Mannose-Binding Lectin in Human Health and Disease

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Introduction

Mannose-binding lectin (MBL), also known as mannose-binding protein or mannan-binding lectin, was first discovered by Kawasaki in 1978 (1978). Five years later, MBL was isolated from human and rat liver (Wild et al. 1983) and from a variety of species (Kozutsumi et al. 1980; Townsend and Stahl 1981; Kawasaki et al. 1983; Oka et al. 1988). MBL is mainly produced by the liver but low amounts have been found in the small intestine (Uemura et al. 2002).

The protein’s first description occurred in 1968, a decade before its discovery, where the protein was referred to as having an opsonic activity in relation to immune deficiency. In this report, an infant with a serum dependent defect of phagocytosis was described (Miller et al. 1968). The girl who was suffering from severe dermatitis and recurrent bacterial infections, was found to lack a plasma component detected by the opsonization of baker’s yeast. The phagocytic deficiency was improved by infusion of fresh plasma which resulted also in clinical improvement. Studies on serum from the patient’s mother and her relatives, revealed that the condition was

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hereditary. Investigations by Super et al. (1989) found that 25% of hospitalized children with recurrent infections had an opsonic defect. Later, the missing plasma component in these children was linked to MBL and that the originally described phagocytic defect, was due to MBL deficiency (Turner 1996).

After the discovery of MBL, studies showed that the protein could activate the complement system upon binding to surfaces which displayed mannan (Kawasaki et al. 1983; Ikeda et al. 1987). Further studies revealed that MBL in serum was associated with a serine protease, and therefore called MBL-associated serine protease (MASP) (Matsushita and Fujita 1992). Subsequently, three MASPs, now named MASP 1, 2 and 3 were characterized. In serum, the MBL circulates in complex with MASPs and initiates the lectin pathway of the complement system when binding to its target and is also associated with coagulation events. In this review, we will give a comprehensive overview of the literature on MBL by discussing its structure, function, interaction with its serine proteases, genetics and its role in association with various pathologies.

**MBL Structure**

MBL is a collectin, which is a Group III C-type lectin. The C-type lectin superfamily is a large group of proteins that are characterized by the presence of one or more C-type lectin or carbohydrate recognition domains (CRDs) and is involved in innate defense systems (Van De Wetering et al. 2004). Collectins are characterized by a collagen-like region and a C-type carbohydrate domain (CRD) in their C-terminal end (Fig. 1a). The MBL CRD specifically recognizes a monosaccharide which exposes horizontal 3′- and 4′ OH groups (Kjaer et al. 2013). MBL is an oligomeric molecule of 25 kDa polypeptides that form a trimer, referred to as the subunit (Fig. 1b), that further assemble into oligomeric forms (Fig. 1c). Each subunit is made up of three identical polypeptide chains (Holmskov et al. 2003; Garred et al. 2006) (Fig. 1b). Each peptide chain consists of four regions: an N-terminal tail region, followed by a collagenous region, a short α-helical neck domain, and each chain terminates in the C-terminal calcium-dependent carbohydrate-recognition domain (CRD) (Garred et al. 2006) (Fig. 1a).

The N-terminal tail region consists of 21 amino acids (aa), three of which are cysteines (Fig. 1a). It has been shown that the N-terminal region provides stability to the subunit by intra-subunit disulfide bonds (Hansen and Holmskov 1998) and the cysteines seem to be responsible for the oligomerization of the subunit (Jensen et al. 2005). The collagenous region (59 aa) has 19 Gly-X-Y repeats (Gly-X-Y, where X and Y may be any amino acids) with a GlyGLn interruption at the eighth triplet (Fig. 1a). It is assumed that the break between the two collagen repeats induces a bend or flexibility, the so-called “kink” (Gal and Ambrus 2001). The collagenous region is followed by a short α-helical coiled-coil neck region (33 aa) which links the final domain, a globular CRD (115 aa) (Fig. 1a). The only crystal structures that have been determined by X-ray crystallography so far are these of the
CRDs with the α-helical coil neck region (PDB 1HUP, 1RTM) (Sheriff et al. 1994; Weis and Drickamer 1994) as well as the collagen-like peptide (PDB 3PON) (Gingras et al. 2011) and the primary structure of the peptide is solved (Ezekowitz et al. 1988).

