP-D in the mucosal defense outside the lungs (Murray et al. 2002), eg. gastrointestinal tract.

4.4 Role of Collectins in Microbial Infection

Collectins are important soluble pattern-recognition receptors (PRRs) of the humoral arm of the innate immune response. Collectins are able to recognise and bind to a wide variety of microbes and are involved in their clearance and forming a central link to adaptive immunity against microbial infections. In this section, we will discuss the well-known collectins: MBL, SP-A and SP-D, as well as newly discovered collectins: liver collectin (CL-L1), kidney collectin (CL-K1), and placenta collectin (CL-P1). We will also briefly discuss bovine collectins, conglutinin, CL-43 and CL-46. Microbes can be cleared by collectins via a number of mechanisms such as aggregation, opsonisation, phagocytosis, microbial growth inhibition, complement activation, as well as modulation of adaptive immunity.

4.5 Interaction of Collectins with Bacteria

4.5.1 SP-A and SP-D

Pulmonary surfactant is composed of 90% phospholipids and 10% proteins (made up of surfactant proteins, SP-A, SP-B, SP-C and SP-D. Whilst, SP-B and SP-C are hydrophobic and essential for the physiology of the alveolar surfaces, SP-A and SP-D are hydrophilic and contribute to lung immunity. An early study showed that pulmonary surfactant enhanced the killing of Staphylococcus aureus by alveolar macrophages (AM), in vitro (LaForce et al. 1973). Both Gram-negative and Gram-positive bacteria are recognised by SP-A and SP-D, enhancing their phagocytosis by AMs (Fig. 4.3) (Pikaar et al. 1995). For Gram-negative bacteria, SP-A and SP-D both bind to lipopolysaccharide (LPS) but differ in preferential targets on the molecule. SP-A binds to the lipid A moiety of rough LPS (which lacks the O-antigen and shortened oligosaccharides) (Van Iwaarden et al. 1994), and enhances phagocytosis of bacteria by AM (Kalina et al. 1995), but not to smooth LPS (which contains the O-antigen) (Van Iwaarden et al. 1994). In contrast, SP-D binds strongly to smooth LPS from Escherichia coli and Salmonella species but does not recognise the lipid A moiety or oligosaccharide deficient LPS (Kuan et al. 1992). This indicates that SP-D preferentially targets the core terminal saccharides in the bacterial ligand, whilst SP-A prefers lipid A. SP-D has also been shown to bind to rough LPS via its trimeric carbohydrate recognition domain (CRD), (targeting shortened oligosaccharides) and agglutinating E. coli (Kuan et al. 1992), and rough LPS from Klebsiella
In addition to LPS, SP-A is able to bind to capsular polysaccharides of *Klebsiella* species, enhancing their phagocytosis by AM (Kabha et al. 1997). However, bacterial peptidoglycan is not a ligand for SP-A (Murakami et al. 2002).

SP-A and SP-D directly inhibit the growth of several Gram-negative bacteria by increasing the membrane permeability of the bacterial cell wall (Fig. 4.3) (Wu et al. 2003). SP-A and SP-D also inhibit biosynthetic functions in strains of *E. coli*, *K. pneumoniae* and *Enterobacter aerogenes* (Wu et al. 2003). Similarly, SP-A inhibits the growth of *P. aeruginosa* by increasing membrane permeability (Van Iwaarden et al. 1994), but the bacterium can resist through quorum-sensing and the secretion of a flagellum-mediated exoprotease that degrades SP-A (Kuang et al. 2011a). Furthermore, SP-A downregulates TNF-α secretion via toll-like receptor 2/NF-κB mediated pathway, indicating its role in modulating inflammatory responses against bacterial ligands (Murakami et al. 2002).

SP-A can bind to the outer membrane protein (OMP) of *Haemophilus influenzae* type A and to a lesser extent, type B (McNeely and Coonrod, 1994). SP-A can also aggregate and opsonise *H. influenzae* type A, facilitating killing by AM (McNeely and Coonrod 1994). Similarly, SP-A binds to the capsular polysaccharide of some strains of *K. pneumoniae*, agglutinating the bacteria and increase phagocytosis by macrophages (Kabha et al. 1997), and treatment with SP-A plus SP-B (N-terminal saponin domain of SP-B) significantly reduced bacterial infection and enhanced neutrophil recruitment (Coya et al. 2015). SP-A has a bacteriostatic effect on *Mycoplasma pneumoniae* via binding to di-saturated phosphatidylglycerols on the bacterial membrane (Piboonpocanun et al. 2005). SP-A can interact with *Mycobacterium tuberculosis* putative adhesin Apa glycoprotein on its surface (Ragas et al. 2007). SP-D can also bind to Gram-positive bacterial ligands such as lipoteichoic acid and peptidoglycan via its CRD (van de Wetering et al. 2001) and to lipoolarabinomannan (LAM) from *M. tuberculosis* and *Mycobacterium
SP-A and SP-D can also directly facilitate phagocytosis without the need for microbial binding, by up-regulating the expression of cell surface phagocytic receptors in macrophages, such as mannose receptor (Beharka et al. 2002; Kudo et al. 2004). In SP-A−/− knockout mice, expression of mannose receptor is down-regulated, showing that SP-A is important in regulating the expression of this receptor (Beharka et al. 2002). Similarly, SP-A is able to enhance phagocytosis of Streptococcus pneumoniae by AM, independent of its binding to the bacterium, via the increased expression of scavenger receptor A (SR-A) (Kuronuma et al. 2004). Interestingly, the vast majority of clinical strains of the opportunist Pseudomonas aeruginosa secrete an elastase that degrades SP-A and facilitates evasion of opsonisation by the collectin during phagocytosis (Kuang et al. 2011b).

SP-A and SP-D can also play important roles in modulating the intracellular environment after phagocytosis by stimulating reactive oxygen and nitrogen intermediates facilitating the killing of intracellular pathogens. This is of particular note in mycobacteria, which are specialist intracellular bacteria. SP-A enhances the killing of intracellular Mycobacterium bovis BCG by increasing nitric oxide (NO) production, in addition to enhancing the release of inflammatory mediators such as TNF-α (Weikert et al. 2000). In contrast, in IFN-γ primed AM, SP-A decreases NO production in response to intracellular infection with M. tuberculosis and M. avium by inhibiting TNF-α secretion and nuclear factor-kappa B (NF-κB) activation (Pasula et al. 1999; Hussain et al. 2003). SP-A can also enhance the intracellular killing of Mycoplasma pulmonis via a NO dependent mechanism (Hickman-Davis et al. 1998).

Bacteria-derived cell-wall molecules such as LPS and peptidoglycan are potent stimulators of inflammation and can also interact with pattern-recognition receptors (PRRs) such as CD14 or toll-like receptors (TLR), via pathogen-associated molecular patterns (PAMPs), and activate downstream intracellular signalling. SP-A and SP-D can also directly bind to PRRs (e.g. TLR and CD14) and thus can modulate the inflammatory response. SP-A and SP-D can alter LPS interactions with CD14 via different mechanisms (SP-A via neck domain; SP-D via CRD) (Sano et al. 2000). Furthermore, via direct interaction with CD14, SP-A inhibits production of TNF-α induced by smooth LPS, but not rough LPS in U937 macrophages (Sano et al.
In SP-A−/− knockout mice, TNF-α induced by smooth LPS, significantly increased, compared to wild-type mice (Borron et al. 2000), whilst SP-A has also been shown to inhibit TNF-α induction by peptidoglycan via direct binding to TLR-2 (Murakami et al. 2002). Thus, SP-A significantly decreases peptidoglycan or smooth LPS-induced pro-inflammatory responses (via NF-κB activation). SP-A has no effect or increases the inflammatory response induced by rough LPS. In tuberculosis, SP-A has pleiotropic effects being able to promote inflammation in the presence of infection and suppresses inflammation in uninfected macrophages, probably protecting uninfected lung areas from the deleterious effects of inflammation (Gold et al. 2004).

In humans, SP-A exists in two isoforms, SP-A1 and SP-A2, which are encoded by distinct genes. Fully assembled SP-A protein contains both gene products. A number of studies have described polymorphisms in these genes and the SP-D gene which may have a role in susceptibility to microbial infection, particularly tuberculosis. Polymorphisms within and flanking the SP-A1 and SP-A2 genes have been described which indicate protection or susceptibility toward pulmonary TB in the populations studied in Mexico, Ethiopia, India and China (Floros et al. 2000; Madan et al. 2002; Malik et al. 2006; Vaid et al. 2006; Yang et al. 2014). Two SP-A1 alleles (SFTPA1 307A, SFTPA1 776T) and two SP-A2 alleles (SFTPA2 355C and SFTPA2 751C) were associated with tuberculosis susceptibility in Ethiopia (Malik et al. 2006). The SFTPA2 751A/C polymorphism and the haplotype 1A3 in SP-A2, which both affect the amino acids in CRD region of SP-A, may alter binding to M. tuberculosis and thus were found to be strongly linked with tuberculosis susceptibility (Malik et al. 2006). Another study also found two polymorphisms (SP-A2 G1649C and SP-A2 A1660G) in the introns of SP-A1 that were associated with tuberculosis in an Indian population, but none in the SP-A1 gene (Madan et al. 2002). In a Chinese population, the polymorphism 1649G in the SP-A2 gene was strongly associated with tuberculosis, mirroring the findings in the Ethiopian and Indian populations (Yang et al. 2014). The SP-A2 1649G leads to a transversion (proline to alanine), affecting the triple helical structure of SP-A (Yang et al. 2014). In SP-D, the polymorphism, G459A, is significantly associated with tuberculosis susceptibility in an Indian population, but the molecular basis for susceptibility is not understood (Vaid et al. 2006). These observations illustrate the complexities of host-pathogen interactions in bacterial infection mediated by these collectins.

4.5.2 MBL

MBL is the recognition subcomponent of the lectin pathway of the complement system and is present mostly in the serum. The structure of MBL is similar to that of SP-A, and in the presence of Ca2+, it has been observed to target terminal sugars (e.g. D-mannose, L-fucose, and N-acetyl-D-glucosamine), on the surface of a number of Gram-positive and Gram-negative bacterial species (Ip et al. 2009; Lugo-Villarino et al. 2011). The binding of MBL to microbial surfaces can activate complement
through MBL-associated serine proteases (MASPs), resulting in enhanced microbial clearance via opsonisation (C3 and C4 deposition) and complement-mediated lysis. However, MBL also has complement-independent activity such as inhibition of bacterial adhesion (Jack et al. 2005) and opsonisation to enhance bacterial uptake (Kuhlman et al. 1989; Polotsky et al. 1997; Jack et al. 2005). Strong in vitro binding of MBL to *S. aureus*, *Streptococcus pyogenes*, *Listeria monocytogenes* and non-encapsulated *Neisseria meningitidis* has been described (Levitz et al. 1993; van Emmerik et al. 1994; Neth et al. 2000). Moderate levels of MBL binding were observed in *E. coli*, *Haemophilus influenzae* and *Klebsiella* species, whilst no binding has been observed for *P. aeruginosa*, *Enterococcus* species and *Streptococcus pneumoniae* (Levitz et al. 1993; van Emmerik et al. 1994; Neth et al. 2000). Bacterial pathogens have involved strategies to interfere with MBL binding and functions for survival, via the synthesis of a polysaccharide capsule and sialylation of LPS ligands on the bacterial surface which reduces the binding of MBL (Jack et al. 2005; Krarup et al. 2005). This effectively masks or alters the bacterial ligands for MBL interaction. A number of studies have characterised the bacterial ligands for MBL. MBL is able to bind to peptidoglycan and lipoteichoic acid from *S. aureus* (Polotsky et al. 1996; Nadesalingam et al. 2005a, b), LAM from *M. avium* (Polotsky et al. 1997), and mannosylated lipoarabinomannan (ManLAM) from a number of mycobacteria (*M. tuberculosis*, *M. bovis*, *M. kansasii*, *M. gordonae* and *M. smegmatis*) (Bartlomiejczyk et al. 2014). There is also a report of MBL binding to the antigen 85 (Ag85) complex of M. tuberculosis (Swierzko et al. 2016). Neisseria (*M. meningitidis* and *M. gonorrhoeae*) are Gram-negative diplococci that have shorter versions of LPS on their surface called lipooligosaccharides (LOS) that are commonly terminated in sialic (neuraminic) acid, instead of the O-antigen. Neisseria bacteria are able to decrease binding of MBL to their surface by the sialylation on LOS (Jack et al. 1998; Devyatayarova-Johnson et al. 2000; Jack et al. 2001; Gulati et al. 2002). *M. meningitidis* can also interfere with MBL binding through encapsulation (van Emmerik et al. 1994), whilst *M. gonorrhoeae* is not able to form capsules. Encapsulation seems to be less robust at decreasing MBL binding than sialylation of LOS (Jack et al. 1998). Bound MBL can activate complement and the ability of Neisseria species to cascade complement all the way to C9 (membrane attack complex (MAC)) is crucial for protection against infection, since they are otherwise poorly phagocytosed by neutrophils and macrophages when opsonised by C3 (Ross and Densen 1984). MBL bound to the surface of Neisseria is able to increase bacterial killing via increased complement activation (Jack et al. 1998, 2001; Gulati et al. 2002), and similar observations of bactericidal activity have been reported for *E. coli* and Salmonella species (Kawasaki et al. 1989; Ihara et al. 1991). For most other bacteria, complement activation to the C3 deposition stage is enough for protection via increased phagocytosis through opsonisation by complement products on the bacterial cell surface. MBL can increase C3b deposition on *S. aureus* (Neth et al. 2002), but this does not appear to result in increased complement activation (Cunnion et al. 2001). MBL targets wall teichoic acid in *S. aureus* and this interaction is particularly important in infants that have not developed adaptive immunity, leading to bacterial clearance via MBL-mediated complement activation (Kurokawa et al. 2016).
In addition to its complement-mediated activities, MBL is also has various intrinsic effects, being able to act as an opsonin independently and other direct effects. MBL enhances uptake and intracellular killing of Salmonella by neutrophils and monocytes (Kuhlman et al. 1989), but this may also involve interaction with fibronectin (Ghiran et al. 2000). Recently, MBL has also been shown to have a direct inhibitory effect on flagellar activity in pathogenic Salmonella bacteria, impairing their motility (Xu et al. 2016). MBL can also increase uptake of mycobacteria by macrophages (Polotsky et al. 1997) and *N. meningitidis* by neutrophils, monocytes and macrophages (Jack et al. 2001), but this uptake by neutrophils may not result in intracellular killing (Drogari-Apiranthitou et al. 1997). MBL also appears to improve the efficiency of internalisation of bacteria bound to the macrophage plasma membrane (Neth et al. 2002). MBL co-interacts with TLR2 in sensing *S. aureus* and thus influencing the subsequent inflammatory response (Nauta et al. 2003; Ip et al. 2008).

MBL deficiency increases susceptibility to microbial infection even though the majority of MBL-deficient individuals are usually healthy (Eisen and Minchinton 2003). The concentration of MBL in the plasma varies considerably in humans (0–10, 000 ng/ml) due to polymorphisms in the MBL gene (Steffensen et al. 2000). MBL deficiency is commonly observed in around 25% of Caucasians (having low levels (<500 ng/ml)), which renders them susceptible to infection (Valdimarsson et al. 2004). MBL-deficient mice are susceptible to *S. aureus* infection (Shi et al. 2004), whilst MBL deficiency increases susceptibility to postburn infection with *P. aeruginosa* (Moller-Kristensen et al. 2006). A large cohort study has also found a strong association between MBL deficiency and meningococcal infection, and pneumococcal pneumonia, in patients undergoing chemotherapy (Gaynor et al. 1995; Kronborg et al. 2002; Roy et al. 2002). In contrast, normal or increased levels of MBL are linked to frequent infection with *M. tuberculosis* and *M. leprae* (Garred et al. 1994, 1997b), probably through complement-mediated phagocytosis of the pathogen. Up to 30% of healthy individuals have polymorphisms linked to MBL deficiency and these, together with serum levels, have been associated with susceptibility to tuberculosis and other inflammatory diseases in some ethnic populations (Takahashi and Ezekowitz 2005; Thiel et al. 2006; Goyal et al. 2016).

### 4.5.3 CL-L1, CL-K1, CL-P1 and the Bovine-Unique Collectins, Conglutinin, CL-43 and CL-46

Of the three more recently discovered collectins (CL-L1, CL-K1, CL-P1), CL-L1 and CL-P1 have been shown to have bacterial interactions. CL-K binds to *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *M. tuberculosis* (Keshi et al. 2006; Hansen et al. 2010; Troegeler et al. 2015), whilst CL-P1 can bind to *E. coli* and *S. aureus* (Ohtani et al. 1999; Jang et al. 2009). Both CL-L1 and CL-K1 can activate the complement lectin pathway as can the heteromeric form CL-LK, which interacts with the MASP3s (Henriksen et al. 2013). CL-P1 can activate the alternative and classical pathways
via its interaction with C-reactive protein (CRP) (Roy et al. 2016). There is limited data on the activity of CL-LK in vivo and in vitro, but due to average serum concentrations being below that of MBL (0.3 μg/ml vs. 1.5 μg/ml), pathogen recognition and clearance through complement activation is likely to have a minor role to play for these collectins. It is not clear whether these collectins can act directly as opsonins in a complement-independent manner. CL-L1 can bind D-mannose, N-acetylglucosamine, D-galactose, L-fucose and D-fructose in a Ca²⁺ dependent manner (Ohtani et al. 1999; Axelgaard et al. 2013). Similarly, CL-K1 can also bind L-fucose, D-mannose and N-acetylmannosamine (Ohtani et al. 1999; Hansen et al. 2010). Furthermore, CL-LK was recently demonstrated to be a PRR for M. tuberculosis, being able to primarily target mannose-capped lipoarabinomannan (ManLAM), in a Ca²⁺ dependent manner, on the surface of the mycobacterium, but not to M. smegmatis due to the lack of mannose caps on its LAM (Troegeler et al. 2015). Mice deficient in CL-K1 did not show altered susceptibility to M. tuberculosis infection and CL-LK opsonised M. tuberculosis did not result in altered phagocytosis or intracellular survival of the pathogen in human macrophages (Troegeler et al. 2015). Interestingly, the levels of CL-LK in serum of tuberculosis patients is reduced, compared to controls, correlating inversely to the immune response to M. tuberculosis and suggesting that it may be useful as a biomarker for the disease (Troegeler et al. 2015).

Conglutinin was the first mammalian collectin to be discovered and is found in Bovidae, together with other lesser known collectins (CL-43 and CL-46) (Hansen and Holmskov 2002). Conglutinin is similar in overall structure to SP-D and is able to bind to microbial surfaces in the presence of Ca²⁺ (Hansen and Holmskov 2002). Conglutinin is secreted by the liver and found predominantly in bovine serum at an average concentration of 12 μg/ml (Holmskov et al. 1998). Conglutinin has been shown to have anti-microbial properties. Low serum levels of conglutinin have been associated with acute infections (e.g. pneumonia and metritis) and predisposition to respiratory infection (Ingram and Mitchell 1971; Holmskov et al. 1998). Conglutinin is able to bind many microbes, including Gram-negative bacteria such as E. coli and Salmonella typhimurium (Friis-Christiansen et al. 1990; Friis et al. 1991), LPS and peptidoglycan (Wang et al. 1995) and Gram-positive bacteria such as mycobacteria (Dec et al. 2012; Mehmood et al. 2019). Conglutinin is uniquely able to bind to iC3b, via the mannose sugars on the α-chain of iC3b (Laursen et al. 1994). Conglutinin is able to bind and agglutinate iC3b-coated erythrocytes (Lachmann and Muller-Eberhard 1968; Laursen et al. 1994), and as well as E. coli, increasing the respiratory burst of phagocytes (Friis et al. 1991). Conglutinin has also been shown to be protective against bacterial infection in vivo, being able to increase the survival of mice experimentally infected with highly virulent strains of S. typhimurium (Friis-Christiansen et al. 1990). A recombinant truncated form of conglutinin, composed of the α-helical neck region and the CRD of conglutinin (Wang et al. 1995), was recently shown to bind to able to bind to the vaccine strain Mycobacterium bovis BCG (probably via LAM), and act as an anti-opsonin both in the presence and absence of complement deposition. Thus, Conglutinin can interfere with the uptake of the bacterium by THP-1 macrophages and alter their inflammatory response (Mehmood et al. 2019). This suggests that conglutinin interferes with uptake of mycobacteria by macrophages.
via two important mechanisms: (1) blocking interaction of mycobacterial LAM with mannose receptor, and (2) blocking iC3b interaction with complement receptors CR3 and CR4 (Mehmood et al. 2019). These data potentially have important implications for bovine tuberculosis.

CL-43 and CL-46 are also bovine-unique collectins, but their role in the physiology and innate immunity against bacteria has not been fully studied. There is one report of CL-43 binding to *E. coli* strain K12, enhancing attachment to phagocytes (Hansen and Holmskov 2002).