Three polypeptide chains associate to form a homotrimeric subunit comprising the collagen-like triple helix, an α-helical coiled-coil, the so-called neck region, and three CRDs (Turner 1996) (Fig. 1c). The subunit is stabilized by disulfide bonds between cysteine residues and hydrophobic interactions in the N-terminal region (Lu et al. 1990) and these three cysteines form interchain disulfide bonds that mediate formation of higher oligomeric forms (Super et al. 1992).

A trimer of MBL is the basic building block that is organized in oligomers ranging from dimers and trimers and extend up to hexamers and octamers (Jensenius

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**Fig. 1** Polypeptide, monomeric and oligomeric structures of mannose-binding lectin (MBL). An MBL monomer is a homotrimer of three polypeptides, each subunit consists of a cysteine-rich N-terminal region, a collagen-like domain with Gly-X-Y repeats and a C-terminal carbohydrate recognition domain (CRD) (a). The structural unit of MBL consists of three subunits (b) and the oligomer is composed of up to six structural units (corresponding to 18 subunits) linked by disulfide bonds (c).
et al. 2009) (Fig. 1c), each displaying 6–24 CRDs providing MBL high avidity towards targets with suitably displayed ligand (Dahl et al. 2001; Jensen et al. 2007). Moreover, the prominent forms of human MBL are trimers and tetramers, whereas pentamers and hexamers occur in much lower amounts (Lu et al. 1990; Teillet et al. 2005). It has been assumed that oligomeric MBLs form bouquet-like structures, called “bunch of tulips”, which is similar to the structure of complement C1q (Lu et al. 1990). However, imaging studies have revealed that MBL adopts a near-planar, fan-shaped structure in solution (Jensenius et al. 2009; Miller et al. 2012; Nan et al. 2017).

MBL is secreted into the blood stream as a large multimeric complex and is primarily produced by the liver, although other sites of production, such as the intestine, have been proposed (Uemura et al. 2002). The protein circulates as a complex with MASPs which get activated upon binding to its ligands (Fig. 1c). The ligand specificity of MBL is determined by the CRD, which is able to bind a range of oligosaccharides including mannose, N-acetylglucosamine (GlcNAc) and L-fucose (Turner 1996).

**Various Functions of MBL**

**Binding of MBL with Ligands and Pathogens**

The key difference between innate and adaptive immunity exists in the flexibility, kinetics and specificity of the immune response (Beutler 2004). In innate immunity, a well-defined pool of germline-encoded pattern recognition receptors (PRRs) can bind to highly conserved structures termed as pathogen-associated molecular patterns (PAMPs), which can be found in large groups of invading microorganisms. The PRRs are either present on many effector cells of the immune system, e.g. macrophages or dendritic cells, or are secreted in the serum (Beutler 2004). Certainly, the arrangement of PAMPs, in which carbohydrates are involved, on the surfaces of bacteria, fungi, viruses and protozoans is distinct from the carbohydrates found in eukaryotes, thereby helping in distinguishing self (non-infectious) from non-self (infectious) (Janeway and Medzhitov 2002). Upon carbohydrate pattern recognition on a pathogen, the PRRs trigger effector cells to destroy the invading microorganism. Several classes of PRRs have now been identified, where the three general categories are: signaling, endocytic and secreted. MBL belongs to the last class (Nuytinck and Shapiro 2004). By having the role of an opsonin, the protein binds to microbial cell walls to tag them for recognition from the complement system and phagocytes.

It has been shown that the binding of a single MBL CRD to microbial carbohydrates is relatively weak, with a $K_d$ of approximately $10^{-3}$ M (Turner 1996). Significant functional avidity can be achieved when multimeric interactions occur between the CRDs of the multimeric protein, altogether 18 in a hexameric MBL, and the cell surface carbohydrates (Lu et al. 1990). CRD’s ability to recognize and
bind a range of oligosaccharides (Turner 1996), makes MBL a very important protein in first-line immune defense (Neth et al. 2000).