### 4.6 Interaction of Collectins with Viruses

#### 4.6.1 SP-A and SP-D

There are numerous studies that describe direct interaction of SP-A and SP-D with a range of viruses, enhancing their phagocytosis, as well as neutralising viral infection of host cells (Fig. 4.3). Experiments on SP-A −/− and SP-D −/− knockout mice infected with influenza A virus (IAV) suggest that both collectins are protective, but this is dependent on viral strain-specific factors, such as the nature of glycosylation in HA and NA (LeVine et al. 2001, 2002; Hawgood et al. 2004). Also, mice lacking both SP-A and SP-D, have an IAV infection phenotype almost identical to SP-D −/− mice (Hawgood et al. 2004). Moreover, SP-D, but not SP-A, enhanced the clearance of IAV infection in the mouse lung (LeVine et al. 2001). Thus, these studies suggest that SP-D plays a more significant role than SP-A in the host innate immune response to infection with IAV.

SP-A binds to IAV, neutralises the virus and inhibits the release of viral particles from infected cells, by targeting mannose residues of viral surface haemagglutinin (HA) or neuraminidase (NA) (Malhotra et al. 1994; Benne et al. 1995). SP-D strongly inhibits hemagglutination activity of IAV, resulting in viral aggregation and neutralisation (Hartshorn et al. 1994). SP-D is also able to inhibit NA activity, with inhibition being stopped in the presence of D-mannose (Reading et al. 1997). SP-D has a stronger inhibitory effect on NA compared to SP-A (Tecle et al. 2007). SP-D binds to mannosylated, N-linked sugars on viral HA and NA via its CRD, resulting in potent anti-IAV infectivity (Hartshorn et al. 1994, 2000). SP-D was able to inhibit virus-induced HA activity, block the enzymatic activity of viral NA, and neutralise the ability of seasonal H1N1 strains of IAV to infect human respiratory epithelial cells (Job et al. 2010). However, in the same study, some pandemic H1N1 were found to be resistant to SP-D inhibition that correlated with the degree of N-glycosylation in the globular head of HA (Job et al. 2010). It has been shown that porcine SP-D has an increased ability to inhibit, not just seasonal IAV strains, but also a number of pandemic and avian strains (van Eijk et al. 2003; Hillaire et al. 2012). This is important as pigs are a source of IAV pandemic strains (H1N1) that can be transmitted
to humans, so studying porcine SP-D could provide further insights into this host reservoir.

A recombinant truncated form of SP-A (rfhSP-A) made up of α-helical neck and CRD, promotes IAV infection, replication, upregulation of viral factors (M1) in lung epithelial A549 cells and enhances the pro-inflammatory response (Al-Qahtani et al. 2019). This contrasts with full-length SP-A which inhibits IAV infection and dampens the pro-inflammatory response, demonstrating that the full-length SP-A molecule is required for IAV protection (Al-Qahtani et al. 2019). However, in a similar study, a recombinant truncated form of SP-D (rfhSP-D) was shown to inhibit IAV entry, down-regulate viral factors (M1) and down-regulate the pro-inflammatory response (Al-Ahdal et al. 2018). These opposing effects of rfhSP-A and rfhSP-D provide further insight into IAV pathogenesis and the possible utility of rfhSP-D as a therapeutic molecule. In bronchoalveolar lavage (BAL), SP-D enhances IAV uptake and virus-induced respiratory burst by neutrophils (White et al. 2005), but other collectins (SP-A), mucins and gp-340 dampen SP-D’s effect, and thus, significantly reduce the ability of SP-D to promote neutrophil oxidative response (White et al. 2005). Therefore, the net effect of BAL is to increase neutrophil uptake of IAV while reducing the respiratory burst response to virus (White et al. 2005).

SP-A is also able to bind to herpes simplex virus type 1 (HSV-1) via viral N-linked sugars and enhance phagocytosis of the virus by macrophages (van Iwaarden et al. 1991; Van Iwaarden et al. 1992a, b). The mechanism of binding of SP-A to HSV-1 is similar to binding to IAV, involving interaction with the sialylated carbohydrate on the collectin’s CRD. SP-A also has an opsonin activity, increasing uptake of HSV-1 by AM (van Iwaarden et al. 1991). Similarly, SP-A binds to cytomegalovirus and enhances viral entry into rat lung cells (Weyer et al. 2000). It is unknown whether SP-D has any activity against other Herpesviridae. SP-A is able to bind to respiratory syncytial virus (RSV) targeting the F2 subunit of the viral F antigen and is able neutralise the virus (Ghildyal et al. 1999; Sano et al. 1999, 2000). Children with severe RSV infection have reduced levels of SP-A and SP-D in BAL samples compared to healthy controls (Kerr and Paton 1999). In SP-A−/− knockout mice, RSV infection was more severe than in SP-A+/+ mice and the addition of exogenous SP-A to SP-A−/− mice reduced viral load and inflammation, and enhanced RSV clearance (LeVine et al. 1999). SP-D can bind to RSV protein G and is able to neutralise RSV infectivity in vitro (Hickling et al. 1999). Interestingly, RSV itself can alter SP-A expression in human pulmonary epithelial cells, upon infection by interfering with protein translation (Bruce et al. 2009). SP-A binds to Human Immunodeficiency Virus 1 (HIV-1) via the viral envelope gp120 glycoprotein and inhibits direct infection of CD4+ T cells (Gaiha et al. 2008). Yet, in dendritic cells (DC), SP-A increases HIV uptake, through enhanced binding to gp120 and facilitates transfer of HIV from DC to CD4+ T cells (Gaiha et al. 2008). SP-D is also able to bind to HIV gp120 and inhibit viral infectivity (Meschi et al. 2005), whilst rfhSP-D was also able to bind to gp120 and prevent infection of Jurkat T cells, U937 monocyctic cells and PBMC, and significantly suppress the HIV-1 induced cytokine storm in these cells (Pandit et al. 2014). Interestingly, a direct protein–protein interaction between rfhSP-D and
DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin) modulates the capture of HIV-1 and its transfer to CD4+ T cells, revealing a novel and distinct anti-viral mechanism against HIV-1 by SP-D (Dodagatta-Marri et al. 2017). This same rhSP-D has also been recently shown to restrict the transfer of HIV across the vaginal epithelial barrier, by altering the gene expression signature of the epithelium (Pandit et al. 2019). These recent studies demonstrate the therapeutic potential of rhSP-D against HIV infection.

Elevated levels of serum SP-D have been reported in severe acute respiratory syndrome (SARS) coronavirus infected patients (Wu et al. 2009). SP-D is able to bind to the glycosylated spike protein (S-protein) on the SARS coronavirus (Leth-Larsen et al. 2007). Both SP-A and SP-D bind to coronavirus strain HCoV-229E, and inhibit viral infection of human bronchial epithelial (16HBE) cells. Whilst SP-A only modestly reduced infection in AM, whereas SP-D had no effect (Funk et al. 2012). Human and porcine SP-D can interact with Ebola virus glycoprotein and enhance viral infection in pulmonary cells, suggesting that SP-D may enhance viral spread (Favier et al. 2018). SP-A has been shown to enhance clearance of pulmonary adenovirus infection and inhibit lung inflammation (Harrod et al. 1999). Bovine SP-D is also able to bind to bovine rotaviruses via the VP7 glycoprotein and neutralise infectivity (Reading et al. 1998). SP-D binds to the A27 protein of vaccinia virus. SP-D−/− knockout mice challenged with vaccinia virus resulted in increased mortality, compared to SP-D+/+ mice, suggesting that SP-D has a protective role against vaccinia infection (Perino et al. 2013).

4.6.2 MBL

MBL is able to interact with a number of viral pathogens and its effect is generally protective, although there are examples of negative as well as positive outcomes for infection as a result of MBL-mediated binding (Fig. 4.4). Several studies have shown that MBL is a potent inhibitor of IAV infection (Hartley et al. 1992; Hartshorn et al. 1993b; Reading et al. 1995, 1997). Moreover, MBL also has the added ability to deposit complement on IAV-infected cells (Reading et al. 1995). There are also elevated levels of MBL in the lung during IAV infection, suggesting that it may be important for protection against IAV pathogenesis (Reading et al. 1997; Fidler et al. 2009). MBL can inhibit viral hemagglutination and directly neutralise IAV in either a complement-dependent or independent manner (Hartshorn et al. 1993b; Anders et al. 1994; Kase et al. 1999). MBL binds to IAV HA and NA, and without involving complement, neutralises the virus (Kase et al. 1999). However, some IAV strains are resistant to the effects of MBL which is dependent on the degree of glycosylation on the viral HA globular domain (Reading et al. 1997; Job et al. 2010; Tokunaga et al. 2011). Furthermore, MBL−/− mice were more susceptible to infection from highly glycosylated viral strains of IAV than wild-type mice (Chang et al. 2010). However, pandemic strain H1N1 and avian influenza A H9N2 produced more severe disease (enhanced production of pro-inflammatory response) in wild-type mice compared
Fig. 4.4 Anti-viral activity of mannose-binding lectin (MBL). MBL binds to viruses, including influenza virus, acting as an opsonin (not through direct neutralisation), eliminating viral particles by phagocytosis. Binding of MBL to carbohydrate groups found on the surface of viral particles triggers the lectin activation pathway of complement leading to lysis to MBL$^{-/-}$ mice, suggesting that MBL may have a deleterious effect in some IAV infections (Ling et al. 2012).

MBL is able to neutralise HIV-1 in vitro by binding to the N-linked mannose glycans of viral gp120, and binding to HIV-1 infected CD4$^+$ T cells and monocytes and inhibiting reverse transcriptase activity (Ezekowitz et al. 1989; Teodorof et al. 2014). Another study has also shown MBL can also bind to viral gp41 as well as gp120 (Saifuddin et al. 2000), whilst MBL also activates complement on gp120 binding (Haurum et al. 1993). Studies have shown a tentative link between low levels of MBL and increased risk of HIV-1 transmission or progression to AIDS, but this remains contentious (Garred et al. 1997a; Takahashi and Ezekowitz 2005; Ballegaard et al. 2014). There has also been a report of a positive correlation between the rate of AIDS progression and MBL plasma concentration (Mangano et al. 2008). However, other studies have found no correlation between MBL levels and AIDS disease progression (Nielsen et al. 1995; McBride et al. 1998). In general, SP-D is better able to inhibit HIV-1 than MBL, but as is the case for MBL, SP-D’s inhibitory activity against HIV-1 is lower than what has been observed for IAV (Meschi et al. 2005). MBL has also been shown to contribute to HIV-1 pathogenesis, where MBL mediates enhancement of HIV-1 dissemination to the brain by soluble gp120, which is taken up by the CXCR4 receptor on neurones, and then intracellularly trafficked by MBL, thus resulting in the apoptosis of neuronal cells (Bachis et al. 2006; Teodorof et al. 2014).

Epidemiological studies have revealed association of MBL with hepatitis B virus (HBV) and hepatitis C virus (HCV) infection and disease severity, based on genetic polymorphisms (Thomas et al. 1996; Matsushita et al. 1998; Yuen et al. 1999; Sasaki et al. 2000; Hakozaki et al. 2002). However, one study found no link between MBL
polymorphisms and HBV infection (Hohler et al. 1998). MBL is able to bind to HCV envelope glycoproteins, E1 and E2, and is able to activate complement (via MASP-2), resulting in the neutralisation of HCV particles (Brown et al. 2010). MBL probably binds to N-linked glycosylated forms or HBV surface antigen (HBsAg) (Brown et al. 2007), but it is unknown whether this interaction neutralises the infectivity of the virus.

MBL is also able to bind to Ebola virus via its envelope glycoprotein (GP), which contains high mannose glycan sites, and is able to inhibit the binding of Ebola (and Marburg) viruses to DC-SIGN, blocking attachment to host cells and also neutralising the virus through complement activation (Ji et al. 2005). Furthermore, soluble GP is a key component of viral pathogenesis and MBL was found to be able to negate GP activity and the virally induced cytokine storm (Escudero-Perez et al. 2014), and thus MBL could be involved in protection against increased vascular permeability which is a characteristic of Ebola haemorrhagic disease. Nevertheless, high dose MBL therapy in a mouse model, where mice were given recombinant human MBL at levels greater than seven times above average human levels, survived otherwise fatal Ebola viral infection and became resistant to reinfection (Michelow et al. 2011).

There is limited or circumstantial data on the interaction of MBL with a number of other viral pathogens. In mice, MBL appears to modulate the immune responses to HSV-2 (Gadjeva et al. 2004), MBL deficiency seems to be linked with recurrent infections (Gadjeva et al. 2004; Seppanen et al. 2009). MBL also binds to flaviviruses such as Dengue and West Nile virus and is able to neutralise infection through complement-dependent and independent mechanisms (Avirutnan et al. 2011; Fuchs et al. 2011). Genetic polymorphism affecting MBL serum levels may also contribute to the pathogenesis and disease severity of Dengue fever (Avirutnan et al. 2011).

4.6.3 CL-L1, CL-K1, CL-P1 and the Bovine-Unique Collectins, Conglutinin, CL-43 and CL-46

For collectins CL-L1, CL-K1, CL-P1, there is limited data on their interaction with viruses. Only CL-K1 has been shown to bind IAV and partially decrease the infectivity of the virus (Hansen et al. 2010; Selman and Hansen 2012). The binding of CL-L1 and CL-P1 to viruses has not been reported.

Like SP-D, conglutinin binds to IAV resulting in the inhibition of hemagglutination and infectivity of the virus (Hartshorn et al. 1993a). Conglutinin binds via its CRD to the high mannose sites on the viral HA. IAV treated with conglutinin also boosted neutrophil respiratory burst (Hartshorn et al. 1993a). Conglutinin, CL-43 and bovine SP-D have been reported to bind the bovine rotavirus Nebraska calf diarrhoea virus, targeting its VP7 glycoprotein (Reading et al. 1998). Binding resulted in hemagglutination and neutralisation of rotavirus, with CL-43 showing the highest activity against the virus; it is the first report of collectin activity against a non-enveloped virus (Reading et al. 1998). However, conglutinin has a higher inhibitory
activity against IAV (strain HKx31) than bovine SP-D or CL-43 (Reading et al. 1998). Conglutinin binds to HSV-2 and enhances infection in mice (Fischer et al. 1994). It is also able to bind to HIV-1 gp160 and inhibit interaction of the virus with the CD4 receptor (Andersen et al. 1991). Interestingly, a collectin-like protein analogous to bovine conglutinin, was purified from human serum (called conglutinin-like protein) and this was demonstrated to bind to HIV-1 gp120 via its CRD and inhibit viral infectivity (Ushijima et al. 1992).

4.7 Interaction of Collectins with Fungi

Collectins are able to recognise and bind to a number of fungi, both primary and opportunistic fungal pathogens, at various stages in their life cycle. Collectins can exhibit direct growth inhibition and enhance phagocytosis of fungi; in some cases, they can contribute to the fungal pathogenesis.

4.7.1 SP-A and SP-D

Both SP-A and SP-D can bind to the conidia of Aspergillus fumigatus, via its β-(1-6)-glucan carbohydrate structures on the fungal cell surface in a Ca\(^{2+}\) dependent manner (Fig. 4.3) (Madan et al. 1997a; Allen et al. 2001a, b). SP-A and SP-D can cause inhibition of conidia infectivity via agglutination, enhancement of phagocytosis and intracellular killing of A. fumigatus conidia by neutrophils and AM (Madan et al. 1997a). The fungal ligands of SP-A are 2 N-linked glycosylated glycoproteins (gp45 and gp55) isolated from culture filtrate and are also used for ELISA diagnosis of allergic aspergillosis (Madan et al. 1997b). Fungal melanin was recently determined to be the primary ligand for SP-D on the A. fumigatus conidia cell surface, and is able to facilitate fungal phagocytosis and modulate the anti-fungal immune response (Wong et al. 2018).

Utilising a mouse model of invasive pulmonary aspergillosis (IPA), SP-D, but not SP-A, was found to be protective against a normally fatal challenge of A. fumigatus conidia (Madan et al. 2001a, b). In this study, IPA mice-treated intranasally with purified human SP-D or rfhSP-D showed 60 and 80% survival respectively (Madan et al. 2001a, b). The basis of this therapeutic protection by SP-D and rfhSP-D was observed to be enhanced phagocytosis of conidia by macrophages and neutrophils, fungistatic effects on the growth of conidia and a dampening of pathogenic Th2 cytokines (IL-4 and IL-5), whilst enhancing protective Th1 cytokines (TNF-α and IFN-γ) (Singh et al. 2009). SP-D\(^{-/-}\) knockout mice are more susceptible to IPA (Madan et al. 2010). However, SP-A\(^{-/-}\) knockout mice demonstrate resistance to IPA, suggesting that SP-A may be involved in the pathogenesis of IPA (Madan et al. 2010).

Both SP-A and SP-D also have a direct effect on Histoplasma capsulatum, inhibiting its growth by increasing the permeability of the fungal membrane (McCormack et al.
However, no aggregation of *H. capsulatum* was observed by SP-A or SP-D, and neither collectin altered the phagocytosis of the fungus or inhibited the growth of macrophage-infected *H. capsulatum* (McCormack et al. 2003).

SP-A is also able to bind to Cryptococcus neoformans, both in its encapsulated and non-encapsulated yeast form, but this does not result in increased phagocytosis of the acapsular form (Walenkamp et al. 1999). SP-A binding was Ca²⁺-dependent and was inhibited by glucose and mannose, but not galactose (Walenkamp et al. 1999). Intranasal infection with *C. neoformans* gave the same survival outcome in SP-A−/− knockout mice and wild-type mice, suggesting that the fungus is resistant to SP-A mediated host defence mechanisms (Giles et al. 2007). A subsequent study found that SP-D increases the phagocytosis of hypocapsular *C. neoformans* by murine macrophages and that this facilitated fungal survival (Geunes-Boyer et al. 2009). Other studies have also shown that SP-D can agglutinate *C. neoformans* and *A. fumigatus* (Schelenz et al. 1995; Madan et al. 1997a). Furthermore, SP-D can bind to both encapsulated and acapsular *C. neoformans* and can aggregate acapsular *C. neoformans* in particular (van de Wetering et al. 2004a). The cryptococcal capsular components glucuronoxylomannan (GXM) and mannoprotein 1 (MP1) are the ligands for SP-D (van de Wetering et al. 2004a). SP-D is able to facilitate *C. neoformans* infection further by protecting the fungus against oxidative stress allowing for disease progression in the mouse model of infection (Geunes-Boyer et al. 2012).

SP-D is also able to bind Blastomyces dermatitidis, via β-glucan on its surface, and subsequently block interactions with β-glucan-receptors on AM (Lekkala et al. 2006). This study also showed a reduction in TNF-α, dampening the host inflammatory response and thus may facilitate disease progression (Lekkala et al. 2006). SP-D and SP-A can also bind to Coccidioides posadasii via its surface antigens. In a mouse model of infection, *C. posadasii* infection is able to suppress the expression of pulmonary SP-A and SP-D, possibly facilitating fungal disease progression and dissemination (Awasthi et al. 2004). SP-D can also bind to Candida albicans via its surface antigens and agglutinate the pathogen and directly inhibiting its growth without the requirement of macrophage dependent phagocytosis (van Rozendaal et al. 2000). Similarly, SP-A is able to bind to *C. albicans* and interfere with attachment to AM, inhibiting phagocytosis (Rosseau et al. 1997). SP-A is also able to dampen the pro-inflammatory response elicited by *C. albicans* by human AM and monocytes, which may be important in regulating excessive inflammation in the lung during Candida infection (Rosseau et al. 1999). In Saccharomyces cerevisiae, SP-D is observed to bind to its surface, but not SP-A, whilst the fungal ligand for SP-D is yeast β-(1-6)-glucan (Allen et al. 2001a, b).

The opportunistic fungus, Pneumocystis is able to infect a number of mammals with each species of the fungus displaying strict host specificity. For example, *P. carinii* and *P. wakefieldiae* infect rats, *P. murina* infects mice, *P. oryctolagi* infects rabbits, and *P. jirovecii* infects humans. SP-A and SP-D are able to recognise and bind Pneumocystis species via the major surface glycoprotein (MSG; also known as gpA) of the fungus (O’Riordan et al. 1995; McCormack et al. 1997a, b). MSG contains an N-linked carbohydrate chain made up of glucose, mannose, and N-acetyl-glucosamine and is involved in attachment of the fungus to alveolar epithelium.
Cruciform dodecamers and other large oligomers of SP-D have a higher affinity of binding to *P. carinii* than do smaller oligomeric versions of SP-D (Vuk-Pavlovic et al. 2001). SP-D is also able to recognise *Pneumocystis* cysts via surface β-glucans (Vuk-Pavlovic et al. 2001). However, SP-D binding does not appear to increase the phagocytosis of the fungus (McCormack et al. 1997a, b; Vuk-Pavlovic et al. 2001). Despite this, SP-D does aggregate *P. carinii* in large complexes that may restrict phagocytosis by macrophages and may allow for persistence of the fungus within the host lungs (Vuk-Pavlovic et al. 2001). Pneumocystis pneumonia does alter the expression of SP-A in the lungs (Atochina et al. 2001), with a threefold increase in the levels of SP-A and SP-D (Phelps et al. 1996; Aliouat et al. 1998; Qu et al. 2001), but decreases total phospholipid content (Atochina et al. 2001).

Human SP-A enhances attachment of *P. carinii* to rat AM in vitro (Williams et al. 1996). SP-A also reduces phagocytosis of *P. carinii* in human AM in vitro (Koziel et al. 1998). These data suggest that increased levels of SP-A during *Pneumocystis pneumonia* (Phelps et al. 1996) may contribute to the pathogenesis through binding to the fungus and interfering with its AM recognition (Koziel et al. 1998). Immunosuppressed SP-A<sup>−/−</sup> mice also have increased susceptibility to *P. carinii* infection (Linke et al. 2001), whilst removal of immunosuppression resulted in efficient clearance of the infection (Linke et al. 2006), showing that SP-A does not enhance *P. carinii* clearance, but does modulate the host immune response during the resolution of infection. SP-D modulates interaction of *P. carinii* with AM (Limper et al. 1995) and also aggregates *P. carinii*, impairing phagocytosis by AM (Yong et al. 2003). In SP-D<sup>−/−</sup> mice, there was delayed clearance of *P. carinii* infection, increased inflammation and altered nitric oxide response (Atochina et al. 2004). Similarly, in immunosuppressed mice, SP-D was found to enhance *P. carinii* infection (Vuk-Pavlovic et al. 2006).

### 4.7.2 MBL

MBL has been reported to interact with various primary and opportunistic fungal pathogens. Low serum levels of MBL have been linked to increased likelihood of fungal disease (Mullighan et al. 2002; Granell et al. 2006). MBL is able to bind to *A. fumigatus* (Neth et al. 2000), *B. dermatitidis* (Koneti et al. 2008), *C. albicans* (Kitz et al. 1992; Neth et al. 2000; Ip and Lau et al. 2004; van Asbeck et al. 2008), *Candida parapsilosis* (van Asbeck et al. 2008), and *C. neoformans* (Chaka et al. 1997; van Asbeck et al. 2008). The ligands for MBL binding to *C. albicans* and *C. neoformans* are mannan and mannoprotein, respectively (Chaka et al. 1997; Ip and Lau, 2004), whilst 1,3-β-glucan and mannose are the MBL ligands on *B. dermatitidis* and *A. fumigatus*, respectively (Neth et al. 2000; Koneti et al. 2008).

MBL is able to bind *A. fumigatus* conidia showing aggregation, enhancing phagocytosis, and complement deposition (Kaur et al. 2007). However, MBL binding of conidia did not always result in the killing of *A. fumigatus* by phagocytes (Madan et al. 2005a, b; Kaur et al. 2007). Moreover, MBL may be less important in this
context, since it is mainly a serum protein and may not be in significant levels in the lung. Nevertheless, genetic polymorphisms in the MBL gene have been shown to be associated with severe aspergillosis (Crosdale et al. 2001; Vaid et al. 2007). Similarly, MBL deficiency is a risk factor for aspergillosis in immunocompromised patients, cancer patients and transplant recipients. In the mouse model of infection, MBL deficiency does not necessarily affect the survival of mice infected with *A. fumigatus* conidia, due to redundancy since mice having two copies of the MBL gene (Mbl1 and Mbl2), encoding MBL-A and MBL-C proteins in mouse serum (Hogaboam et al. 2004). However, treatment with recombinant MBL does enhance survival in IPA mice (Kaur et al. 2007). Thus, the role of MBL in *A. fumigatus* infection may also depend on the route of infection and the level of immunosuppression of the host.

MBL interaction with *B. dermatitidis* has only been studied in the mouse system. Both MBL mouse proteins (MBL-A and MBL-C) bind to *B. dermatitidis* yeast cells (Koneti et al. 2008). Inhibition of macrophage response to *B. dermatitidis* is also mediated by MBL, binding to 1,3-β-glucan ligand on *B. dermatitidis*, and thus inhibiting 1,3-β-glucan interaction with Dectin-1 receptor on macrophages and also decreasing TNF-α production (Brown et al. 2002; Kimberg and Brown 2008). Moreover, macrophage production of G-CSF, IFN-γ, MCP-1, and RANTES were significantly inhibited by MBL in response to *B. dermatitidis*, but not IL-6 (Brummer et al. 2007).

MBL can bind to *C. albicans* yeast and pseudohyphae and to *C. parapsilosis* yeast cells (Denton and Disalvo 1964; Sugar and Picard 1988; Brummer et al. 2005; van Asbeck et al. 2008). MBL is able to aggregate *C. albicans* resulting in its growth inhibition and complement deposition of C4b and C3b on its surface via MASPs (Ip and Lau 2004; van Asbeck et al. 2008). Similar levels of MBL-mediated complement deposition were also observed for *C. parapsilosis* (van Asbeck et al. 2008). However, the binding of MBL to *C. albicans* may inhibit its phagocytosis by macrophages or dendritic cells (Zimmerman et al. 1992; Schelenz et al. 1995; Chaka et al. 1997; Vuk-Pavlovic et al. 2001; Ip and Lau 2004; van de Wetering et al. 2004a). MBL seems to inhibit *Candida*-induced macrophage responses in THP-1 cells through TLR-2 and TLR-4, suggesting that *C. albicans* modifies TLR signalling pathways in the macrophage (Wang et al. 2013). However, in the case of neutrophils, MBL enhances the phagocytosis of both *C. albicans* and *C. parapsilosis* yeast cells (van Asbeck et al. 2008). MBL greatly facilitates complement-mediated uptake of *C. albicans* via CR1 receptor in neutrophils and this results in the stimulation of reactive oxygen species by intracellular Dectin-1, which recognises the phagocytosed fungal β-1,3 glucan (Li et al. 2012). The binding of MBL with *C. albicans* yeast also increases TNF-α production by monocytes in vitro (Ghezzi et al. 1998) and in vivo (Lillegard et al. 2006). Double knockout (MBL-A and MBL-C) mice were found to be more susceptible to systemic infection with *C. albicans* compared to wild-type mice (Held et al. 2008). Vaginal candidiasis is an important mycosis in women. MBL protein is present in vaginal secretions (Pellis et al. 2005); MBL levels seem to increase in vulvovaginal candidiasis. However, MBL levels were found to be lower in women
with recurrent vulvovaginal candidiasis, because of polymorphisms in their MBL
gene (Babula et al. 2003; Liu et al. 2006; Giraldo et al. 2007; Donders et al. 2008;
Milanese et al. 2008). The precise role of MBL in candidiasis remains to be fully
explored.

MBL can bind to acapsular *C. neoformans* yeast cells (Chaka et al. 1997), but this
does not cause aggregation (Eisen et al. 2008). However, MBL binding to acapsular *C.
neoformans* did facilitate complement deposition and enhancement of fungal phago-
cytosis by neutrophils (van Asbeck et al. 2008). Furthermore, TNF-α production was
induced in peripheral blood mononuclear cells by *C. neoformans* mannoprotein and
this effect was enhanced by MBL (Chaka et al. 1997). It is unknown whether MBL
binds to *H. capsulatum* or *P. carinii*. It is unlikely that MBL binds to *H. capsula-
tum*, since the cell wall contains 1,3-α-glucan (Rappleye et al. 2007); however, in *P.
carinii*, the cell surface of cyst forms does contain β-1,3-glucan (Williams et al. 1996),
which may bind MBL. In Coccidioides species, it is also unknown whether MBL
interaction occurs, but patients with active coccidioidomycosis have been shown to
have low serum MBL levels, compared to healthy individuals previously infected
with Coccidioides, and that low levels of MBL were associated with polymorphisms
in their MBL gene (Corredor et al. 1999).

### 4.7.3 CL-L1, CL-K1, CL-P1 and the Bovine-Unique
**Collectins, Conglutinin, CL-43 and CL-46**

Very few studies have investigated the interaction of these minor collectins with
fungal species. CL-K1 can bind *C. albicans* (Selman and Hansen 2012) and cellular
extracts (mannan) of *S. cerevisiae* (Keshi et al. 2006; Selman and Hansen 2012).
CL-P1 has also been reported to bind to *S. cerevisiae* and mediate phagocytosis of
yeast-derived zymosan, suggesting that CL-P1 mediates phagocytosis for fungi in
the vascular endothelium (Ohtani et al. 1999; Jang et al. 2009). Interestingly, CP-P1
also partially binds to *A. fumigatus*, via its CRD, and in association with properdin,
can activate the complement alternative pathway, resulting in C3b deposition and
formation of the membrane attack complex (Ma et al. 2015). This shows a novel
mechanism of triggering the alternative pathway of complement (Ma et al. 2015).
There are no reports of CL–L1 interaction with fungi.

There are also limited reports of the binding of bovine-unique collectins to fungi.
CL-43 is able to bind to acapsular *C. neoformans* in vitro in a Ca^{2+}-dependent man-
ner (Schelenz et al. 1995), and immobilised yeast mannan (Holmskov et al. 1996).
Conglutinin is able to bind to glycoproteins and polysaccharides derived from *S.
cerevisiae* (N-acetylglucosamine, mannose, mannan) (Loveless et al. 1989; Lim and
Holmskov 1996).
4.8 Interaction of Collectins with Protozoal and Helminth Pathogens

An area of collectin that is yet to be fully explored is the interaction of collectins with protozoal and helminth pathogens, which are responsible for some of the most important global infections. There are limited studies and these are mostly based on genetic polymorphisms in collectin genes that are associated with predisposition or severity of these diseases. There is a limited number of functional studies on the role of collectins in protozoal and helminth infections.

Increases in levels of SP-D were observed in serum, renal and cerebral tissues in mice experimentally infected with *Plasmodium berghei*, compared to control mice (Cahayani et al. 2016). Low MBL serum levels and genetic polymorphisms in the MBL gene have been associated with more severe malaria, particularly in children (Luty et al. 1998; Holmberg et al. 2008). MBL can bind to *P. falciparum* protein extracts, but it does not appear to inhibit the parasite directly (Klabunde et al. 2002). MBL does not opsonise *P. falciparum*, but it can bind to *P. falciparum*-infected erythrocytes, recognising the 78-kDa glucose-regulated stress glycoprotein of the parasite (Garred et al. 2003). MBL binding to *P. falciparum* merozoite adhesins have also been reported, having the ability to activate complement (Korir et al. 2014).

The complement lectin pathway can be activated by Trypanosoma and Leishmania (Cestari et al. 2013). MBL binds to glycosylated antigens on *Trypanosoma cruzi*, on the surface of metacyclic trypomastigotes, resulting in complement activation (Cestari Idos et al. 2009). In a mouse model of *T. cruzi* infection, MBL influences host resistance and pathology (Rothfuchs et al. 2012). In some strains of *T. cruzi*, MBL mediates resistance to complement lysis of the parasite and enhances invasion of host cells (Evans-Osses et al. 2014).

MBL also binds to major cell surface glycoconjugates (lipophosphoglycans) on Leishmania parasites, triggering lectin pathway activation and promastigote lysis (Green et al. 1994; Ambrosio and De Messias-Reason 2005). Certain genotypes of the MBL2 gene were also predictive for the risk for developing visceral leishmaniasis and other clinical complications in infections with *Leishmania chagasi* (Alonso et al. 2007). Similarly, there was a strong correlation found between serum levels of MBL and the probability of developing visceral leishmaniasis (Santos et al. 2001). Monocytes challenged with MBL-opsonised *L. chagasi* promastigotes secreted higher levels of TNF-α and IL-6 than controls, suggesting that MBL may play an important role in pathogenesis (Santos et al. 2001).

In helminth infections, MBL binds to the surface glycoproteins of *Schistosoma mansoni* cercariae and adult worms and is able activate the lectin pathway (Klabunde et al. 2000). Curiously, no differences in serum MBL levels were observed between patients infected with Schistosoma and in healthy controls (Klabunde et al. 2000). Another study has shown that high MBL serum levels are associated with protection in schistosomiasis (Antony et al. 2013). Interestingly, high levels of MBL and CL-K1 were inversely correlated with urogenital infections with *S. haematobium* (Antony...
et al. 2015b). Although CL-K1 has not been shown to bind directly to the parasitic worm, it was observed to be a risk factor for urinary schistosomiasis (Antony et al. 2015a). Furthermore, concomitantly elevated IL-6 levels were also observed in urinary schistosomiasis cases compared to controls that correlated with MBL levels (Antony et al. 2015b). Similar findings linking IL-6 and MBL have also been described in patients with visceral leishmaniasis (Santos et al. 2001; Antony et al. 2015b).

SP-D has also been shown to bind to fucosylated glycoconjugates (α-1–3 linked fucose) on the surface of S. mansoni larval stages, although the significance of this interaction remains unclear (van de Wetering et al. 2004b, c). However, a recent study has suggested that SP-D is essential for protection against helminth infection, using the experimental model nematode Nippostrongylus brasiliensis (Thawer et al. 2016). N. brasiliensis infection of SP-D−/− knockout mice resulted in severe susceptibility to parasitic disease, whilst treatment with rhSP-D enhanced parasite clearance and anti-parasitic immune responses (Thawer et al. 2016). SP-D was determined to bind to N. brasiliensis larvae via its CRD, and to enhance their killing by AM (Thawer et al. 2016).

4.9 Collectins and Allergy

A considerable number of in vitro and in vivo studies have focused on the immunomodulatory functions of collectins and their contribution to the host defense system. Through activation of complement, and production of pro-inflammatory cytokines, MBL makes a major impact on the generation and regulation of the immune-mediated inflammatory response. Allergen-mediated activation of the complement lectin pathway has been demonstrated (Varga et al. 2003). Allergen extracts (parietaria (PA) and house dust (HD) mite) were shown to bind purified MBL, and trigger the lectin complement pathway. Differences in plasma MBL levels may affect the degree of complement activation in different individuals, thus, susceptibility to allergic diseases. Significantly elevated serum MBL levels were observed in pediatric mild-asthma patients, suggesting the possible role of MBL in the pathogenesis of asthma by contributing to airway inflammation, or increasing the risk of asthma development (Uguz et al. 2005). Enhanced levels of serum MBL also correlate with an increased peripheral blood eosinophils in these individuals. It is also suggested that oxidative stress increases the MBL synthesis, and triggers complement activity. MBL can initiate complement activation following oxidative stress in asthma (Collard et al. 2000; Nadeem et al. 2003; Uguz et al. 2005), and aggravate inflammation. Significantly increased MBL levels and MBL pathway was also detected in patients with bronchial asthma, rhinitis and allergic bronchopulmonary aspergillosis (ABPA) (Kaur et al. 2005).

A higher level of plasma MBL is likely to contribute to activation of lectin pathway, and an increased severity, including enhanced blood eosinophil counts. In addition, production of MBL in the liver is suggested to increase by up to three fold in response
to environmental stimuli. Therefore, higher levels of plasma MBL in allergic patients, compared to the non-allergic patients, may result from elevated hepatic synthesis caused by allergen exposure. Furthermore, the circulating level of mouse MBL-A was also measured in Aspergillus fumigatus allergen-sensitised and non-sensitised mice. Increased level of mMBL-A was observed following allergic sensitisation, suggesting that challenging these mice with allergen may contribute to a higher level of MBL in sensitised mice as well as allergic patients (Kaur et al. 2005). Earlier in vivo studies using mouse MBLs have reported the likely role of MBL-A as a mediator of inflammation (Santos et al. 2001; Takahashi et al. 2002). Moreover, a substantial decline in the airway hyperresponsiveness to A. fumigatus conidia was seen in MBL-A–deficient mice (MBL-A−/−) when compared to MBL-A+/+ control mice, which suggest the possible role of MBL-A and its ability to trigger progression of airway hyper-responsiveness (Hogaboam et al. 2004).

Since levels of plasma MBL are genetically determined, it is of interest to study the genetic polymorphisms in MBL in relation to allergic susceptibility. In order to address the correlation between polymorphisms in the MBL gene and the progression of atopic diseases, Nagy et al. found a contribution of variant MBL alleles to the susceptibility to acute or chronic Chlamydia pneumoniae infection in asthmatic children (Nagy et al. 2003). Another study that focused on the genetic association of MBL-related single nucleotide polymorphisms (SNPs) with allergic patients (Kaur et al. 2006), reported the identification of G1011A, an intronic SNP found in the MBL gene, and presence of 1011A allele of SNP G1011A to be associated with an enhanced level of plasma MBL. SNP G1011A has also been suggested to play a role in regulating MBL expression. Additional polymorphisms were found at positions 550 (H/L variants) and 221 (X/Y variants) in the promoter region of the MBL gene, which associated with high MBL levels in the plasma. 1011A allele was also associated with bronchial asthmatic patients with allergic rhinitis and ABPA, which positively correlated with allergic markers, including high peripheral blood eosinophil counts, and reduced levels of forced expiratory volume at timed interval of 1 s (FEV1) in these patients. However, no structural SNPs have been observed within the MBL gene in these allergic patients.

As carbohydrate recognition immune molecules, both SP-A and SP-D have been shown to interact with gp55 and gp45 of A. fumigatus in a calcium and carbohydrate specific dependent manner (Madan et al. 1997b). Both these collagenous molecules inhibit specific IgE binding to these glycoproteins, and block allergen triggered histamine release from human basophils isolated from Derp- and A. fumigatus-sensitised patients (Madan et al. 1997a, b). Dodecameric forms of human SP-D mediate binding, aggregation, and phagocytosis of starch granules, containing grass pollen allergens from Dactylis glomerata and Phleum pratense via alveolar macrophages (Erpenbeck et al. 2005). SP-D can suppress proliferation of PBMCs isolated from children with Derp–sensitive asthma (Wang et al. 1998), and suppress secretions of IL-2 by PBMCs (Borron et al. 1998). Suppressive effects of SP-A on the production and release of IL-8 by eosinophils were also reported, which is stimulated by ionomycin in a concentration-dependent manner (Cheng et al. 1998). Since IgE cross-linking, release of histamine and PMBCs proliferation are crucial immunological factors
contributing to the development of asthmatic symptoms, both SP-A and SP-D are crucial immune modulators in resisting allergenic challenge, as well as suppressing substantial hypersensitivity reactions in the lungs (Kishore et al. 2002).

Intranasal administration of SP-D or rfhSP-D caused reduced levels of peripheral and pulmonary eosinophilia, and the effect persisted up to 16 days in the ABPA mice. These observations therefore indicate the potential of SP-D as a therapeutic agent (Kishore et al. 2002; Madan et al. 2001a, 2005a, b). In addition, protective role of rfhSP-D has also reported in murine model of Derp allergens-induced pulmonary hypersensitivity (Singh et al. 2003). Shifting of Th2 to a Th1 following SP-D treatments appeared to be crucial to the protective mechanism, since, IFN-γ gamma is suggested to inhibit differentiation of Th2 in response to IL-4 (Elser et al. 2002). Additionally, production of nitric oxide was significantly inhibited when Derp mice derived alveolar macrophages are pre-incubated with rfhSP-D, and resulted in low levels of TNF-α in the rfhSP-D treated Derp mice (Liu et al. 2005). Culturing alveolar macrophages with allergen and SP-D has induced an increased production of IL-10, IL-12, and IFN-γ, indicating a positive correlation between macrophages and SP-D triggered inhibition of airway inflammation and airway hyper-responsiveness (AHR) (Takeda et al. 2003).

A study by Madan et al. has focused on the susceptibility of SP-A−/− and SP-D−/− mice to challenge with A. fumigatus allergen compared to wild-type mice (Madan et al. 2005a, b).

Intrinsic hypereosinophilia and seven fold increase in IL-5 and IL-13 levels were seen in both SP-A−/− and SP-D−/− mice. However, lower levels of IFN-γ to IL-4 ratio in the lungs were observed, suggesting the possible Th2 basis of immune response. Treating these mice with exogenous intranasal SP-A and SP-D resulted in reversal of Th2 polarisation. SP-D−/− mice was reported to be more susceptible to A. fumigatus allergen-induced pulmonary hypersensitivity when compared to wild-type mice. However, resistant to sensitisation was seen with SP-A−/− mice. Intranasal administration of SP-D or rfhSP-D led to rescue of the sensitised SP-D−/− mice, while SP-A−/− mice demonstrated an enhanced levels of IL-5 and IL-13, causing greater pulmonary eosinophilia. Genetic polymorphisms in the collagen region of SP-A2 (SP-A2 G1649C and SP-A2 A1660G) may also increase susceptibility to allergic bronchopulmonary aspergillosis (ABPA) (Saxena et al. 2003).