The bacterial targets that have been identified in vitro for MBL are numerous. Mannose and N-acetylglucosamine oligosaccharides, which MBL binds with high affinity, are present on the surface of various strains of Gram-positive and Gram-negative bacteria, fungi and yeast particles (Neth et al. 2000). It has been reported that MBL binds strongly to Candida species, Aspergillus fumigatus, Staphylococcus aureus, and β-hemolytic group A streptococci. An intermediate binding of MBL has been found for Escherichia coli, Klebsiella species, and Haemophilus influenzae type b. Contrary to β-hemolytic group B streptococci, Streptococcus pneumoniae, and Staphylococcus epidermis which MBL binds weakly (Neth et al. 2000). The latter observation suggests that MBL binding is significantly weakened by the presence of a capsule (Turner 1996), or by the addition of sialic acids on the bacterial surfaces (Eisen and Minchinton 2003). Consequently, various strains of one bacterial species may vary significantly with regards to binding of MBL (Thiel and Gadjeva 2009).

MBL’s recognition and binding is not limited to microbial carbohydrates to initiate complement activation cascade, but the protein binds also to phospholipids (Kilpatrick 1998), nucleic acids (Palaniyar et al. 2004) and non-glycosylated proteins (Estabrook et al. 2004); characteristics that are probably related to the clearance of apoptotic cells and avoidance of autoimmunity (Nuytinck and Shapiro 2004). Engagement of MBL with apoptotic and necrotic cells has been reported where MBL facilitates the uptake of these cells by macrophages (Nauta et al. 2003).

Many publications suggest that MBL’s involvement may be expanded above complement activation. It has been proven that MBL is able also to promote complement-independent opsonophagocytosis, modulate inflammation and probably promote apoptosis (Ogden et al. 2001; Nauta et al. 2003; Turner 2003; Saevarsdottir et al. 2004). Additionally, MBL and the MBL-associated serine proteases-1 and -2 have been associated with the coagulation system (Gulla et al. 2010; Dobó et al. 2016b) and recent studies demonstrated their involvement in the ongoing COVID-19 pandemic (Erikkson et al. 2020; Rambaldi et al. 2020). Therefore, MBL seems to play a central role in innate immunity, given its contribution in microbial recognition, clearance, inflammation and apoptosis. It is reasonable to expect that MBL deficiency may result in impaired host immune defenses, and consequently, have been associated with several diseases. Indeed, a huge number of studies has shown MBL’s association with several diseases.

**Physiological Role of MBL**

As described briefly above, at least four distinct functions of MBL have been reported so far:

(a) activation of complement; (b) promotion of (complement-independent) opsonophagocytosis; (c) modulation of inflammation, and (d) promotion of apoptosis
MBL’s association with the complement system has been studied extensively, whereas the other three MBL associated mechanisms are not so clear yet. In addition to these functions, recent studies describe the involvement of MBL beyond innate immunity. MBL and MASP are associated with the coagulation system where the proteins show coagulation factor-like activities (Gulla et al. 2010; Dobó et al. 2016b).

Activation of the complement system occurs via three pathways: the classical pathway (CP), the lectin pathway (LP), and the alternative pathway (AP). All pathways converge onto a common terminal pathway (TP) via generation of a C3-convertase, resulting in opsonization and lysis of invading pathogens and altered self-structures, and recruitment of inflammatory cells. The CP is activated through binding of C1q to immune complexes. The LP is activated when the complexes of MBL or ficolins or other collectins with MASP bind to the carbohydrates on the surface of pathogens (Fujita et al. 2004). MASP convert C2 and C4 into a C3-convertase, the C4b2a complex, which is the same complex generated by the CP. The alternative pathway is activated by C3b generated during the activation of the classical and lectin pathway and by other mechanisms; therefore, it is acting mainly as an amplification loop for those two complement pathways.

MBL’s association with the complement system has mostly been reported to be involved in the lectin pathway, where the serine proteases MASP-1 and MASP-2 are the key enzymes of the pathway. While MASP-3 has been reported to be involved in the activation of the alternative pathway by activating the complement component pro-Factor D (Dobó et al. 2016a; Pihl et al. 2017).