### 4.10 Collectin (and C1q) Receptors

The collectins are structurally related to the complement protein C1q (having a collagenous region and similar overall tertiary structure. A common receptor for SP-A, MBL and C1q was described in 1990 (Malhotra et al. 1990) (Fig. 4.5), as collagen region binding cC1qR. This was subsequently identified as Calreticulin (~56kDa). Two other candidate receptors were subsequently proposed:
Collectin receptors on immune cells. Collectins have been shown to bind a number of receptors and putative receptors, which lead to immunomodulatory responses. Binding of collectins to Toll-like receptor 2 (TLR-2), TLR-4, SP-A receptor 210 (SP-R210), CD91-calreticulin, and signal inhibitory regulatory protein-α (SIRP-α) alters production of pro-inflammatory mediators. For example, SP-A and SP-D binds to SIRP-α via their collagenous tails, and stimulates pro-inflammatory chemokine production via calreticulin/CD91 interaction. Furthermore, bacterium bound collectins induces the conformational changes of calreticulin/CD91 interaction, which then activates P38-mitogen-activated protein kinase (MAPK) signalling pathway, leading to transcriptional activation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), and expression of pro-inflammatory cytokines, including tumour necrosis factor alpha (TNF-α). SIRP-α is abundantly expressed in macrophages, and ligation of SIRP-α by lung collectins are crucial in preventing damage to the airways caused by the production of pro-inflammatory responses. Thereby, phosphorylated cytoplasmic region of SIRP-α recruits SHP-1 (Src homology region 2 domain-containing phosphatase-1), which in turn dephosphorylates protein substrates involved in mediating physiological effects. Thus, the interaction between SIRP-α and SHP-1 negatively regulates P38-MAP kinase signalling, and stimulates NF-κB activity, and cells become resistant to TNF-mediated effects, such as apoptosis.

1. C1qR (C1q receptor associated with phagocytosis stimulated by C1q, MBL or SP-A): but this has subsequently been shown not to bind any of these ligands. It may be an adhesion receptor (McGreal et al. 2002; Norsworthy et al. 2004).
2. CR1, the complement C3b receptor, does interact with C1q and MBL, but functional aspects are not yet widely explored (Jacquet et al. 2018).
3. Calreticulin remains the main candidate as a receptor/adapter involved in phagocytosis mediated by C1q and collectins (Ogden et al. 2001; Vandivier et al. 2002). Calreticulin bound to the cell surface CD91 mediates uptake of apoptotic cells.
to which C1q, MBL, SP-A and SP-D are bound. It also mediates uptake of microorganisms targeted by the collectins.

SP-A and SP-D can interact with phagocytic receptors and are able to influence receptor-mediated uptake of bacteria (Lawson and Reid 2000). SP-A enhances the phagocytosis of *S. aureus* by monocytes but does not induce intracellular killing or the production of reactive oxygen intermediates (ROI) (Geertsma et al. 1994). SP-A is also able to enhance the uptake of *M. tuberculosis* and *M. avium* by macrophages via the increased expression of mannose receptor (Gaynor et al. 1995; Kudo et al. 2004), whilst SP-A enhances the scavenger receptor A (SR-A)-mediated uptake of *Streptococcus pneumoniae* by AM (Kuronuma et al. 2004). SP-A is also reported to bind to a 210-kDa SP-A receptor (SPR210) in U937 macrophages and rat AM and mediate uptake of *Mycobacterium bovis* bacillus Calmette-Guérin (BCG) via this receptor (Chroneos et al. 1996; Weikert et al. 1997); in rat macrophages, this led to enhanced mycobacterial killing and an increase in the production of inflammatory mediators, TNF-α and nitric oxide (Weikert et al. 2000). SP-A and SP-D can also bind to the major LPS receptor, CD14 that is present on alveolar macrophages. SP-A binds to the peptide portion of CD14, whilst SP-D interacts with the glycan of the receptor (Sano et al. 2000). SP-A modulates LPS-induced cellular responses by direct interaction with CD14 (Sano et al. 1999), serving as an important mechanism for the recognition and clearance of this endotoxin. As noted above, SP-A and SP-D can interact with the versatile protein calreticulin (Malhotra et al. 1990). When SP-A and SP-D bind to surface target ligands such as LPS or apoptotic cells, multiple collagen regions are presented on the surface, which interact with the Calreticulin-CD91 receptor complex (Gardai et al. 2003). This can then lead to the promotion of phagocytosis and initiation of cell signalling pathways leading to the production of pro-inflammatory cytokines and priming of adaptive immunity (Ogden et al. 2001; Vandivier et al. 2002; Gardai et al. 2003). In contrast, SP-A and SP-D can also suppress inflammatory responses by binding to signal regulating protein α (SIRP-α) on macrophages and epithelia via their CRD region, and this leads to a signalling pathway that blocks pro-inflammatory mediator production (Fig. 4.5) (Table 4.2) (Gardai et al. 2003). Therefore, the orientation of binding of SP-A and SP-D (collagen or lectin (CRD)) domains to host receptors Calreticulin-CD91 or SIRP-α, respectively, have opposing effects and illustrate a dual function of these collectins, which could be, (1) protection of the naïve lung via maintenance of immune homeostasis and (2) protection via the triggering of inflammation to clear pathogens, allergens, necrotic and apoptotic cells. Another receptor, gp-340 has also been found to bind to SP-D and SP-A (Holmskov et al. 1997a; Tino and Wright 1999), but any microbial interaction has been described for Influenza virus (Hartshorn et al. 2006a, b) and not bacteria, whilst binding of SP-A to gp-340 stimulates macrophage chemotaxis (Tino and Wright 1999).

Calreticulin (cC1qR) is a collectin binding protein of 56 kDa, and is known to bind C1q, MBL, SP-A, conglutinin and CL-43 (Fig. 4.5) (Table 4.2) (Malhotra et al. 1993). This interaction is independent of calcium ions, and ionic in nature. It is mediated by the collagen domain ‘c’ of the collectins (cC1qR). The C1q binding site has
Table 4.2  Binding proteins and Receptors for lung collectins

| Binding proteins/receptors | Cells expressing the receptors | Protein domain | Proposed functions |
|----------------------------|--------------------------------|----------------|-------------------|
| Calreticulin/CD91          | Ubiquitous                     | Collagen region of SP-A and SP-D | Phagocytosis and production of pro-inflammatory cytokines |
| C1qRp/CD93                 | Monocytes, macrophages, neutrophils, platelets, endothelial cells and microglia | Reported as a receptor, but may not bind C1q or collectins | Initially proposed to have roles in phagocytosis |
| gp340                      | Soluble opsonin                | CRD region of SP-A and SP-D | Stimulation and migration of alveolar macrophages |
| CD14                       | Alveolar macrophages           | Neck region of SP-A which interacts with the peptide portion containing the leucine-rich repeats of CD14, CRDs of SP-D that binds and interact with carbohydrate moiety of CD14 | CD14-LPS modulation and release of pro-inflammatory cytokines and chemokines |
| SIRP α/CD172               | Antigen presenting cells, endothelial cells, myeloid cells, and neurons | CRD of SP-A and SP-D | Inhibition of pro-inflammatory cytokine and chemokine production |
| SPR210                     | Type II cells, alveolar macrophages, and bone marrow derived macrophages | SP-A- 36 residues collagen region composed of RGD motif | Regulation of phospholipid secretion and cytokine production, phagocytosis, and inhibition of T-cell proliferation |

been mapped to the S-domain of calreticulin (Stuart et al. 1996). Conglutinin and CL-43 also bind C1qR and calreticulin (Dec and Wernicki 2006). SP-A receptor 210 (SP-R210) is a 210 kDa oligomeric molecule that earlier has been purified from the macrophage cell line U937 by affinity chromatography (Fig. 4.5 (Table 4.2) (Chronneos et al. 1996). SP-R210 is another candidate receptor for SP-A, and also found in type II cells and alveolar macrophages. The direct interaction between SP-R210 and SP-A occurs through the collagen region of SP-A. Antibodies raised against SP-R210 inhibit SP-A binding to alveolar type II cells and alveolar macrophages, thus, prevent SP-A-mediated uptake of Mycobacterium bovis, and block SP-A-bacillus Calmette-Guerin complexes to phagocytes. Furthermore, SP-R210 inhibited SP-A-mediated
phospholipid secretion by alveolar type II cells (Weikert et al. 1997). Additionally, a study by Yang et al. reported SP-R210 as a cell surface myosin 18A (Yang et al. 2005), and expressed in multiple isoforms. Gp340 is a 340 kDa SP-D binding glycoprotein purified from lung bronchoalveolar lavage of alveolar proteinosis patients (Holmskov et al. 1997), and belongs to the scavenger receptor superfamily, consisting of multiple scavenger receptor type B domains (Holmskov et al. 1999). Furthermore, gp340 has been shown to be identical to salivary agglutinin, and its binding interaction with *Streptococcus mutans* and *Helicobacter pylori* has been reported (Ligtenberg et al. 2001). The direct binding of SP-D to gp340 occurs in a calcium dependent manner, and is inhibited by EDTA. The interaction is not affected by the presence of maltose, suggesting that the binding is a protein-protein interaction via the CRD region of SP-D rather than a lectin-carbohydrate interaction. Similar binding pattern was observed between gp340 and rfhSP-D, composed of trimeric neck region and CRD (Holmskov et al. 1997). Gp340 exists in a soluble form, and acts as an adaptor for SP-A and SP-D, but how gp340 is anchored in the membrane and the mechanism of binding to cell surface has not been elucidated fully yet (Table 4.2). SP-D can bind to human neutrophil defensins (HNPs) via its neck and CRD region (Hartshorn et al. 2006a, b). The interaction between SP-D and HNPs can trigger anti-viral activity in the BAL fluid. HD6, human β-defensins, and human neutrophil peptide (HNP)-4 bind SP-D with weaker affinity, while HNP-1-3 bind SP-D with high affinity and trigger inhibition of SP-D mediated anti-viral activity (Doss et al. 2009). Additionally, SP-D binds human decorin from amniotic fluid in a calcium dependent manner via sulphated N-acetyl galactosamine moiety of decorin (Nadesalingam et al. 2003). rfhSP-D interacts with dermanatan sulphate moiety of decorin, and core protein of decorin interacts with SP-D via the collagen-like region.

The interaction between lung collectins (SP-A and SP-D) and native as well as recombinant CD14 has been reported (Table 4.2) (Sano et al. 1999). CD14 is a soluble receptor for LPS, and the neck domain of SP-D has been shown to bind the leucine-rich peptide portion of CD14, whilst the carbohydrate moiety of CD14 interacts with the lectin domain of SP-D (Sano et al. 1999). Thus, both these surfactant proteins appear to modulate the cellular response to smooth and rough LPS by interaction with CD14. (Sano et al. 1999). Furthermore, the association of SP-A and SP-D with toll-like receptors (TLR), and or the TLR-associated molecule, could be one of the mechanisms by which they function as modulators of inflammation an inflammatory mediators (Sano et al. 1999). Studies have reported direct involvement of SP-A in TLR2 signalling, and inhibition of downstream gene activation (Murakami et al. 2002). SP-A interacts directly with TLR4 and myeloid differentiation factor 2 (MD-2), which are known critical signalling receptors for LPS (Billod et al. 2016). Thus, binding of SP-A with extracellular domain of TLR4 and MD-2 was revealed in a calcium-dependent manner, involving the CRD region. Additionally, SP-A has attenuated cell surface binding of smooth LPS, and induced NF-κB activation in cells expressing TLR4 and MD-2 (Murakami et al. 2002). SP-D does not have significant effect on TLR4 expression, but it down-regulates the TLR4-mediated signalling against LPS (Henning et al. 2008). Thus, SP-A’s ability to dampen TLR2 and
TLR4 signalling is associated with decrease in the phosphorylation of IkappaBalpha, a key regulator of NF-κB activity, and nuclear translocation of p65, resulting in reduced TNF-α secretion in response to TLR ligands. Furthermore, the same study also reported diminished phosphorylation of Akt, an essential regulator of NF-κB and potentially MAPKs. Therefore, there is a critical role for SP-A in modulating lung inflammatory reactions by regulating macrophage-mediated TLR4 activity.

As noted above, calreticulin was identified as a common receptor for C1q, MBL and SP-A (Malhotra et al. 1990). Calreticulin is mainly an intracellular protein but it is present on cell surfaces bound to CD91 and, thus, acts as an adaptor or co-receptor while binding to collagenous region of these collectins (Fig. 4.5) (Table 4.2) (Ogden et al. 2001; Vandivier et al. 2002). Uptake of apoptotic cells by phagocytes mediated by C1q or MBL binding to calreticulin-CD91 complex was revealed (Vandivier et al. 2002). HLA class I heavy chain (Arosa et al. 1999), or CD59 have been shown to act as a calreticulin-binding proteins on cells which do not express CD91, allowing C1q or MBL coated particles to adhere to the cells. Although a number of collectin receptors have been identified, there is still a need to fully elucidate how collectins stimulate phagocytes, and mediate phagocytosis, as well as other signalling transduction pathways. More studies on the structural aspects of receptors are needed, especially how these receptors are anchored in the membrane of immune and non-immune cells and, which co-receptors and signalling pathways are involved.

In conclusion, collectins appear to play important roles in controlling lung allergy, inflammation and hypersensitivity, in addition to dealing with a wide variety of pathogens at pulmonary and extra-pulmonary sites. They act against pulmonary allergens through their ability to resist allergen challenge by interfering with allergen triggered IgE interaction, degranulation of mast/basophils, cellular infiltration, and polarisation of helper Th response. Their roles have been also implicated in altering profiles of pro-inflammatory cytokines and chemokines as a result of infection, and allergen challenge. Further research is needed to characterise specific collectin receptors that are crucial for collectin functions other than phagocytosis.

References

Al-Ahdal MN, Murugaiah V, Varghese PM, Abozaid SM, Saba I, Al-Qahtani AA, Pathan AA, Kouser L, Nal B, Kishore U (2018) Entry inhibition and modulation of pro-inflammatory immune response against influenza A virus by a recombinant truncated surfactant protein D. Front Immunol 9:1586
Aliouat EM, Escamilla R, Cariven C, Vieu C, Mullet C, Dei-Cas E, Prevost MC (1998) Surfactant changes during experimental pneumocystosis are related to Pneumocystis development. Eur Respir J 11:542–547
Allen MJ, Laederach A, Reilly PJ, Mason RJ (2001a) Polysaccharide recognition by surfactant protein D: novel interactions of a C-type lectin with nonterminal glucosyl residues. Biochemistry 40(26):7789–7798
Allen MJ, Voelker DR, Mason RJ (2001b) Interactions of surfactant proteins A and D with Saccharomyces cerevisiae and Aspergillus fumigatus. Infect Immun 69:2037–2044
Alonso DP, Ferreira AF, De Miranda Santos IK, Do Socorro Pires E Cruz M, Accio De Carvalho F, Abatepaulo AR, Lamounier Costa D, Werneck GL, Farias TJ, Soares MJ, Costa CH (2007) Genotypes of the mannan-binding lectin gene and susceptibility to visceral leishmaniasis and clinical complications. J Infect Dis 195:1212–1217

Al-Qahtani AA, Murugaiah V, Bashir HA, Pathan AA, Abozaid SM, Makarov E, Nal B, Kishore U, Al-Ahdal MN (2019) Full-length human Surfactant protein A inhibits Influenza A virus infection of A549 lung epithelial cells: a recombinant form containing neck and lectin domains promotes infectivity. Immunobiology (in Press)

Ambrosio AR, De Messias-Reason JJ (2005) Leishmania (Vianna) braziliensis: interaction of mannos-binding lectin with surface glycoconjugates and complement activation. An antibody-independent defence mechanism. Parasite Immunol 27:333–340

Anders EM, Hartley CA, Reading PC, Ezekowitz RA (1994) Complement-dependent neutralization of influenza virus by a serum mannos-binding lectin. J Gen Virol 75(Pt 3):615–622

Andersen O, Sorensen AM, Svehag SE, Fenouillet E (1991) Conglutinin binds the HIV-1 envelope glycoprotein gp 160 and inhibits its interaction with cell membrane CD4. Scand J Immunol 33:81–88

Antony JS, Ojurongbe O, Van Tong H, Ouf EA, Engleitner T, Akindele AA, Sina-Agbaje OR, Adeyeba AO, Kremsner PG, Velavan TP (2013) Mannose-binding lectin and susceptibility to schistosomiasis. J Infect Dis 207:1675–1683

Atochina EN, Beck JM, Scanlon ST, Preston AM, Beers MF (2001) Pneumocystis carinii pneumonia alters expression and distribution of lung collectins SP-A and SP-D. J Lab Clin Med 137(6):429–439

Arora M, Munoz E, Tenner AJ (2001) Identification of a site on mannan-binding lectin critical for enhancement of phagocytosis. J Biol Chem 276(46):43087–43094

Axelgaard E, Jensen L, Dyrlund TF, Nielsen HJ, Enghild JJ, Thiel S, Jensenius JC (2013) Investigations on collectin liver 1. J Biol Chem 288:23407–23420

Babula O, Lazdane G, Kroica J, Ledger WJ, Witkin SS (2003) Relation between recurrent vulvovaginal candidiasis, vaginal concentrations of mannos-binding lectin, and a mannos-binding lectin gene polymorphism in Latvian women. Clin Infect Dis 37:733–737

Bachis A, Aden SA, Nosheny RL, Andrews PM, Mochetti I (2006) Axonal transport of human immunodeficiency virus type 1 envelope protein glycoprotein 120 is found in association with neuronal apoptosis. J Neurosci 26:6771–6780

Ballegaard V, Haugaard AK, Garred P, Nielsen SD, Munthe-Fog L (2014) The lectin pathway of complement: advantage or disadvantage in HIV pathogenesis? Clin Immunol 154:13–25

Bartlomiejczyk MA, Swierzko AS, Brzostek A, Dziadek J, Cedzynski M (2014) Interaction of lectin pathway of complement-activating pattern recognition molecules with mycobacteria. Clin Exp Immunol 178:310–319
Beharka AA, Gaynor CD, Kang BK, Voelker DR, McCormack FX, Schlesinger LS (2002) Pulmonary surfactant protein A up-regulates activity of the mannose receptor, a pattern recognition receptor expressed on human macrophages. J Immunol 169:3565–3573

Benne CA, Kraaijeveld CA, Van Strijp JA, Brouwer E, Harmsen M, Verhoef J, Van Golde LM, Van Iwaarden JF (1995) Interactions of surfactant protein A with influenza A viruses: binding and neutralization. J Infect Dis 171:335–341

Bilod JM, Lacetera A, Guzmán-Caldecote J, Martín-Santamaría S (2016) Computational approaches to toll-like receptor 4 modulation. Molecules 21(8)

Boron PJ, Crouch EC, Lewis JF, Wright JR, Possmayer F, Fraher LJ (1998) Recombinant rat surfactant-associated protein D inhibits human T lymphocyte proliferation and IL-2 production. J Immunol 161(9):4599–4603

Boron P, McIntosh JC, Korfhagen TR, Whitsett JA, Taylor J, Wright JR (2000) Surfactant-associated protein A inhibits LPS-induced cytokine and nitric oxide production in vivo. Am J Physiol Lung Cell Mol Physiol 278:L840–L847

Bräuer L, Kindler C, Jäger K, Sel S, Nölle B, Pleyer U, Ochs M, Paalens F (2007) Detection of surfactant proteins A and D in human tear fluid and the human lacrimal system. Invest Ophthalmol Vis Sci 48(9):3945–3953

Brown GD, Taylor PR, Reid DM, Willment JA, Williams DL, Martinez-Pomares L, Wong SY, Gordón S (2002) Dectin-1 is a major beta-glucan receptor on macrophages. J Exp Med 196:407–412

Brown KS, Ryder SD, Irving WL, Sim RB, Hickling TP (2007) Mannan binding lectin and viral hepatitis. Immunol Lett 108:34–44

Brown KS, Keogh MJ, Owsianka AM, Adair R, Patel AH, Arnold JN, Ball JK, Sim RB, Tarr AW, Hickling TP (2010) Specific interaction of hepatitis C virus glycoproteins with mannann binding lectin inhibits virus entry. Protein Cell 1:664–674

Brown-Augsburger P, Hartshorn K, Chang D, Rust K, Fliszar C, Welgus HG, Crouch EC (1996) Site-directed mutagenesis of Cys-15 and Cys-20 of pulmonary surfactant protein D. Expression of a trimeric protein with altered anti-viral properties. J Biol Chem 271(23):13724–13730

Bruce SR, Atkins CL, Colasurdo GN, Alcorn JL (2009) Respiratory syncytial virus infection alters surfactant protein A expression in human pulmonary epithelial cells by reducing translation efficiency. Am J Physiol Lung Cell Mol Physiol 297:L559–L567

Brudner M, Karpel M, Lear C, Chen L, Yantosca LM, Scully C, Sarraju A, Sokolovska A, Zariiffard MR, Eisen DP, Mungall BA, Kotton DN, Omari A, Huang IC, Farzan M, Takahashi K, Stuart L, Stahl GL, Ezekowitz AB, Spear GT, Olinger GG, Schmidt EV, Michelow IC (2013) Lectin-dependent enhancement of Ebola virus infection via soluble and transmembrane C-type lectin receptors. PLoS ONE 8:e60838

Brummer E, Kethineni N, Stevens DA (2005) Immunological basis for susceptibility and resistance to pulmonary blastomycosis in mouse strains. Cytokine 32:12–19

Brummer E, Capilla J, Bythadka L, Stevens DA (2007) Production of IL-6, in contrast to other cytokines and chemokines, in macrophage innate immune responses: effect of serum and fungal (Blastomyces) challenge. Cytokine 39:163–170

Cahayani WA, Norahmawati E, Budiarti N, Fitrri LE (2016) Increased CD11b and hypoxia-inducible factors-αalpha expressions in the lung tissue and surfactant protein-D levels in serum are related with acute lung injury in severe malaria of C57BL/6 mice. Iran J Parasitol 11:303–315

Cestari Idos S, Krarup A, Sim RB, Inal JM, Ramirez MI (2009) Role of early lectin pathway activation in the complement-mediated killing of Trypanosoma cruzi. Mol Immunol 47:426–437

Cestari I, Evans-Osses I, Schlaphach LJ, De Messias-Reason I, Ramirez MI (2013) Mechanisms of complement lectin pathway activation and resistance by trypanosomatid parasites. Mol Immunol 53:328–334

Chaka W, Verheul AF, Vaishnav VV, Cherniak R, Scharringa J, Verhoef J, Snijpe H, Hoepelman AI (1997) Induction of TNF-alpha in human peripheral blood mononuclear cells by the mannoprotein of Cryptococcus neoformans involves human mannose binding protein. J Immunol 159:2979–2985
Chang WC, White MR, Moyo P, Mcclear S, Thiel S, Hartshorn KL, Takahashi K (2010) Lack of the pattern recognition molecule mannose-binding lectin increases susceptibility to influenza A virus infection. BMC Immunol 11:64

Cheng G, Ueda T, Nakajima H, Nakajima A, Kinjyo S, Motojima S, Fukuda T (1998) Suppressive effects of SP-A on ionomycin-induced IL-8 production and release by eosinophils. Int Arch Allergy Immunol 117(Suppl 1):59–62

Chiba H, Pattanajitvilai S, Evans AJ, Harbeck RJ, Voelker DR (2002) Human surfactant protein D (SP-D) binds Mycoplasma pneumoniae by high affinity interactions with lipids. J Biol Chem 277:20379–20385

Chroneos ZC, Abdolrasulnia R, Whitsett JA, Rice WR, Shepherd VL (1996) Purification of a cell-surface receptor for surfactant protein A. J Biol Chem 271(27):16375–16383

Collard CD, Väkevä A, Morrissey MA, Agah A, Rollins SA, Reenstra WR, Buras JA, Meri S, Stahl GL (2000) Complement activation after oxidative stress: role of the lectin complement pathway. Am J Pathol 156(5):1549–1556

Colley KJ, Baenziger JU (1987) Identification of the post-translational modifications of the core-specific lectin. The core-specific lectin contains hydroxyproline, hydroxylysine, and glucosylgalactosylhydroxylysine residues. J Biol Chem 262(21):10290–10295

Corredor GG, Castano JH, Peralta LA, Diez S, Arango M, Mcewen J, Restrepo A (1999) Isolation of Paracoccidioides brasiliensis from the nine-banded armadillo Dasyus novemcinctus, in an endemic area for paracoccidioidomycosis in Colombia. Rev Iberoam Micol 16:216–220

Coya JM, Akinbi HT, Saenz A, Yang L, Weaver TE, Casals C (2015) Natural anti-infective pulmonary proteins: in vivo cooperative action of surfactant protein SP-A and the lung antimicrobial peptide SP-BN. J Immunol 195:1628–1636

Crozdale DJ, Poulton KV, Ollier WE, Thomson W, Denning DW (2001) Mannose-binding lectin gene polymorphisms as a susceptibility factor for chronic necrotizing pulmonary aspergillosis. J Infect Dis 184:653–656

Crouch E, Parghi D, Kuan SF, Persson A (1992) Surfactant protein D: subcellular localization in nonciliated bronchiolar epithelial cells. Am J Physiol 263(1 Pt 1):L60–L66

Cunnion KM, Lee JC, Frank MM (2001) Capsule production and growth phase influence binding of complement to Staphylococcus aureus. Infect Immun 69:6796–6803

Dec M, Wernicki A (2006) Conglutinin, CL-43 and CL-46–three bovine collectins. Pol J Vet Sci 9(4):265–275

Dec M, Wernicki A, Puchalski A, Urban-Chmiel R, Radej S (2012) Effect of conglutinin on phagocytic activity of bovine granulocytes. Pol J Vet Sci 15:455–462

Denton JF, Disalvo AF (1964) Isolation of blastomyces dermatitidis from natural sites at Augusta, Georgia. Am J Trop Med Hyg 13:716–722

Devyatyrova-Johnson M, Rees IH, Robertson BD, Turner MW, Klein NJ, Jack DL (2000) The lipopolysaccharide structures of Salmonella enterica serovar Typhimurium and Neisseria gonorrhoeae determine the attachment of human mannose-binding lectin to intact organisms. Infect Immun 68:3894–3899

Dodagatta-Marri E, Mitchell DA, Pandit H, Sonawani A, Murugaiah V, Idicula-Thomas S, Nal B, Al-Mozaini MM, Kaur A, Madan T, Kishore U (2017) Protein-protein interaction between surfactant protein D and DC-SIGN via C-type lectin domain can suppress HIV-1 transfer. Front Immunol 8:834

Donders GG, Babula O, Bellen G, Linhares IM, Witkin SS (2008) Mannose-binding lectin gene polymorphism and resistance to therapy in women with recurrent vulvovaginal candidiasis. Br J Obs Gyn 115:1225–1231

Doss M, White MR, Tecle T, Gantz D, Crouch EC, Jung G, Ruchala P, Waring AJ, Lehrer RI, Hartshorn KL (2009) Interactions of alpha-, beta-, and theta-defensins with influenza A virus and surfactant protein D. J Immunol 182(12):7878–7887.

Drickamer K, Taylor ME (2015) Recent insights into structures and functions of C-type lectins in the immune system. Curr Opin Struct Biol 34:26–34.
Drickamer K, Dordal MS, Reynolds L (1986) Mannose-binding proteins isolated from rat liver contain carbohydrate-recognition domains linked to collagenous tails. Complete primary structures and homology with pulmonary surfactant apoprotein. J Biol Chem 261(15):6878–6887

Drogari-Apiranthitou M, Fijen CA, Thiel S, Platonov A, Jensen L, Dankert J, Kuijper EJ (1997) The effect of mannan-binding lectin on opsonophagocytosis of Neisseria meningitidis. Immunopharmacology 38:93–99

Eisen DP, Minchinton RM (2003) Impact of mannose-binding lectin on susceptibility to infectious diseases. Clin Infect Dis 37:1496–1505

Eisen DP, Dean MM, O’Sullivan MV, Heatley S, Minchinton RM (2008) Mannose-binding lectin deficiency does not appear to predispose to cryptococcosis in non-immunocompromised patients. Med Mycol 46:371–375

Elser B, Lohoff M, Kock S, Giaisi M, Kirchhoff S, Krammer PH, Li-Weber M (2002) IFN-gamma represses IL-4 expression via IRF-1 and IRF-2. Immunity 17(6):703–712

Erpenbeck VJ, Malherbe DC, Sommer S, Schmiedl A, Steinhilber W, Ghiro AJ, Krug N, Wright JR, Hohlfeld JM (2005) Surfactant protein D increases phagocytosis and aggregation of pollen-allergen starch granules. Am J Physiol Lung Cell Mol Physiol 288(4):L692–L698

Escudero-Perez B, Volchkova VA, Dolnik O, Lawrence P, Volchkov VE (2014) Shed GP of Ebola virus triggers immune activation and increased vascular permeability. PLoS Pathog 10:e1004509

Evans-Osses I, Mojoli A, Beltrame MH, Da Costa DE, Darocha WD, Velavan TP, De Messias-Reason I, Ramirez M (2014) Differential ability to resist to complement lysis and invade host cells mediated by MBL in R4 and 860 strains of Trypanosoma cruzi. FEBS Lett 588:956–961

Ezekowitz RA, Day LE, Herman GA (1988) A human mannose-binding protein is an acute-phase reactant that shares sequence homology with other vertebrate lectins. J Exp Med. 167(3):1034–1046

Ezekowitz RA, Kuhlman M, Groopman JE, Byrn RA (1989) A human serum mannose-binding protein inhibits in vitro infection by the human immunodeficiency virus. J Exp Med 169:185–196

Favier AL, Reynard O, Gout E, Van Eijk M, Haagsman HP, Crouch E, Volchkov V, Peyrefitte C, Thielens NM (2018) Involvement of surfactant protein D in Ebola virus infection enhancement via glycoprotein interaction. Viruses 11

Ferguson JS, Voelker DR, Mccormack FX, Schlesinger LS (1999) Surfactant protein D binds to Mycobacterium tuberculosis bacilli and lipoarabinomannan via carbohydrate-lectin interactions resulting in reduced phagocytosis of the bacteria by macrophages. J Immunol 163:312–321

Ferguson JS, Voelker DR, Ufnar JA, Dawson AJ, Schlesinger LS (2002) Surfactant protein D inhibition of human macrophage uptake of Mycobacterium tuberculosis is independent of bacterial agglutination. J Immunol 168:1309–1314

Fidler KJ, Hilliard TN, Bush A, Johnson M, Geddes DM, Turner MW, Alton EW, Klein NJ, Davies JC (2009) Mannose-binding lectin is present in the infected airway: a possible pulmonary defence mechanism. Thorax 64:150–155

Fisher JH, Mason R (1995) Expression of pulmonary surfactant protein D in rat gastric mucosa. Am J Respir Cell Mol Biol 12(1):13–18

Fischer PB, Ellermann-Eriksen S, Thiel S, Jensenius JC, Mogensen SC (1994) Mannan-binding protein and bovine conglutinin mediate enhancement of herpes simplex virus type 2 infection in mice. Scand J Immunol 39:439–445

Floros J, Lin HM, Garcia A, Salazar MA, Guo X, Diangelo S, Montano M, Luo J, Pardo A, Selman M (2000) Surfactant protein genetic marker alleles identify a subgroup of tuberculosis in a Mexican population. J Infect Dis 182:1473–1478

Friis P, Svehag SE, Andersen O, Gahrn-Hansen B, Leslie RG (1991) Conglutinin exhibits a complement-dependent enhancement of the respiratory burst of phagocytes stimulated by E. coli. Immunology 74:680–684

Friis-Christiansen P, Thiel S, Svehag SE, Dessau R, Svendsen P, Andersen O, Laursen SB, Jensenius JC (1990) In vivo and in vitro antibacterial activity of conglutinin, a mammalian plasma lectin. Scand J Immunol 31:453–460
Fuchs A, Pinto AK, Schwaeble WJ, Diamond MS (2011) The lectin pathway of complement activation contributes to protection from West Nile virus infection. Virology 412:101–109
Funk CJ, Wang J, Ito Y, Travanty EA, Voelker DR, Holmes KV, Mason RJ (2012) Infection of human alveolar macrophages by human coronavirus strain 229E. J Gen Virol 93:494–503
Gadjeva M, Paludan SR, Thiel S, Slavov V, Ruseva M, Erikkson K, Lowhagen GB, Shi L, Takahashi K, Ezekowitz A, Jensenius JC (2004) Mannan-binding lectin modulates the response to HSV-2 infection. Clin Exp Immunol 138:304–311
Gaiha GD, Dong T, Palaniyar N, Mitchell DA, Reid KB, Clark HW (2008) Surfactant protein A binds to HIV and inhibits direct infection of CD4+ cells, but enhances dendritic cell-mediated viral transfer. J Immunol 181:601–609
Gardai SJ, Xiao YQ, Dickinson M, Nick JA, Voelker DR, Greene KE, Henson PM (2003) By binding SIRPalpha or calreticulin/CD91, lung collectins act as dual function surveillance molecules to suppress or enhance inflammation. Cell 115(1):13–23
Garred P, Harboe M, Oettinger T, Koch C, Svejgaard A (1997a) Mannan-binding lectin in the sub-Saharan HIV and tuberculosis epidemics. Scand J Immunol 46:204–208
Garred P, Nielsen MA, Kurtzhals JA, Malhotra R, Madsen HO, Goka BQ, Akanmori BD, Sim RB, Hvid L (2003) Mannose-binding lectin is a disease modifier in clinical malaria and may function as opsonin for Plasmodium falciparum-infected erythrocytes. Infect Immun 71:5245–5253
Gaynor CD, Mccormack FX, Voelker DR, Mtoni I, Svejgaard A, Shao J (1997b) Mannan-binding lectin in the sub-Saharan HIV and tuberculosis epidemics. Scand J Immunol 46:204–208
Garred P, Madsen HO, Balslev U, Hofmann B, Pedersen C, Gerstoft J, Svejgaard A (1997a) Susceptibility to HIV infection and progression of AIDS in relation to variant alleles of mannose-binding lectin. Lancet 349:236–240
Garred P, Richter C, Andersen AB, Madsen HO, Mtoni I, Svejgaard A, Shao J (1997b) Mannan-binding lectin in the sub-Saharan HIV and tuberculosis epidemics. Scand J Immunol 46:204–208
Garred P, Nielsen MA, Kurtzhals JA, Malhotra R, Madsen HO, Goka BQ, Akanmori BD, Sim RB, Hvid L (2003) Mannose-binding lectin is a disease modifier in clinical malaria and may function as opsonin for Plasmodium falciparum-infected erythrocytes. Infect Immun 71:5245–5253
Geunes-Boyer S, Oliver TN, Janbon G, Lodge JK, Heitman J, Perfect JR, Wright JR (2009) Surfactant protein D increases phagocytosis of hypcapsular Cryptococcus neoformans by murine macrophages and enhances fungal survival. Infect Immun 77:2783–2794
Geunes-Boyer S, Beers MF, Perfect JR, Heitman J, Wright JR (2012) Surfactant protein D facilitates Cryptococcus neoformans infection. Infect Immun 80:2444–2453
Ghezzi MC, Raponi G, Angeletti S, Mancini C (1998) Serum-mediated enhancement of TNF-alpha release by human monocytes stimulated with the yeast form of Candida albicans. J Infect Dis 178:1743–1749
Ghildyal R, Hartley C, Varrasso A, Meanger J, Voelker DR, Anders EM, Mills J (1999) Surfactant protein A binds to the fusion glycoprotein of respiratory syncytial virus and neutralizes virion infectivity. J Infect Dis 180:2009–2013
Ghiran I, Barbushov SF, Klickstein LB, Tas SW, Jensenius JC, Nicholson-Weller A (2000) Complement receptor 1/CD35 is a receptor for mannann-binding lectin. J Exp Med 192:1797–1808
Giles SS, Zaas AK, Reidy MF, Perfect JR, Wright JR (2007) Cryptococcus neoformans is resistant to surfactant protein A mediated host defense mechanisms. PLoS ONE 2:e1370
Giraldo PC, Babula O, Goncalves AK, Linares IM, Amaral RL, Ledger WJ, Witkin SS (2007) Mannose-binding lectin gene polymorphism, vulvovaginal candidiasis, and bacterial vaginosis. Obstet Gynecol 109:1123–1128
Gold JA, Hoshino Y, Tanaka N, Rom WN, Raju B, Condos R, Weiden MD (2004) Surfactant protein A modulates the inflammatory response in macrophages during tuberculosis. Infect Immun 72:645–650
Goyal S, Klassert TE, Slevogt H (2016) C-type lectin receptors in tuberculosis: what we know. Med Microbiol Immunol 205:513–535
Granell M, Urbano-Ispizua A, Suarez B, Rovira M, Fernandez-Aviles F, Martinez C, Ortega M, Urriburu C, Gaya A, Roncero JM, Navarro A, Carreras E, Mensa J, Vives J, Rozman C, Montserrat E, Lozano F (2006) Mannan-binding lectin pathway deficiencies and invasive fungal infections following allogeneic stem cell transplantation. Exp Hematol 34:1435–1441

Green PJ, Feizi T, Stoll MS, Thiel S, Prescott A, Mcconville MJ (1994) Recognition of the major cell surface glycoconjugates of Leishmania parasites by the human serum mannan-binding protein. Mol Biochem Parasitol 66:319–328

Gulati S, Sastry K, Jensenius JC, Rice PA, Ram S (2002) Regulation of the mannan-binding lectin pathway of complement on Neisseria gonorrhoeae by C1-inhibitor and alpha 2-macroglobulin. J Immunol 168:4078–4086

Hakozaki Y, Yoshita M, Sekiyama K, Seike E, Iwamoto J, Mitani K, Mine M, Morizane T, Ohtani K, Suzuki Y, Wakamiya N (2002) Mannan-binding lectin and the prognosis of fulminant hepatic failure caused by HBV infection. Liver 22:29–34

Hansen S, Holmskov U (2002) Lung surfactant protein D (SP-D) and the molecular diverted descendants: conglutinin, CL-43 and CL-46. Immunobiology 205:498–517

Hansen S, Thiel S, Willis A, Holmskov U, Jensenius JC (2000) Purification and characterization of two mannan-binding lectins from mouse serum. J Immunol 164(5):2610–2618

Hansen S, Holm D, Moeller V, Vitved L, Bendixen C, Reid KB, Skjoedt K, Holmskov U (2002) CL-46, a novel collectin highly expressed in bovine thymus and liver. J Immunol 169(10):5726–5734

Hansen S, Selman L, Palaniyar N, Ziegler K, Brandt J, Kliem A, Jonasson M, Skjoedt MO, Nielsen O, Hartshorn K, Jorgensen TJ, Skjodt K, Holmskov U (2010) Collectin 11 (CL-11, CL-K1) is a MASP-1/3-associated plasma collectin with microbial-binding activity. J Immunol 185:6096–6104

Harrod KS, Trapnell BC, Otake K, Korchhagen TR, Whitsett JA (1999) SP-A enhances viral clearance and inhibits inflammation after pulmonary adenoviral infection. Am J Physiol 277:L580–L588

Hartley CA, Jackson DC, Anders EM (1992) Two distinct serum mannose-binding lectins function as beta inhibitors of influenza virus: identification of bovine serum beta inhibitor as conglutinin. J Virol 66:4358–4363

Hartshorn KL, Sastry K, Brown D, White MR, Okarma TB, Lee YM, Tauber AI (1993a) Conglutinin acts as an opsonin for influenza A viruses. J Immunol 151:6265–6273

Hartshorn KL, Sastry K, White MR, Anders EM, Super M, Ezekowitz RA, Tauber AI (1993b) Human mannos-binding protein functions as an opsonin for influenza A viruses. J Clin Invest 91:1414–1420

Hartshorn KL, Crouch EC, White MR, Eggleton P, Tauber AI, Chang D, Sastry K (1994) Evidence for a protective role of pulmonary surfactant protein D (SP-D) against influenza A viruses. J Clin Invest 94:311–319

Hartshorn KL, White MR, Voelker DR, Coburn J, Zaner K, Crouch EC (2000) Mechanism of binding of surfactant protein D to influenza A viruses: importance of binding to haemagglutinin to antiviral activity. Biochem J 351(Pt 2):449–458

Hartshorn KL, White MR, Tecle T, Holmskov U, Crouch EC (2006a) Innate defense against influenza A virus: activity of human neutrophil defensins and interactions of defensins with surfactant protein D. J Immunol 176(11):6962–6972

Hartshorn KL, Ligtengberg A, White MR, Van Eijk M, Hartshorn M, Pemberton L, Holmskov U, Crouch E (2006b) Salivary agglutinin and lung scavenger receptor cysteine-rich glycoprotein 340 have broad anti-influenza activities and interactions with surfactant protein D that vary according to donor source and sialylation. Biochem J 393:545–553

Haurum JS, Thiel S, Jones IM, Fischer PB, Laursen SB, Jensenius JC (1993) Complement activation upon binding of mannan-binding protein to HIV envelope glycoproteins. AIDS 7:1307–1313

Hawgood S, Brown C, Edmondson J, Stumbaugh A, Allen L, Goerke J, Clark H, Poulain F (2004) Pulmonary collectins modulate strain-specific influenza virus infection and host responses. J Virol 78:8565–8572
Held K, Thiel S, Loos M, Petry F (2008) Increased susceptibility of complement factor B/C2 double knockout mice and mannan-binding lectin knockout mice to systemic infection with Candida albicans. Mol Immunol 45:3934–3941