Several reports have been shown that MBL is able to promote opsonophagocytosis in a complement-independent manner. The first report about this function of MBL was by Kuhlman et al. (1989) where the Gram-negative bacterium Salmonella montevideo, exposing a mannose-rich O-polysaccharide, was found to be ingested by monocytes in an MBL-dependent manner. The experiments were performed with both human MBL (20 μg/mL) and recombinant MBL (rMBL) (1 μg/mL) expressed in CHO cells (Kuhlman et al. 1989).

Super et al. (1992) performed further studies by studying the differences in functionality between the wild-type rMBL and the mutant (in codon 54) rMBL and showed that both forms of recombinant proteins had a similar potential of mediating the uptake of Salmonella montevideo by human neutrophils, suggesting that the mutant form didn’t lose the ability to bind to the bacterium and opsonize it.

Direct opsonization was reported also by other studies. Hartshorn et al. (1993) reported that human MBL could bind to Influenza A virus which displays high mannose oligosaccharide and enhance the H2O2 production by neutrophils. Similar effect was observed also between wild type rMBL and mutant rMBL (mutation on codon 54).

Thus, MBL has a direct interaction with receptors on the surface of phagocytes. Several putative receptors or MBL-binding proteins have since been proposed. Amongst these receptors, cC1qR appears to be the main candidate, which was later found to be identical to the intracellular protein calreticulin (Malhotra et al. 1990). Other suggested receptors which are linked to promote opsonophagocytosis by
MBL, are the C1qRp (Tenner et al. 1995) and CR1 (Ghiran et al. 2000). C1qRp was subsequently found to be a mitochondrial protein and found not to bind MBL (McGreal et al. 2002; Norsworthy et al. 2004) but CR1, the complement C3b receptor, interacts with MBL (Ghiran et al. 2000; Jacquet et al. 2018) but this functional activity has to be further explored.

On the other hand, van Asbeck et al. (2008) showed that MBL is an opsonin only in the presence of complement. Since complement activation will amplify opsonisation, such findings depend on assay sensitivity. They performed opsonophagocytosis assays with complement-deficient sera and phagocytosis was not observed from the binding of MBL in the absence of downstream complement components, whereas phagocytosis was enhanced via C3b-dependent opsonization recognized by complement receptors on PMNs, suggesting that MBL doesn’t act as a direct opsonin. Other studies have also reported similar results. Certainly, the phagocytic potential of MBL alone is less well understood and more studies must be done.

There is increasing evidence from studies which report that the protein has a major role in the modulation of inflammation, independent of complement activation (Jack et al. 2001) and MBL as a pleiotropic immunomodulator affects numerous cell types of innate and adaptive immunity. Studies have shown that MBL modifies cytokine response through a cooperation with Toll-like receptors 2 and 6 in the phagosome (Ip et al. 2008), or through LPS and Toll-like receptor 4 (Wang et al. 2011). Other studies reported that MBL is able to bind human monocytes and reduce inflammatory responses (Wang et al. 2013; Tang et al. 2015) and additionally interact with human T cells and suppress T cell activation (Zhao et al. 2017). Additionally, a recent publication showed that the protein can bind to human peripheral NK cells and regulate inflammatory cytokine production (Zhou et al. 2019). Nonetheless, the underlying mechanisms of MBL-mediated modulation of inflammation are not clear and further work is necessary to define these mechanisms, providing new therapeutic opportunities in inflammatory and autoimmune diseases.

It has been also reported that MBL takes part in a very important function of the immune system, in the recognition of altered or damaged self and subsequently in facilitating their clearance (Nauta et al. 2003; Stuart et al. 2005). MBL can bind apoptotic cells and initiate their uptake by macrophages (Ogden et al. 2001). It was suggested that calreticulin associates with CD91 through which MBL is bound on the macrophage surface and mediates uptake of apoptotic cells in addition to the uptake of microorganisms (Ogden et al. 2001; Duus et al. 2010).

Recent findings indicate a linkage of MBL to the coagulation system. The MBL-associated serine protease-1 (MASP-1) and -2 (MASP-2) have been shown to be responsible for the procoagulant activity of the lectin pathway by activating components of the coagulation system (Dobó et al. 2016b; Krarup et al. 2008; Gulla et al. 2010). MASP-1 acts as a thrombin-like enzyme by cleaving thrombin substrates such as fibrinogen and Factor XIII, proteins involved in the clotting process (Krarup et al. 2008) and thrombin-activatable fibrinolysis inhibitor (TAFI) which prevents fibrinolysis (Hess et al. 2012). Both MASP-1 and MASP-2 have been described to cleave and activate prothrombin to generate thrombin, leading to
the formation of a fibrin clot (Krarup et al. 2007; Dobó et al. 2016b). Additionally, studies revealed that the serine proteases MASP-1 and MASP-2 in complexes with their recognition molecules MBL or ficolins can generate insoluble fibrin clots (Gulla et al. 2010). Furthermore, products of coagulation events, such as fibrin or activated platelets, have been shown to activate MASP-1 and MASP-2 suggesting an ongoing crosstalk between the lectin pathway and the coagulation system in hypercoagulable states (Kozarcanin et al., 2016). Both complement and coagulation systems may play an important role in severe COVID-19, a disease caused by the severe acute respiratory coronavirus 2 (SARS-CoV-2), the etiological agent responsible for the ongoing pandemic. Recent reports describe coagulopathy and thrombotic events in patients with severe COVID-19 (Miesbach and Makris 2020). Thrombosis can be caused by endothelial injury, which is a central pathological component of COVID-19 pathophysiology (Ackermann et al. 2020; Rambaldi et al. 2020; Varga et al. 2020). Complement activation through the lectin pathway has been correlated with the complications of this disease. It was shown that MBL is strongly related to thrombosis and to plasma D-dimer levels, an indicator of coagulopathy (Eriksson et al. 2020). Furthermore, MASP-2 and products of lectin pathway activation can be found in affected microvasculature in biopsy specimens from patients with severe COVID-19 disease (Magro 2020) and MASP-2 has been reported to be associated with lung injury in coronavirus infection (Rambaldi et al. 2020). Therefore, inhibition of the complement system is investigated as a potential treatment for severe COVID-19. Recent studies have shown clinical improvement in COVID-19 patients following treatment with inhibitors for the complement components MASP-2 (Rambaldi et al. 2020), C3 (Mastaglio et al. 2020) or C5 (Diurno et al. 2020), suggesting that complement suppression may provide an effective therapeutic approach to treat severe COVID-19 (Gao et al. 2020). A recent study showed clinical improvement and survival of all hospitalized patients with severe COVID-19 when treated with Narsoplimab (OMS721; Omeros Corporation, Seattle, WA), a MASP-2 inhibitor (Rambaldi et al. 2020). The observations from this study support further the involvement and importance of the lectin pathway in the pathophysiology of this disease, suggesting lectin pathway inhibition to be a promising treatment for lung injury and thrombosis in COVID-19 (Rambaldi et al. 2020).

**MBL-Associated Serine Proteases**

As a pattern recognition molecule, MBL binds to a range of sugars on viruses, bacteria, yeasts, fungi and protozoa and activates the complement system in an antibody and C1-independent manner (Turner 2003). The recognition domains of the MBL bind simultaneously to a pattern ligand to obtain complement activation. This activation is mediated by complexes of MBL with serine proteases, called MBL-associated serine proteases (MASPs). The name MASP is related to their association with MBL, but nowadays it is also known that MASPs can be found also in
complexes with L-ficolin (Matsushita et al. 2000), H-ficolin (Matsushita et al. 2002), M-ficolin and collectin 11.

These serine proteases are present as zymogens in the circulating complexes and become activated upon the pattern recognition molecules binding to their targets (Dobó et al. 2016b). Binding induces conformational changes in these complexes, which leads to either autoactivation of the serine proteases (Wallis 2007; Héja et al. 2012; Kjaer et al. 2013; Degn et al. 2014), or activation by neighboring complexes (Degn et al. 2014), resulting in the activation of the complement cascade. There are three MBL-associated serine proteases (MASPs) which form complexes with MBL oligomers, MASP-1 (Matsushita and Fujita 1992), MASP-2 (Thiel et al. 1997) and MASP-3 (Dahl et al. 2001), and two non-enzymatic associated proteins, Map 44 (Degn et al. 2009) and Map 19 (Stover et al. 1999). MASP-1 and MASP-2 activate the lectin pathway of the complement system (Schwaeble et al. 2002; Héja et al. 2012), while MASP-3 is responsible for the activation of alternative pathway component, pro-Factor D (FD) (Iwaki et al. 2011; Dobó et al. 2016a; Pihl et al. 2017). MBL molecules circulate as a complex with MASPs and initiate the complement cascade only after binding to their targets, therefore the structural understanding of the MBL/MASP complex is important. Formation of the complex takes place at the collagenous region of MBL which interacts in a calcium-dependent manner with the CUB1-EGF-CUB2 domains of the MASPs (Thielens et al. 2001) (Fig. 2).