Henning LN, Azad AK, Parsa KV, Crowther JE, Trandapani S, Schlesinger LS (2008) Pulmonary surfactant protein A regulates TLR expression and activity in human macrophages. J Immunol 180(12):7847–7858

Henriksen ML, Brandt J, Andrieu JP, Nielsen C, Jensen PH, Holmskov U, Jorgensen TJ, Palarasah Y, Thielens NM, Hansen S (2013) Heteromeric complexes of native collectin kidney 1 and collectin liver 1 are found in the circulation with MASPs and activate the complement system. J Immunol 191:6117–6127

Herias MV, Hogenkamp A, van Asten AJ, Tersteeg MH, van Eijk M, Haagsman HP (2007) Expression sites of the collectin SP-D suggest its importance in first line host defence: power of combining in situ hybridisation, RT-PCR and immunohistochemistry. Mol Immunol 44(13):3324–3332 (Epub 2007 Apr 8)

Hickling TP, Bright H, Wing K, Gower D, Martin SL, Sim RB, Malhotra R (1999) A recombinant trimeric surfactant protein D carbohydrate recognition domain inhibits respiratory syncytial virus infection in vitro and in vivo. Eur J Immunol 29:3478–3484

Hickman-Davis JM, Lindsey JR, Zhu S, Matalon S (1998) Surfactant protein A mediates mycoplasmacidal activity of alveolar macrophages. Am J Physiol 274:L270–L277

Hillaume ML, Van Eijk M, Nieuwkoop NJ, Vogelzang-Van Trierum SE, Foucher RA, Osterhaus AD, Haagsman HP, Rimmelzaaen GF (2012) The number and position of N-linked glycosylation sites in the hemagglutinin determine differential recognition of seasonal and 2009 pandemic H1N1 influenza virus by porcine surfactant protein D. Virus Res 169:301–305

Hogaboam CM, Takahashi K, Ezekowitz RA, Kunkel SL, Schuh JM (2004) Mannose-binding lectin deficiency alters the development of fungal asthma: effects on airway response, inflammation, and cytokine profile. J Leukoc Biol 75(5):805–814

Hohler T, Wunschel M, Gerken G, Schneider PM, Meyer Zum Buschenfelde KH, Rittner C (1998) No association between mannose-binding lectin alleles and susceptibility to chronic hepatitis B virus infection in German patients. Exp Clin Immunogenet 15:130–133

Holmberg V, Schuster F, Dietz E, Sagarriga Visconti JC, Anemana SD, Bienzle U, Mockenhaupt FP (2008) Mannose-binding lectin variant associated with severe malaria in young African children. Microbes Infect 10:342–348

Holmskov U, Malhotra R, Sim RB, Jensenius JC (1994) Collectins: collagenous C-type lectins of the innate immune defense system. Immunol Today 15(2):67–74

Holmskov U, Fischer PB, Rothmann A, Hojrup P (1996) Affinity and kinetic analysis of the bovine plasma C-type lectin collectin-43 (CL-43) interacting with mannan. FEBS Lett 393:314–316

Holmskov U, Lawson P, Teisner B, Tornoe I, Willis AC, Morgan C, Koch C, Reid KB (1997) Isolation and characterization of a new member of the scavenger receptor superfamily, glycoprotein-340 (gp-340), as a lung surfactant protein-D binding molecule. J Biol Chem 272(21):13743–13749

Holmskov U, Jensenius JC, Tornoe I, Lovendahl P (1998) The plasma levels of conglutinin are heritable in cattle and low levels predispose to infection. Immunology 93:431–436

Holmskov U, Mollenhauer J, Madsen J, Vitved L, Gronlund J, Tornoe I, Kliem A, Reid KB, Pousta A, Skjodt K (1999) Cloning of gp-340, a putative opsonin receptor for lung surfactant protein D. Proc Natl Acad Sci U S A 96(19):10794–10799

Hoppe HJ, Reid KB (1994) Collectins–soluble proteins containing collagenous regions and lectin domains—and their roles in innate immunity. Protein Sci 3(8):1143–1158 (Review)

Hussain S, Wright JR, Martin WJ 2 (2003) Surfactant protein A decreases nitric oxide production by macrophages in a tumor necrosis factor-alpha-dependent mechanism. Am J Respir Cell Mol Biol 28:520–527

Ihara S, Takahashi A, Hatsuse H, Sumitomo K, Doi K, Kawakami M (1991) Major component of Ra-reactive factor, a complement-activating bactericidal protein, in mouse serum. J Immunol 146:1874–1879
Ingram DG, Mitchell WR (1971) Conglutinin level in dairy cattle: changes associated with disease. Am J Vet Res 32:875–878

Iobst ST, Drickamer K (1994) Binding of sugar ligands to Ca\(^{2+}\)-dependent animal lectins. II. Generation of high-affinity galactose binding by site-directed mutagenesis. J Biol Chem 269(22):15512–15519

Ip WK, Lau YL (2004) Role of mannose-binding lectin in the innate defense against \textit{Candida albicans}: enhancement of complement activation, but lack of opsonic function, in phagocytosis by human dendritic cells. J Infect Dis 190:632–640

Ip WK, Takahashi K, Moore KJ, Stuart LM, Ezekowitz RA (2008) Mannose-binding lectin enhances Toll-like receptors 2 and 6 signaling from the phagosome. J Exp Med 205:169–181

Ip WK, Takahashi K, Ezekowitz RA, Stuart LM (2009) Mannose-binding lectin and innate immunity. Immunol Rev 230:9–21

Jack DL, Dodds AW, Anwar N, Ison CA, Law A, Frosch M, Turner MW, Klein NJ (1998) Activation of complement by mannose-binding lectin on isogenic mutants of \textit{Neisseria meningitidis} serogroup B. J Immunol 160:1346–1353

Jack DL, Jarvis GA, Booth CL, Turner MW, Klein NJ (2001) Mannose-binding lectin accelerates complement activation and increases serum killing of \textit{Neisseria meningitidis} serogroup C. J Infect Dis 184:836–845

Jack DL, Lee ME, Turner MW, Klein NJ, Read RC (2005) Mannose-binding lectin enhances phagocytosis and killing of \textit{Neisseria meningitidis} by human macrophages. J Leukoc Biol 77:328–336

Jacquet M, Cioci G, Fouet G, Bally I, Thielen M, Huguet C, Rossi V (2018) C1q and mannose-binding lectin interact with CR1 in the same region on CCP24-25 modules. Front Immunol 7(9):453

Jang S, Ohtani K, Fukuoh A, Yoshizaki T, Fukuda M, Motomura W, Mori K, Fukuzawa J, Kitamoto N, Yoshida I, Suzuki Y, Wakamiya N (2009) Scavenger receptor collectin placenta 1 (CL-P1) predominantly mediates zymosan phagocytosis by human vascular endothelial cells. J Biol Chem 284:3956–3965

Ji X, Olinger GG, Aris S, Chen Y, Gewurz H, Spear GT (2005) Mannose-binding lectin binds to Ebola and Marburg envelope glycoproteins, resulting in blocking of virus interaction with DC-SIGN and complement-mediated virus neutralization. J Gen Virol 86:2535–2542

Job ER, Deng YM, Tate MD, Bottazzi B, Crouch EC, Dean MM, Mantovani A, Brooks AG, Reading PC (2010) Pandemic H1N1 influenza A viruses are resistant to the antiviral activities of innate immune proteins of the collectin and pentraxin superfamilies. J Immunol 185:4284–4291

Kabha K, Schmegner J, Keisary Y, Parolis H, Schlepper-Schaeffer J, Ofek I (1997) SP-A enhances phagocytosis of Klebsiella by interaction with capsular polysaccharides and alveolar macrophages. Am J Physiol 272:L344–L352

Kalina M, Blau H, Rikit S, Kravtsov V (1995) Interaction of surfactant protein A with bacterial lipopolysaccharide may affect some biological functions. Am J Physiol 268:L144–L151

Kase T, Suzuki Y, Kawai T, Sakamoto T, Ohtani K, Edo S, Maeda A, Okuno Y, Kurimura T, Wakamiya N (1999) Human mannan-binding lectin inhibits the infection of influenza A virus without complement. Immunology 97:385–392

Kasper M, Sims G, Koslowski R, Kuss H, Thuenmeter M, Mehrenbach H, Auten RL (2002) Increased surfactant protein D in rat airway goblet and Clara cells during ovalbumin-induced allergic airway inflammation. Clin Exp Allergy 32(8):1251–1258

Kaur S, Gupta VK, Shah A, Thiel S, Sarma PU, Madan T (2005) Plasma mannan-binding lectin levels and activity are increased in allergic patients. J Allergy Clin Immunol 116(6):1381–1383

Kaur S, Gupta VK, Shah A, Thiel S, Sarma PU, Madan T (2006) Elevated levels of mannan-binding lectin (MBL) and eosinophilia in patients of bronchial asthma with allergic rhinitis and allergic bronchopulmonary aspergillosis associate with a novel intronic polymorphism in MBL. Clin Exp Immunol 143(3):414–419

Kaur S, Gupta VK, Thiel S, Sarma PU, Madan T (2007) Protective role of mannan-binding lectin in a murine model of invasive pulmonary aspergillosis. Clin Exp Immunol 148:382–389
Kawasaki T, Etoh R, Yamashina I (1978) Isolation and characterization of a mannan-binding protein from rabbit liver. Biochem Biophys Res Commun 81(3):1018–1024
Kawasaki N, Kawasaki T, Yamashina I (1989) A serum lectin (mannan-binding protein) has complement-dependent bactericidal activity. J Biochem 106:483–489
Kerr MH, Paton JY (1999) Surfactant protein levels in severe respiratory syncytial virus infection. Am J Respir Crit Care Med 159:1115–1118
Keshi H, Sakamoto T, Kawai T, Ohtani K, Katoh T, Jang SJ, Motomura W, Yoshizaki T, Fukuda M, Koyama S, Fukuzawa J, Fukuoh A, Yoshida I, Suzuki Y, Wakamiya N (2006) Identification and characterization of a novel human collectin CL-K1. Microbiol Immunol 50(12):1001–1013
Kimberg M, Brown GD (2008) Dectin-1 and its role in antifungal immunity. Med Mycol 46:631–636
Kishore U, Wang JY, Hoppe HJ, Reid KB (1996) The alpha-helical neck region of human lung surfactant protein D is essential for the binding of the carbohydrate recognition domains to lipopolysaccharides and phospholipids. Biochem J 318(Pt 2):505–511
Kishore U, Madan T, Sarma PU, Singh M, Urban BC, Reid KB (2002) Protective roles of pulmonary surfactant proteins, SP-A and SP-D, against lung allergy and infection caused by Aspergillus fumigatus. Immunobiology 205(4–5):610–618
Kishore U, Greenough TJ, Waters P, Shrive AK, Ghai R, Kamran MF, Bernal AL, Reid KB, Madan T, Chakraborty T (2006) Surfactant proteins SP-A and SP-D: structure, function and receptors. Mol Immunol 43(9):1293–1315
Kitz DJ, Stahl PD, Little JR (1992) The effect of a mannose binding protein on macrophage interactions with Candida albicans. Cell Mol Biol 38:407–412
Klabunde J, Berger J, Jensonius JC, Klinkert MQ, Zelek UE, Kremsner PG, Kun JF (2000) Schistosoma mansoni: adhesion of mannan-binding lectin to surface glycoproteins of cercariae and adult worms. Exp Parasitol 95:231–239
Klabunde J, Uhlemann AC, Tebo AE, Kimmel J, Schwarz RT, Kremsner PG, Kun JF (2002) Recognition of Plasmodium falciparum proteins by mannan-binding lectin, a component of the human innate immune system. Parasitol Res 88:113–117
Koneti A, Linke MJ, Brummer E, Stevens DA (2008) Evasion of innate immune responses: evidence for mannose binding lectin inhibition of tumor necrosis factor alpha production by macrophages in response to Blastomyces dermatitidis. Infect Immun 76:994–1002
Korir JC, Nyakoe NK, Awinda G, Waitumbi JN (2014) Complement activation by merozoite antigens of Plasmodium falciparum. PLoS ONE 9:e105093
Koziel H, Phelps DS, Fishman JA, Armstrong MY, Richards FF, Rose RM (1998) Surfactant protein-A reduces binding and phagocytosis of Pneumocystis carinii by human alveolar macrophages in vitro. Am J Respir Mol Biol 18:834–843
Kozutsumi Y, Kawasaki T, Yamashina I (1980) Isolation and characterization of a mannan-binding protein from rabbit serum. Biochem Biophys Res Commun 95(2):658–664
Krarup A, Sorensen UB, Matsushita M, Jensonius JC, Thiel S (2005) Effect of capsulation of opportunistic pathogenic bacteria on the pattern recognition molecules mannan-binding lectin, L-ficolin, and H-ficolin. Infect Immun 73:1052–1060
Kronborg G, Weis N, Madsen HO, Pedersen SS, Wejse C, Nielsen H, Skinhoj P, Garred P (2002) Variant mannoside-binding lectin alleles are not associated with susceptibility to or outcome of invasive pneumococcal infection in randomly included patients. J Infect Dis 185:1517–1520
Kuan SF, Rust K, Crouch E (1992) Interactions of surfactant protein D with bacterial lipopolysaccharides. Surfactant protein D is an Escherichia coli-binding protein in bronchoalveolar lavage. J Clin Invest 90:97–106
Kuang Z, Hao Y, Hwang S, Zhang S, Kim E, Akinbi HT, Schurr MJ, Irvin RT, Hassett DJ, Lau GW (2011a) The Pseudomonas aeruginosa flagellum confers resistance to pulmonary surfactant protein-A by impacting the production of exoproteases through quorum-sensing. Mol Microbiol 79:1220–1235
Kuang Z, Hao Y, Walling BE, Jeffries JL, Ohman DE, Lau GW (2011b) Pseudomonas aeruginosa elastase provides an escape from phagocytosis by degrading the pulmonary surfactant protein-A. PLoS ONE 6:e27091
Kudo K, Sano H, Takahashi H, Kuronuma K, Yokota S, Fujii N, Shimada K, Yano I, Kumazawa Y, Voelker DR, Abe S, Kuroki Y (2004) Pulmonary collectins enhance phagocytosis of *Mycobacterium avium* through increased activity of mannose receptor. J Immunol 172:7592–7602

Kuhlman M, Joiner K, Ezekowitz RA (1989) The human mannose-binding protein functions as an opsonin. J Exp Med 169(5):1733–1745

Kurokawa K, Takahashi K, Lee BL (2016) The staphylococcal surface-glycopolymer wall teichoic acid (WTA) is crucial for complement activation and immunological defense against *Staphylococcus aureus* infection. Immunobiology 221:1091–1101

Kuronuma K, Sano H, Kato K, Kudo K, Hyakushima N, Yokota S, Takahashi H, Fujii N, Suzuki H, Kodama T, Abe S, Kuroki Y (2004) Pulmonary surfactant protein A augments the phagocytosis of *Streptococcus pneumoniae* by alveolar macrophages through a casein kinase 2-dependent increase of cell surface localization of scavenger receptor A. J Biol Chem 279:21421–21430

Lachmann PJ, Muller-Eberhard HJ (1968) The demonstration in human serum of “conglutinogen-activating factor” and its effect on the third component of complement. J Immunol 100:691–698

Laforce FM, Kelly WJ, Huber GL (1973) Inactivation of staphylococci by alveolar macrophages with preliminary observations on the importance of alveolar lining material. Am Rev Respir Dis 108:784–790

Laursen SB, Thiel S, Teisner B, Holmskov U, Wang Y, Sim RB, Jensenius JC (1994) Bovine conglutinin binds to an oligosaccharide determinant presented by iC3b, but not by C3, C3b or C3c. Immunology 81:648–654

Lawson PR, Reid KB (2000) The roles of surfactant proteins A and D in innate immunity. Immunol Rev 173:66–78

Lekkala M, Levine AM, Linke MJ, Crouch EC, Linders B, Brummer E, Stevens DA (2006) Effect of lung surfactant collectins on bronchoalveolar macrophage interaction with *Blastomyces dermatitidis*: inhibition of tumor necrosis factor alpha production by surfactant protein D. Infect Immun 74:4549–4556

Lemos MP, Mckinney J, Rhee KY (2011) Dispensability of surfactant proteins A and D in immune control of *Mycobacterium tuberculosis* infection following aerosol challenge of mice. Infect Immun 79:1077–1085

Leth-Larsen R, Zhong F, Chow VT, Holmskov U, Lu J (2007) The SARS coronavirus spike glycoprotein is selectively recognized by lung surfactant protein D and activates macrophages. Immunobiology 212:201–211

Levine AM, Gwozdz J, Stark J, Bruno M, Whitsett J, Kortfagen T (1999) Surfactant protein-A enhances respiratory syncytial virus clearance *in vivo*. J Clin Invest 103:1015–1021

Levine AM, Whitsett JA, Hartshorn KL, Crouch EC, Kortfagen TR (2001) Surfactant protein D enhances clearance of influenza A virus from the lung *in vivo*. J Immunol 167:5868–5873

Levine AM, Hartshorn K, Elliott J, Whitsett J, Kortfagen T (2002) Absence of SP-A modulates innate and adaptive defense responses to pulmonary influenza infection. Am J Physiol Lung Cell Mol Physiol 282:L563–L572

Levitz SM, Tabuni A, Treseler C (1993) Effect of mannos-binding protein on binding of *Cryptococcus neoformans* to human phagocytes. Infect Immun 61:4891–4893

Li D, Dong B, Tong Z, Wang Q, Liu W, Wang Y, Chen J, Xu L, Chen L, Duan Y (2012) MBL-mediated opsonophagocytosis of *Candida albicans* by human neutrophils is coupled with intracellular Dectin-1-triggered ROS production. PLoS ONE 7:e50589

Lijtenberg TJ, Bikker FJ, Groenink J, Tornoe I, Leth-Larsen R, Veerman EC, Nieuw Amerongen AV, Holmskov U (2001) Human salivary agglutinin binds to lung surfactant protein-D and is identical with scavenger receptor protein gp-340. Biochem J 359(Pt 1):243–248

Lillegard JB, Sim RB, Thorkildson P, Gates MA, Kozel TR (2006) Recognition of *Candida albicans* by mannann-binding lecint in *vitro* and *in vivo*. J Infect Dis 193:1589–1597