Several unsuccessful attempts have been made to determine a high-resolution structure of a lectin pathway complex and the reason might be the heterogeneity of components and their intrinsic flexibility (Gingras et al. 2011). Based on structural studies that were performed on smaller units, various models of MBL/MASPs complexes have been proposed, some of them are presented briefly here (Fig. 3).

Crystallography and structural studies of both MBL and MASPs have uncovered the binding site of the complex. The MASPs bind on the MBL’s collagen-like domain on the C-terminal side of the hinge region (kink) formed by an interruption in the Gly-X-Y repeat pattern (Davies et al. 2003; Wallis et al. 2004). The binding site of MASPs lies within the three N-terminal domains (CUB1-EGF-CUB2) (Wallis 2007) (Fig. 2a). Studies have shown that all three N-terminal domains are necessary to reproduce the binding properties of full-length proteins. The CUB1-EGF domain alone can bind to MBL, but with lower affinity (Wallis 2007). It should be mentioned here that the binding sites for MASP-2, MASP-1 and -3 overlap, but are not identical (Wallis et al. 2004). A slight loss in affinity has been observed when the N-terminal portion of MBL’s collagen-like domain is removed, which suggests that there may be differences in the interactions of MBL and the three MASPs (Wallis et al. 2004).

The interaction between the collagenous region of MBL and the N-terminal domains of MASPs is calcium dependent and the critical sites are located within the CUB1-EGF fragment of the MASPs (Wallis 2007; Kjaer et al. 2015) (Fig. 2a). From the available crystal structures (of the CUB1-EGF-CUB2 domain), two binding sites for Ca²⁺ have been identified (Feinberg et al. 2003; Teillet et al. 2008), but it is not clear whether the interaction between MBL and MASPs depends on a single
Ca\textsuperscript{2+} (Wallis 2007). The importance of Ca\textsuperscript{2+} has been shown in studies where experiments on MASP-2 deficiency (Stengaard-Pedersen et al. 2003; Sørensen et al. 2005) revealed that an amino acid substitution at position 105 (D105G) in the CUB1 domain of MASP-2 results in lower serum levels and failure of the protein to associate with MBL or ficolins. Asp105 provides one of the ligands for Ca\textsuperscript{2+} at site II in the CUB1 domain and the observed phenotype of the mutation could be explained with reduction in the MASPs ability to bind Ca\textsuperscript{2+} at site II, suggesting that Ca\textsuperscript{2+} is critical for MBL binding (Wallis 2007). The importance of Ca\textsuperscript{2+} has been shown also in studies of MBL deficiency on the collagen-like domain where mutations of Lys46 and Leu47 disrupt the interaction with MASPs, leading to elimination of detectable complement fixation (Wallis et al. 2004). Besides Ca\textsuperscript{2+}, it has been observed that glycosylated residues (glycosylgalactosyl-5-hydroxylysine) are flanked at the binding site of MASPs, suggesting prevention of non-specific interactions with other macromolecules (Wallis 2007).

Most of the reports agree that the complex consists of an MBL oligomer and MASPs dimers (Feinberg et al. 2003; Gingras et al. 2011; Kjaer et al. 2015; Nan et al. 2017) (Fig. 2b), but the studies are contradicting whether MBL is complexed with one or two different types of MASPs. Mayilyan et al. (2006) reported that each oligomer in the circulation binds only one type of MASP, therefore MBL-(MASP-2)
or MBL-(MASP-1)$_2$ will occur rather than complexes with more than one type of MASPs (Fig. 3(i)). This has been verified by other reports showing that dimers and the trimeric and tetrameric predominant oligomers of MBL bind to one homodimer of MASP (Wallis et al. 2004; Teillet et al. 2005). However, other studies have reported that in higher oligomers within a single MBL/MASP complex, different types of MASPs can be found (Degn et al. 2012, 2014) (Fig. 3(ii)). In addition, it has been proposed that low-order MBL oligomers mainly associate with MASP-1 and Map 19, while higher oligomers preferentially form a complex with MASP-2 and MASP-3 (Dahl et al. 2001).