Lim BL, Holmskov U (1996) Expression of the carbohydrate recognition domain of bovine conglutinin and demonstration of its binding to iC3b and yeast mannan. Biochem Biophys Res Commun 218:260–266
Lim BL, Willis AC, Reid KB, Lu J, Laursen SB, Jensensius JC, Holmskov U (1994a) Primary structure of bovine collectin-43 (CL-43). Comparison with conglutinin and lung surfactant protein-D. J Biol Chem 269(16):11820–11824
Lim BL, Wang JY, Holmskov U, Hoppe HJ, Reid KB (1994b) Expression of the carbohydrate recognition domain of lung surfactant protein D and demonstration of its binding to lipopolysaccharides of Gram-negative bacteria. Biochem Biophys Res Commun 202:1674–1680
Limper AH, Crouch EC, O’riondan DM, Chang D, Vuk-Pavlovic Z, Standing JE, Kwon KY, Adlakha A (1995) Surfactant protein-D modulates interaction of Pneumocystis carinii with alveolar macrophages. J Lab Clin Med 126:416–422
Lin Z, deMello D, Phelps DS, Kolunt WA, Page M, Floros J (2001) Both human SP-A1 and SP-A2 genes are expressed in small and large intestine. Pediatr Pathol Mol Med 20(5):367–386
Ling MT, Tu W, Han Y, Mao H, Chong WP, Guan J, Liu M, Lam KT, Law HK, Peiris JS, Takahashi K, Lau YL (2012) Mannose-binding lectin contributes to deleterious inflammatory response in pandemic H1N1 and avian H9N2 infection. J Infect Dis 205:44–53
Linke MJ, Harris CE, Korfhagen TR, Mccormack FX, Ashbaugh AD, Steele P, Whitsett JA, Walzer PD (2001) Immunosuppressed surfactant protein A-deficient mice have increased susceptibility to Pneumocystis carinii infection. J Infect Dis 183:943–952
Linke M, Ashbaugh A, Koch J, Tanaka R, Walzer P (2006) Efficient resolution of Pneumocystis murina infection in surfactant protein A-deficient mice following withdrawal of corticosteroid-induced immunosuppression. J Med Microbiol 55:143–147
Liu CF, Chen YL, Shieh CC, Yu CK, Reid KB, Wang JY (2005) Therapeutic effect of surfactant protein D in allergic inflammation of mite-sensitized mice. Clin Exp Allergy 35(4):515–521
Liu F, Liao Q, Liu Z (2006) Mannose-binding lectin and vulvovaginal candidiasis. Int J Gynaecol Obstet 92:43–47
Loveless RW, Feizi T, Childs RA, Mizuochi T, Stoll MS, Oldroyd RG, Lachmann PJ (1989) Bovine serum conglutinin is a lectin which binds non-reducing terminal N-acetylglucosamine, mannose and fucose residues. Biochem J 258:109–113
Lu J, Teh C, Kishore U, Reid KB (2002) Collectins and ficolins: sugar pattern recognition molecules of the mammalian innate immune system. Biochim Biophys Acta 1572(2–3):387–400
Lugo-Villarino G, Hudrisier D, Tanne A, Neyrolles O (2011) C-type lectins with a sweet spot for Mycobacterium tuberculosis. Eur J Microbiol Immunol (Bp) 1:25–40
Luty AJ, Kun JF, Kremsner PG (1998) Mannose-binding lectin plasma levels and gene polymorphisms in Plasmodium falciparum malaria. J Infect Dis 178:1221–1224
Ma YJ, Hein E, Munthe-Fog L, Skjoedt MO, Bayarri-Olmos R, Romani L, Garred P (2015) Soluble collectin-12 (CL-12) is a pattern recognition molecule initiating complement activation via the alternative pathway. J Immunol 195:3365–3373
Madan T, Eggleton P, Kishore U, Strong P, Aggrawal SS, Sarma PU, Reid KB (1997a) Binding of pulmonary surfactant proteins A and D to Aspergillus fumigatus conidia enhances phagocytosis and killing by human neutrophils and alveolar macrophages. Infect Immun 65:3171–3179
Madan T, Kishore U, Shah A, Eggleton P, Strong P, Wang JY, Aggrawal SS, Sarma PU, Reid KB (1997b) Lung surfactant proteins A and D can inhibit specific IgE binding to the allergens of Aspergillus fumigatus and block allergen-induced histamine release from human basophils. Clin Exp Immunol 110:241–249
Madan T, Kishore U, Singh M, Strong P, Clark H, Hussain EM, Reid KB, Sarma PU (2001a) Surfactant proteins A and D protect mice against pulmonary hypersensitivity induced by Aspergillus fumigatus antigens and allergens. J Clin Invest 107(4):467–475
Madan T, Kishore U, Singh M, Strong P, Hussain EM, Reid KB, Sarma PU (2001b) Protective role of lung surfactant protein D in a murine model of invasive pulmonary aspergillosis. Infect Immun 69:2728–2731
Madan T, Saxena S, Murthy KJ, Muralidhar K, Sarma PU (2002) Association of polymorphisms in the collagen region of human SP-A1 and SP-A2 genes with pulmonary tuberculosis in Indian population. Clin Chem Lab Med 40:1002–1008
Madan T, Reid KB, Singh M, Sarma PU, Kishore U (2005a) Susceptibility of mice genetically deficient in the surfactant protein (SP)-A or SP-D gene to pulmonary hypersensitivity induced by antigens and allergens of \textit{Aspergillus fumigatus}. J Immunol 174(11):6943–6954

Madan T, Reid KB, Singh M, Sarma PU, Kishore U (2005b) Susceptibility of mice genetically deficient in the surfactant protein (SP)-A or SP-D gene to pulmonary hypersensitivity induced by antigens and allergens of \textit{Aspergillus fumigatus}. J Immunol 174:6943–6954

Madan T, Reid KB, Clark H, Singh M, Nayak A, Sarma PU, Hawgood S, Kishore U (2010) Susceptibility of mice genetically deficient in SP-A or SP-D gene to invasive pulmonary aspergillosis. Mol Immunol 47(10):1923–1930

Madsen J, Kliem A, Tornoe I, Skjodt K, Koch C, Holmskov U (2000) Localization of lung surfactant protein D on mucosal surfaces in human tissues. J Immunol 164(11):5866–5870

Madsen J, Tornoe I, Nielsen O, Koch C, Steinhilber W, Holmskov U (2003) Expression and localization of lung surfactant protein A in human tissues. Am J Respir Cell Mol Biol 29(5):591–597

Malhotra R, Thiel S, Reid KB, Sim RB (1990) Human leukocyte C1q receptor binds other soluble proteins with collagen domains. J Exp Med 172(3):955–959, Sep 1

Malhotra R, Haurum J, Thiel S, Sim RB (1992) Interaction of C1q receptor with lung surfactant protein A. Eur J Immunol 22(6):1437–1445

Malhotra R, Willis AC, Jensenius JC, Jackson J, Sim RB (1993) Structure and homology of human C1q receptor (collectin receptor). Immunology 78(3):341–348

Malhotra R, Haurum JS, Thiel S, Sim RB (1994) Binding of human collectins (SP-A and MBP) to influenza virus. Biochem J 304(Pt 2):455–461

Malik S, Greenwood CM, Equale T, Kifle A, Beyene J, Habte A, Tadesse A, Gebrexabher H, Britton S, Schurr E (2006) Variants of the SFTPA1 and SFTPA2 genes and susceptibility to tuberculosis in Ethiopia. Hum Genet 118:752–759

Mangan A, Rocco C, Marino SM, Mecikovsky D, Genre F, Aulicino P, Bologna R, Sen L (2008) Detrimental effects of mannose-binding lectin (MBL2) promoter genotype XA/XA on HIV-1 vertical transmission and AIDS progression. J Infect Dis 198:694–700

Matsushita M, Hikikata M, Ohta Y, Mishiro S (1998) Association of mannose-binding lectin gene haplotype LXPA and LYPB with interferon-resistant hepatitis C virus infection in Japanese patients. J Hepatol 29:695–700

Mcbride MO, Fischer PB, Sumiya M, Mcclure MO, Turner MW, Skinner CJ, Weber JN, Summerfield JA (1998) Mannose-binding protein in HIV-seropositive patients does not contribute to disease progression or bacterial infections. Int J STD AIDS 9:683–688

McCormack FX, Pattanaipitivilai S, Stewart J, Possmayer F, Inchley K, Voelker DR (1997a) The Cys6 intermolecular disulfide bond and the collagen-like region of rat SP-A play critical roles in interactions with alveolar type II cells and surfactant lipids. J Biol Chem 272(44):27971–27979

McCormack FX, Festa AL, Andrews RP, Linke M, Walzer PD (1997b) The carbohydrate recognition domain of surfactant protein A mediates binding to the major surface glycoprotein of \textit{Pneumocystis carinii}. Biochemistry 36:8092–8099

McCormack FX, Damodarasamy M, Elhalwagi BM (1999) Deletion mapping of N-terminal domains of surfactant protein A. The N-terminal segment is required for phospholipid aggregation and specific inhibition of surfactant secretion. J Biol Chem 274(5):3173–3181

McCormack FX, Gibbons R, Ward SR, Kuzmenko A, Wu H, Deepe GS Jr (2003) Macrophage-independent fungicidal action of the pulmonary collectins. J Biol Chem 278:36250–36256

McGreal EP, Ikewaki N, Akatsu H, Morgan BP, Gasque P (2002) Human C1qR is identical with CD93 and the nM1-11 antigen but does not bind C1q. J Immunol 168(10):5222–5232

Mcneely TB, Coonrod JD (1994) Aggregation and opsonization of type A but not type B \textit{Hemophilus influenzae} by surfactant protein A. Am J Respir Cell Mol Biol 11:114–122

Mehmood A, Kouser L, Kaur A, Holmskov U, Al-Ahdal MN, Sim RB, Kishore U, Tslolaki AG (2019) Complement dependent and independent interaction between Bovine Conglutinin and \textit{Mycobacterium bovis} BCG: implications in bovine tuberculosis. Front Immunol 9:3159
Meschi J, Crouch EC, Skolnik P, Yahya K, Holmskov U, Leth-Larsen R, Tornoe I, Tecle T, White MR, Hartshorn KL (2005) Surfactant protein D binds to human immunodeficiency virus (HIV) envelope protein gp120 and inhibits HIV replication. J Gen Virol 86:3097–3107

Michelow IC, Lear C, Scully C, Prugar LI, Longley CB, Yantosca LM, Ji X, Karpel M, Brudner M, Takahashi K, Spear GT, Ezekowtiz RA, Schmidt EV, Olinger GG (2011) High-dose mannose-binding lectin therapy for Ebola virus infection. J Infect Dis 203:175–179

Milanese M, Segat L, De Setta F, Pirulli D, Fabris A, Morgutti M, Crovella S (2008) MBL2 genetic screening in patients with recurrent vaginal infections. Am J Reprod Immunol 59:146–151

Miyamura K, Malhotra R, Hoppe HJ, Reid KB, Phizackerley PJ, Macpherson P, López Bernal A (1994) Surfactant proteins A (SP-A) and D (SP-D): levels in human amniotic fluid and localization in the fetal membranes. Biochim Biophys Acta 1210(3):303–307

Mogues T, Ota T, Tauber AI, Sastry KN (1996) Characterization of two mannose-binding protein cDNAs from rhesus monkey (Macaca mulatta): structure and evolutionary implications. Glycobiology 6(5):543–550

Moller-Kristensen M, Ip WK, Shi L, Gowda LD, Hamblin MR, Thiel S, Jenseniuc JS, Ezekowtiz RA, Takahashi K (2006) Deficiency of mannose-binding lectin greatly increases susceptibility to postburn infection with Pseudomonas aeruginosa. J Immunol 176:1769–1775

Mullighan CG, Heatley S, Doherty K, Szabo F, Grigg A, Hughes TP, Schawar AP, Szer J, Tait BD, Bik To L, Bardy PG (2002) Mannose-binding lectin gene polymorphisms are associated with major infection following allogeneic hemopoietic stem cell transplantation. Blood 99:3524–3529

Murakami S, Iwaki D, Mitsuzawa H, Sano H, Takahashi H, Voelker DR, Akino T, Kuroki Y (2002) Surfactant protein A inhibits peptidoglycan-induced tumor necrosis factor-alpha secretion in U937 cells and alveolar macrophages by direct interaction with toll-like receptor 2. J Biol Chem 277(9):6830–6837 (Epub 2001 Nov 27)

Murray E, Khamri W, Walker MM, Eggelton P, Moran AP, Ferris JA, Knapp S, Karim QN, Worku M, Strong P, Reid KB, Thrusz MR (2002) Expression of surfactant protein D in the human gastric mucosa and during Helicobacter pylori infection. Infect Immun 70(3):1481–1487

Nadeem A, Chhabra SK, Masood A, Raj HG (2003) Increased oxidative stress and altered levels of antioxidants in asthma. J Allergy Clin Immunol 111(1):72–78

Nadesalingam J, Bernal AL, Dodds AW, Willis AC, Mahoney DJ, Day AJ, Reid KB, Palaniyar N (2003) Identification and characterization of a novel interaction between pulmonary surfactant protein D and decorin. J Biol Chem 278(28):25678–25687

Nadesalingam J, Reid KB, Palaniyar N (2005a) Collectin surfactant protein D binds antibodies and interlinks innate and adaptive immune systems. FEBS Lett 579(20):4449–4453

Nadesalingam J, Dodds AW, Reid KB, Palaniyar N (2005b) Mannose-binding lectin recognizes peptidoglycan via the N-acetyl glucosamine moiety, and inhibits ligand-induced pro-inflammatory effect and promotes chemokine production by macrophages. J Immunol 175:1785–1794

Nagy A, Kozma GT, Keszei M, Treszl A, Falus A, Szalai C (2003) The development of asthma in children infected with Chlamydia pneumoniae is dependent on the modifying effect of mannose-binding lectin. J Allergy Clin Immunol 112(4):729–734

Nauta AJ, Raaschou-Jensen N, Roos A, Daha MR, Madsen HO, Borrias-Essers MC, Ryder LP, Koch C, Garred P (2003) Mannose-binding lectin engagement with late apoptotic and necrotic cells. Eur J Immunol 33:2853–2863

Nayak A, Dodagatta-Marri E, Tsolaki AG, Kishore U (2012) An insight into the diverse roles of surfactant proteins, SP-A and SP-D in innate and adaptive immunity. Front Immunol 3:131

Neth O, Jack DL, Dodds AW, Holzel H, Klein NJ, Turner MW (2000) Mannose-binding lectin binds to a range of clinically relevant microorganisms and promotes complement deposition. Infect Immun 68:688–693

Ng KK, Drickamer K, Weis WI (1996) Structural analysis of monosaccharide recognition by rat liver mannose-binding protein. J Biol Chem 271(2):663–674
Ng KK, Park-Snyder S, Weis WI (1998) Ca²⁺-dependent structural changes in C-type mannan-binding proteins. Biochemistry 37(51):17965–17976

Nielsen SL, Andersen PL, Koch C, Jensenius JC, Thiel S (1995) The level of the serum opsonin, mannan-binding protein in HIV-1 antibody-positive patients. Clin Exp Immunol 100:219–222

Norsworthy PJ, Fossati-Jimack L, Cortes-Hernandez J, Taylor PR, Bygrave AE, Thompson RD, Nourshargh S, Walport MJ, Botto M (2004) Murine CD93 (C1qRp) contributes to the removal of apoptotic cells in vivo but is not required for C1q-mediated enhancement of phagocytosis. J Immunol. 172(6):3406–3414

Ogden CA, Decathelineau A, Hoffmann PR, Bratton D, Ghebrehiwet B, Fadok VA, Henson PM (2001) C1q and mannose binding lectin engagement of cell surface calreticulin and CD91 initiates macrophagocytosis and uptake of apoptotic cells. J Exp Med 194:781–795

Ohtani K, Suzuki Y, Eda S, Kawai T, Kase T, Yamazaki H, Shimada T, Keshi H, Sakai Y, Fukuh A, Sakamoto T, Wakamiya N (1999) Molecular cloning of a novel human collectin from liver (CL-L1). J Biol Chem 274(19):13681–13689

Ohtani K, Suzuki Y, Eda S, Kawai T, Kase T, Keshi H, Sakai Y, Fukuh A, Sakamoto T, Itabe H, Suzutani T, Ogasawara M, Yoshida I, Wakamiya N (2001) The membrane-type collectin CL-P1 is a scavenger receptor on vascular endothelial cells. J Biol Chem 276(47):44222–44228

O’riordan DM, Standing JE, Kwon KY, Chang D, Crouch EC, Limper AH (1995) Surfactant protein D interacts with Pneumocystis carinii and mediates organism adherence to alveolar macrophages. J Clin Invest 95:2699–2710

Pandit H, Gopal S, Sonawani A, Yadav AK, Qaseem AS, Warke H, Patil A, Gajbhiye R, Kulkarni V, Al-Mozaini MA, Idicula-Thomas S, Kishore U, Madan T (2014) Surfactant protein D inhibits HIV-1 infection of target cells via interference with gp120-CD4 interaction and modulates pro-inflammatory cytokine production. PLoS ONE 9:e102395

Pandit H, Kale K, Yamamoto H, Thakur G, Rokade S, Chakraborty P, Vasudevan M, Kishore M, Madan T, Fichorova RN (2019) Surfactant Protein D reverses the gene signature of transepithelial HIV-1 passage and restricts the viral transfer across the vaginal barrier. Front Immunol 10:264

Pasula R, Wright JR, Kachel DL, Martin WJ 2 (1999) Surfactant protein A suppresses reactive nitrogen intermediates by alveolar macrophages in response to Mycobacterium tuberculosis. J Clin Invest 103:483–490

Pellis V, De Seta F, Crovella S, Bossi F, Bulla R, Guaschino S, Radillo O, Garred P, Tedesco F (2005) Mannose binding lectin and C3 act as recognition molecules for infectious agents in the vagina. Clin Exp Immunol 139:120–126

Perino J, Thielen NM, Crouch E, Spehner D, Crane GM, Favier AL (2013) Protective effect of surfactant protein D in pulmonary vaccinia virus infection: implication of A27 viral protein. Viruses 5:928–953

Phelps DS, Umstead TM, Rose RM, Fishman JA (1996) Surfactant protein-A levels increase during Pneumocystis carinii pneumonia in the rat. Eur Respir J 9:565–570

Piboonpocanun S, Chiba H, Mitsuzawa H, Martin W, Murphy RC, Harbeck RJ, Voelker DR (2005) Surfactant protein A binds Mycoplasma pneumoniae with high affinity and attenuates its growth by recognition of disaturated phosphatidylglycerols. J Biol Chem 280:9–17

Pikaar JC, Voorhout WF, Van Golde LM, Verhoef J, Van Strijp JA, Van Iwaarden JF (1995) Opsonic activities of surfactant proteins A and D in phagocytosis of gram-negative bacteria by alveolar macrophages. J Infect Dis 172:481–489

Polotsky VY, Fischer W, Ezekowitz RA, Joiner KA (1996) Interactions of human mannose-binding protein with lipoteichoic acids. Infect Immun 64:380–383

Polotsky VY, Belisle JT, Mikusova K, Ezekowitz RA, Joiner KA (1997) Interaction of human mannose-binding protein with Mycobacterium avium. J Infect Dis 175:1159–1168

Qu J, He L, Rong Z, Pan J, Chen X, Morrison DC, Li X (2001) Alteration of surfactant proteins A and D in bronchoalveolar lavage fluid of Pneumocystis carinii pneumonia. Chin Med J (Engl) 114:1143–1146
Ragas A, Roussel L, Puzo G, Riviere M (2007) The Mycobacterium tuberculosis cell-surface glycoprotein apa as a potential adhesin to colonize target cells via the innate immune system pulmonary C-type lectin surfactant protein A. J Biol Chem 282:5133–5142
Rapleye CA, Eissenberg LG, Goldman WE (2007) Histoplasma capsulatum alpha-(1,3)-glucan blocks innate immune recognition by the beta-glucan receptor. Proc Natl Acad Sci USA 104:1366–1370
Reading PC, Hartley CA, Ezekowitz RA, Anders EM (1995) A serum mannose-binding lectin mediates complement-dependent lysis of influenza virus-infected cells. Biochem Biophys Res Commun 217:1128–1136
Reading PC, Morey LS, Crouch EC, Anders EM (1997) Collectin-mediated antiviral host defense of the lung: evidence from influenza virus infection of mice. J Virol 71:8204–8212
Reading PC, Holmskov U, Anders EM (1998) Antiviral activity of bovine collectins against rotaviruses. J Gen Virol 79(Pt 9):2255–2263
Reichhardt MP, Loimaranta V, Thiel S, Finne J, Meri S, Jarva H (2012) The salivary scavenger and agglutinin binds MBL and regulates the lectin pathway of complement in solution and on surfaces. Front Immunol 16(3):205
Ross SC, Densen P (1984) Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. Med (Baltimore) 63:243–273
Rosseau S, Guenther A, Seeger W, Lohmeyer J (1997) Phagocytosis of viable Candida albicans by alveolar macrophages: lack of opsonin function of surfactant protein A. J Infect Dis 175:421–428
Rosseau S, Hammerl P, Maus U, Gunther A, Seeger W, Grimminger F, Lohmeyer J (1999) Surfactant protein A down-regulates proinflammatory cytokine production evoked by Candida albicans in human alveolar macrophages and monocytes. J Immunol 163:4495–4502
Rothfuchs AG, Roffe E, Gibson A, Cheever AW, Ezekowitz RA, Takahashi K, Steindel M, Sher A, Bafica A (2012) Mannose-binding lectin regulates host resistance and pathology during experimental infection with Trypanosoma cruzi. PLoS ONE 7:e47835
Rothmann AB, Mortensen HD, Holmskov U, Højrup P (1997) Structural characterization of bovine collectin-43. Eur J Biochem 243(3):630–635
Roy S, Knox K, Segal S, Griffiths D, Moore CE, Welsh KI, Smarason A, Day NP, Mcpheat WL, Crook DW, Hill AV (2002) MBL genotype and risk of invasive pneumococcal disease: a case-control study. Lancet 359:1569–1573
Roy N, Ohtani K, Matsuda Y, Mori K, Hwang I, Suzuki Y, Inoue N, Wakamiya N (2016) Collectin CL-P1 utilizes C-reactive protein for complement activation. Biochim Biophys Acta 1860:1118–1128
Saijuddin M, Hart ML, Gewurz H, Zhang Y, Spear GT (2000) Interaction of mannose-binding lectin with primary isolates of human immunodeficiency virus type 1. J Gen Virol 81:949–955
Sano H, Sohma H, Muta T, Nomura S, Voelker DR, Kuroki Y (1999) Pulmonary surfactant protein A modulates the cellular response to smooth and rough lipopolysaccharides by interaction with CD14. J Immunol 163(1):387–395
Sano H, Chiba H, Iwaki D, Sohma H, Voelker DR, Kuroki Y (2000) Surfactant proteins A and D bind CD14 by different mechanisms. J Biol Chem 275:22442–22451
Santos IK, Costa CH, Krieger H, Feitosa MF, Zurakowski D, Fardin B, Gomes RB, Weiner DL, Harn DA, Ezekowitiz RA, Epstein JE (2001) Mannan-binding lectin enhances susceptibility to visceral leishmaniasis. Infect Immun 69(8):5212–5215
Sasaki K, Tsutsumi A, Wakamiya N, Ohtani K, Suzuki Y, Watanabe Y, Nakayama N, Koike T (2000) Mannose-binding lectin polymorphisms in patients with hepatitis C virus infection. Scand J Gastroenterol 35:960–965
Sastry K, Zahedi K, Lelias JM, Whitehead AS, Ezekowitz RA (1991) Molecular characterization of the mouse mannose-binding proteins. The mannose-binding protein A but not C is an acute phase reactant. J Immunol 147(2):692–697
Sawada K, Ariki S, Kojima T, Saito A, Yamazoe M, Nishitani C, Shimizu T, Takahashi M, Mizuzawa H, Yokota S, Sawada N, Fujii N, Takahashi H, Kuroki Y (2010) Pulmonary collectins
protect macrophages against pore-forming activity of *Legionella pneumophila* and suppress its intracellular growth. J Biol Chem 285:8434–8443

Saxena S, Madan T, Shah A, Muralidhar K, Sarma PU (2003) Association of polymorphisms in the collagen region of SP-A2 with increased levels of total IgE antibodies and eosinophilia in patients with allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol 111:1001–1007

Schelenz S, Malhotra R, Sim RB, Holmsovk U, Bancroft GJ (1995) Binding of host collectins to the pathogenic yeast *Cryptococcus neoformans*: human surfactant protein D acts as an agglutinin for acapsular yeast cells. Infect Immun 63:3360–3366

Selman L, Hansen S (2012) Structure and function of collectin liver 1 (CL-L1) and collectin 11 (CL-11, CL-K1). Immunobiology 217:851–863

Seppanen M, Lokki ML, Lappalainen M, Hiltunen-Back E, Rovio AT, Kares S, Hurme M, Aittoniemi J (2009) Mannose-binding lectin 2 gene polymorphism in recurrent herpes simplex virus 2 infection. Hum Immunol 70:218–221

Shi L, Takahashi K, Dundee J, Shahroor-Karni S, Thiel S, Jenseniuc JC, Gad F, Hamblin MR, Sastry KN, Ezekowitz RA (2004) Mannose-binding lectin-deficient mice are susceptible to infection with *Staphylococcus aureus*. J Exp Med 199:1379–1390

Shushimita S, van der Pol P, de Bruin RW, Ijzermans JN, van Kooten C, Dor FJ (2015) Mannan-binding lectin is involved in the protection against renal ischemia/reperfusion injury by dietary restriction. PLoS ONE. 10(9):e0137795

Singh M, Madan T, Waters P, Parida SK, Sarma PU, Kishore U (2003) Protective effects of a recombinant fragment of human surfactant protein D in a murine model of pulmonary hypersensitivity induced by dust mite allergens. Immunol Lett 86(3):299–307

Singh M, Madan T, Waters P, Sonar S, Singh SK, Kamran MF, Bernal AL, Sarma PU, Singh VK, Crouch EC, Kishore U (2009) Therapeutic effects of recombinant forms of full-length and truncated human surfactant protein D in a murine model of invasive pulmonary aspergillosis. Mol Immunol 46:2363–2369

Skjoedt MO, Roversi P, Hummelsbøj T, Palarasah Y, Rosbjerg A, Johnson S, Lea SM, Garred P (2012) Crystal structure and functional characterization of the complement regulator mannose-binding lectin (MBL)/ficolin-associated protein-1 (MAP-1). J Biol Chem 287(39):32913–32921

Steffensen R, Thiel S, Varming K, Jersild C, Jenseniuc JC (2000) Detection of structural gene mutations and promoter polymorphisms in the mannan-binding lectin (MBL) gene by polymerase chain reaction with sequence-specific primers. J Immunol Methods 241:33–42

Stuart GR, Lynch NJ, Lu J, Geick A, Moffatt BE, Sim RB, Schweabel WJ (1996) Localisation of the C1q binding site within C1q receptor/calreticulin. FEBS Lett 397(2–3):245–249

Sugar AM, Picard M (1988) Experimental blastomycosis pneumonia in mice by infection with conidia. J Med Vet Mycol 26:321–326

Swierzko AS, Bartlomiejczyk MA, Brzostek A, Lukasiewicz J, Michalski M, Dziadek J, Cedzynski M (2016) Mycobacterial antigen 85 complex (Ag85) as a target for ficolins and mannose-binding lectin. Int J Med Microbiol 306:212–222

Takahashi K, Ezekowitz RA (2005) The role of the mannose-binding lectin in innate immunity. Clin Infect Dis 41(Suppl 7):S440–S444

Takahashi K, Gordon J, Liu H, Sastry KN, Epstein JE, Motwani M, Laursen I, Thiel S, Jenseniuc JC, Carroll M, Ezekowitz RA (2002) Lack of mannose-binding lectin-A enhances survival in a mouse model of acute septic peritonitis. Microbes Infect 4(8):773–784

Takeda K, Miyahara N, Rha YH, Taube C, Yang ES, Joetham A, Kodama T, Balhorn AM, Dakhama A, Duez C, Evans AJ, Voelker DR, Gelfand EW (2003) Surfactant protein D regulates airway function and allergic inflammation through modulation of macrophage function. Am J Respir Crit Care Med 168(7):783–789 (Epub 2003 Jul 25)

Tan SM, Chung MC, Kon OL, Thiel S, Lee SH, Lu J (1996) Improvements on the purification of mannan-binding lectin and demonstration of its Ca(2+)-independent association with a C1s-like serine protease. Biochem J 319(Pt 2):329–332

Tecle T, White MR, Crouch EC, Hartshorn KL (2007) Inhibition of influenza viral neuraminidase activity by collectins. Arch Virol 152:1731–1742
Teodorof C, Divakar S, Soontorniyomkij B, Achim CL, Kaul M, Singh KK (2014) Intracellular mannose binding lectin mediates subcellular trafficking of HIV-1 gp120 in neurons. Neurobiol Dis 69:54–64

Thawer S, Auret J, Schnoeller C, Chetty A, Smith K, Darby M, Roberts L, Mackay RM, Whitwell HJ, Timms JF, Madsen J, Selkirk ME, Brombacher F, Clark HW, Horsnell WG (2016) Surfactant protein-D is essential for immunity to Helminth infection. PLoS Pathog 12:e1005461

Thiel S, Vorup-Jensen T, Stover CM, Schwaeble W, Laursen SB, Poulsen K, Willis AC, Eggleton P, Hansen S, Holmskov U, Reid KB, Jensenius JC (1997) A second serine protease associated with mannan-binding lectin that activates complement. Nature 386(6624):506–510

Thiel S, Frederiksen PD, Jensenius JC (2006) Clinical manifestations of mannan-binding lectin deficiency. Mol Immunol 43:86–96

Thomas HC, Foster GR, Sumiya M, Mcintosh D, Jack DL, Turner MW, Summerfeld JA (1996) Mutation of gene of mannose-binding protein associated with chronic hepatitis B viral infection. Lancet 348:1417–1419

Tino MJ, Wright JR (1999) Glycoprotein-340 binds surfactant protein-A (SP-A) and stimulates alveolar macrophage migration in an SP-A-independent manner. Am J Respir Cell Mol Biol 20:759–768

Tokunaga H, Ushirogawa H, Ohuchi M (2011) The pandemic (H1N1) 2009 influenza virus is resistant to mannan-binding lectin. Virol J 8:50

Troegeler A, Lugo-Villarino G, Hansen S, Rasolofo V, Henriksen ML, Mori K, Ohtani K, Duval C, Mercier I, Benard A, Nigou J, Hudrisier D, Wakamiya N, Neyrolles O (2015) Collectin CL-LK is a novel soluble pattern recognition receptor for Mycobacterium tuberculosis. PLoS ONE 10:e0132692

Uemura T, Sano H, Katoh T, Nishitani C, Mitsuzawa H, Shimizu T, Kuroki Y (2006) Surfactant protein A without the interruption of Gly-X-Y repeats loses a kink of oligomeric structure and exhibits impaired phospholipid liposome aggregation ability. Biochemistry 45(48):14543–14551

Uguz A, Berber Z, Coskun M, Halide Akbas S, Yegin O (2005) Mannose-binding lectin levels in children with asthma. Pediatr Allergy Immunol 16(3):231–235

Ushijima H, Schroder HC, Poznanovic S, Gasic MJ, Matthes E, Muller WE (1992) Inhibition of human immunodeficiency virus-1 infection by human conglutinin-like protein: in vitro studies. Jpn J Cancer Res 83:458–464

Vaid M, Kaur S, Madan T, Singh H, Gupta VK, Murthy KJR, Sarma PU (2006) Association of SP-D, MNL and I-NOS genetic variants with pulmonary tuberculosis. Indian J Hum Genet 12:105–110

Vaid M, Kaur S, Sambatakou H, Madan T, Denning DW, Sarma PU (2007) Distinct alleles of mannose-binding lectin (MBL) and surfactant proteins A (SP-A) in patients with chronic cavitary pulmonary aspergillosis and allergic bronchopulmonary aspergillosis. Clin Chem Lab Med 45:183–186

Valdimarsson H, Vikingsdottir T, Bang P, Saevarsdottir S, Gudjonsson JE, Oskarsson O, Christiansen M, Blou L, Laursen I, Koch C (2004) Human plasma-derived mannose-binding lectin: a phase I safety and pharmacokinetic study. Scand J Immunol 59:97–102

van Asbeck EC, Hoepelman AI, Scharringa J, Herpers BL, Verhoef J (2008) Mannose binding lectin plays a crucial role in innate immunity against yeast by enhanced complement activation and enhanced uptake of polymorphonuclear cells. BMC Microbiol 8:229

van De Wetering JK, Van Eijk M, Van Golde LM, Hartung T, Van Strijp JA, Batenburg JJ (2001) Characteristics of surfactant protein A and D binding to lipoteichoic acid and peptidoglycan, 2 major cell wall components of gram-positive bacteria. J Infect Dis 184:1143–1151

van de Wetering JK, van Golde LM, Batenburg JJ (2004a) Collectins: players of the innate immune system. Eur J Biochem 271(7):1229–1249

van De Wetering JK, Coenjaerts FE, Vaandrager AB, Van Golde LM, Batenburg JJ (2004b) Aggregation of Cryptococcus neoformans by surfactant protein D is inhibited by its capsular component glucuronoxylomannan. Infect Immun 72:145–153
van De Wetering JK, Van Remoortere A, Vaandrager AB, Batenburg JJ, Van Golde LM, Hokke CH, Van Hellemont JJ (2004c) Surfactant protein D binding to terminal alpha1-3-linked fucose residues and to Schistosoma mansoni. Am J Respir Cell Mol Biol 31:565–572

van Eijk M, White MR, Crouch EC, Batenburg JJ, Vaandrager AB, Van Golde LM, Haagsman HP, Hartshorn KL (2003) Porcine pulmonary collectins show distinct interactions with influenza A viruses: role of the N-linked oligosaccharides in the carbohydrate recognition domain. J Immunol 171:1431–1440

van Emmerik LC, Kuijper EJ, Fijen CA, Dankert J, Thiel S (1994) Binding of mannan-binding protein to various bacterial pathogens of meningitis. Clin Exp Immunol 97:411–416

van Iwaarden F, Welmers B, Verhoef J, Haagsman HP, van Golde LM (1990) Pulmonary surfactant protein A enhances the host-defense mechanism of rat alveolar macrophages. Am J Respir Cell Mol Biol 2(1):91–98

van Iwaarden JF, Van Strijp JA, Ebskamp MJ, Welmers AC, Verhoef J, Van Golde LM (1991) Surfactant protein A is opsonin in phagocytosis of herpes simplex virus type 1 by rat alveolar macrophages. Am J Physiol 261:L204–L209

van Iwaarden JF, Shimizu H, Van Golde PH, Voelker DR, Van Golde LM (1992a) Rat surfactant protein D enhances the production of oxygen radicals by rat alveolar macrophages. Biochem J 286(Pt 1):5–8

van Iwaarden JF, van Strijp JA, Visser H, Haagsman HP, Verhoef J, van Golde LM (1992b) Binding of surfactant protein A (SP-A) to herpes simplex virus type 1-infected cells is mediated by the carbohydrate moiety of SP-A. J Biol Chem 267(35):25039–25043

van Iwaarden JF, Pikaar JC, Storm J, Brouwer E, Verhoef J, Oosting RS, Van Golde LM, Van Strijp JA (1994) Binding of surfactant protein A to the lipid A moiety of bacterial lipopolysaccharides. Biochem J 303(Pt 2):407–411

van Rozendaal BA, Van Spriel AB, Van De Winkel JG, Haagsman HP (2000) Role of pulmonary surfactant protein D in innate defense against Candida albicans. J Infect Dis 182:917–922

Vandivier RW, Ogden CA, Fadok VA, Hoffmann PR, Brown KK, Botto M, Walport MJ, Fisher JH, Henson PM, Greene KE (2002) Role of surfactant proteins A, D, and C1q in the clearance of apoptotic cells in vivo and in vitro: calreticulin and CD91 as a common collectin receptor complex. J Immunol 169(7):3978–3986

Varga L, Szilágyi K, Lörincz Z, Berrens L, Thiel S, Závodszyk P, Daha MR, Thielens NM, Arlaud GJ, Nagy K, Spáth P, Füst G (2003) Studies on the mechanisms of allergen-induced activation of the classical and lectin pathways of complement. Mol Immunol 39(14):839–846

Venkatraman Girija U, Furze CM, Gingras AR, Yoshizaki T, Ohtani K, Marshall JE, Wallis AK, Schweable WJ, El-Mezgueldi M, Mitchell DA, Moody PC, Wakamiya N, Wallis R (2015) Molecular basis of sugar recognition by collectin-K1 and the effects of mutations associated with 3MC syndrome. BMC Biol 17(13):27

Voorhout WF, Veenendaal T, Kuroki Y, Ogasawara Y, van Golde LM, Geuze HJ (1992) Immunochemical localization of surfactant protein D (SP-D) in type II cells, Clara cells, and alveolar macrophages of rat lung. J Histochem Cytochem 40(10):1589–1597

Voss T, Melchers K, Scheirle G, Schäfer KP (1991) Structural comparison of recombinant pulmonary surfactant protein SP-A derived from two human coding sequences: implications for the chain composition of natural human SP-A. Am J Respir Cell Mol Biol 4(1):88–94

Vuk-Pavlovic Z, Standing JE, Crouch EC, Limper AH (2001) Carbohydrate recognition domain of surfactant protein D mediates interactions with Pneumocystis carinii glycoprotein A. Am J Respir Cell Mol Biol 24:475–484

Vuk-Pavlovic Z, Mo EK, Icenhour CR, Standing JE, Fisher JH, Limper AH (2006) Surfactant protein D enhances Pneumocystis infection in immune-suppressed mice. Am J Physiol Lung Cell Mol Physiol 290:L442–L449

Walenkamp AM, Verheul AF, Scharringa J, Hoeplerman IM (1999) Pulmonary surfactant protein A binds to Cryptococcus neoformans without promoting phagocytosis. Eur J Clin Invest 29:83–92
Wang JY, Kishore U, Reid KB (1995) A recombinant polypeptide, composed of the alpha-helical neck region and the carbohydrate recognition domain of conglutinin, self-associates to give a functionally intact homotrimer. FEBS Lett 376:6–10

Wang JY, Shieh CC, You PF, Lei HY, Reid KB (1998) Inhibitory effect of pulmonary surfactant proteins A and D on allergen-induced lymphocyte proliferation and histamine release in children with asthma. Am J Respir Crit Care Med 158(2):510–518

Wang M, Wang F, Yang J, Zhao D, Wang H, Shao F, Wang W, Sun R, Ling M, Zhai J, Song S (2013) Mannan-binding lectin inhibits Candida albicans-induced cellular responses in PMA-activated THP-1 cells through Toll-like receptor 2 and Toll-like receptor 4. PLoS ONE 8:e83517

Weikert LF, Edwards K, Chroneos ZC, Hager C, Hoffman L, Shepherd VL (1997) SP-A enhances uptake of bacillus Calmette-Guerin by macrophages through a specific SP-A receptor. Am J Physiol 272:L989–L995

Weikert LF, Lopez JP, Abdolrasulnia R, Chroneos ZC, Shepherd VL (2000) Surfactant protein A enhances mycobacterial killing by rat macrophages through a nitric oxide-dependent pathway. Am J Physiol Lung Cell Mol Physiol 279:L216–L223

Weis WI, Chrlow GV, Murthy HM, Hendrickson WA, Drickamer K (1991a) Physical characterization and crystallization of the carbohydrate-recognition domain of a mannose-binding protein from rat. J Biol Chem 266(31):20678–20686

Weis WI, Kahn R, Fourme R, Drickamer K, Hendrickson WA (1991b) Structure of the calcium-dependent lectin domain from a rat mannose-binding protein determined by MAD phasing. Science 254(5038):1608–1615

Weyer C, Sabat R, Wissel H, Kruger DH, Stevens PA, Prosch S (2000) Surfactant protein A binding to cytomegalovirus proteins enhances virus entry into rat lung cells. Am J Respir Cell Mol Biol 23:71–78

White RT, Damm D, Miller J, Spratt K, Schilling J, Hawgood S, Benson B, Cordell B (1985) Isolation and characterization of the human pulmonary surfactant apoprotein gene. Nature 317(6035):361–363

White CW, Greene KE, Allen CB, Shannon JM (2001) Elevated expression of surfactant proteins in newborn rats during adaptation to hyperoxia. Am J Respir Cell Mol Biol 25(1):51–59

White MR, Crouch E, Vesona J, Tacken PJ, Batenburg JJ, Leth-Larsen R, Holmskov U, Hartshorn KL (2005) Respiratory innate immune proteins differentially modulate the neutrophil respiratory burst response to influenza A virus. Am J Physiol Lung Cell Mol Physiol 289:L606–L616

Williams MD, Wright JR, March KL, Martin WJ 2 (1996) Human surfactant protein A enhances attachment of Pneumocystis carinii to rat alveolar macrophages. Am J Respir Cell Mol Biol 14:232–238

Wong SSW, Rani M, Dodagatta-Marri E, Ibrahim-Granet O, Kishore U, Bayry J, Latge JP, Sahu A, Madan T, Aimanianda V (2018) Fungal melanin stimulates surfactant protein D-mediated opsonization of and host immune response to Aspergillus fumigatus spores. J Biol Chem 293:4901–4912

Wu H, Kuzmenko A, Wan S, Schaffer L, Weiss A, Fisher JH, Kim KS, Mccormack FX (2003) Surfactant proteins A and D inhibit the growth of Gram-negative bacteria by increasing membrane permeability. J Clin Invest 111:1589–1602

Wu YP, Liu ZH, Wei R, Pan SD, Mao NY, Chen B, Han JJ, Zhang FS, Holmskov U, Xia ZL, De Groot PG, Reid KB, Xu WB, Sorensen GL (2009) Elevated plasma surfactant protein D (SP-D) levels and a direct correlation with anti-severe acute respiratory syndrome coronavirus-specific IgG antibody in SARS patients. Scand J Immunol 69:508–515

Xu J, Nakamura S, Islam MS, Guo Y, Ihara K, Tomioka R, Masuda M, Yoneyama H, Isogai E (2016) Mannose-binding lectin inhibits the motility of pathogenic salmonella by affecting the driving forces of motility and the chemotactic response. PLoS ONE 11:e0154165

Yang CH, Szeliga J, Jordan J, Faske S, Sever-Chroneos Z, Dorsett B, Christian RE, Settlage RE, Shabanowitz J, Hunt DF, Whitsett JA, Chroneos ZC (2005) Identification of the surfactant protein A receptor 210 as the unconventional myosin 18A. J Biol Chem 280(41):34447–34457
Yang HY, Li H, Wang YG, Xu CY, Zhao YL, Ma XG, Li XW, Chen H (2014) Correlation analysis between single nucleotide polymorphisms of pulmonary surfactant protein A gene and pulmonary tuberculosis in the Han population in China. Int J Infect Dis 26:31–36
Yong SJ, Vuk-Pavlovic Z, Standing JE, Crouch EC, Limper AH (2003) Surfactant protein D-mediated aggregation of Pneumocystis carinii impairs phagocytosis by alveolar macrophages. Infect Immun 71:1662–1671
Yuen MF, Lau CS, Lau YL, Wong WM (1999) h progression of liver disease in chronic hepatitis B infection. Hepatology 29:1248–1251
Zimmerman PE, Voelker DR, Mccormack FX, Paulsrud JR, Martin WJ 2 (1992) 120-kD surface glycoprotein of Pneumocystis carinii is a ligand for surfactant protein A. J Clin Invest 89:143–149