A variety of models have been proposed to explain the mechanisms of complement activation. However, a detailed description of the physical changes of the complex during complement activation has not been reported yet, mainly due to lack of structural information on the interactions between components. Feinberg et al. (2003) suggested that the MASP dimer fits in MBL by forming a roughly triangular structure where the CUB1-EGF-CUB2 dimer forms the base and the CCP1-CCP2-SP domains comprising the other two sides (Fig. 3a). Other structural studies have shown that MBL, in complex with dimeric MASP, obtains a quite well-defined cone-like structure (Kjaer et al. 2015), contrary to what has been reported for free MBL, which adopts a planar structure (Lu et al. 1990; Miller et al. 2012; Nan et al. 2017). The flexibility which is present at the collagen-CRD hinge in MBL and

![Fig. 3 Schematic models of suggested MBL/MASP complexes in the lectin pathway (LP). The suggested models include both MASP homodimers (orange/orange or violet/violet SP domains in one dimer) and heterodimers (orange/violet SP domains). (a) MASP dimer in MBL which forms a triangular structure. Flexibility between CUB2 and CCP1 domains of MASP will form a structure where the SP domains of the homo- or heterodimer are able to auto-activate themselves (cis-activation) upon MBL's binding to its target (Feinberg et al. 2003; Teillet et al. 2008). (b) Two MBL/MASP complexes where one MBL/MASP complex activates neighboring MASP molecules on an MBL/MASP complex. The inter-molecular activation is called trans-activation (Wallis et al. 2010; Degn et al. 2014).]
possible further flexibility which is upstream at the putative collagen kink (Gal and Ambrus 2001), combined with the flexibility which probably exists in the EGF-CUB2 junction of MASP, would permit MBL to adapt spatially various ligand patterns (Gingras et al. 2011; Kjaer et al. 2015). In addition, flexibility between MASP domains would allow auto-activation of the SP domains (Fig. 3a). Some studies proposed flexibility between CUB2 and CCP1 of MASP which will form a “closed” MASP structure where the SP domains would be able to auto-activate themselves (Feinberg et al. 2003; Teillet et al. 2008). (Fig. 3a). In a recent report, Nan et al. (2017) showed that MASPs are much more flexible than previously thought, and suggested that the SP domains on MASPs could bend toward each other within the complex leading to intra-molecular MASP autoactivation upon MBL’s binding to a mannose-coated surface. Intra-molecular autoactivation has also been shown in other reports, where it has been suggested that MASP in the complex can bend significantly and activate its partner, as occurs for the homologous to MASP, C1s and C1r within the C1q complex (Degn et al. 2012). Another possibility is the inter-molecular activation where an MBL/MASP complex activates neighboring MASP molecules on MBL/MASP complexes (Wallis et al. 2010; Degn et al. 2014). In this case, the MASP dimer protrudes roughly perpendicular from the primary axis of MBL and when the complex binds to its ligand the SP domain of the one complex will activate the other (Kjaer et al. 2015) (Fig. 3b). It should be highlighted that the proposed models of the above studies do not exclude one another; both intra- and inter-molecular interactions are possible for the activation and initiation of the complement lectin pathway (Fig. 3).

Despite the fact that numerous studies have been made on the MBL/MASP complexes, the exact composition of the complex and subsequently the mechanism of complement activation, remain unclear. Crucial steps to determine the structural aspects of the initiation complex are the understanding of how MASP CUB domains recognize the collagen stems in the MBL (Kjaer et al. 2013) and the understanding of the conformational changes of the serine proteases which lead to their activation and hence trigger the complement cascade.

**Serum MBL Levels**

MBL is produced primarily by the liver as an acute-phase reactant (Thiel et al. 1992), hence its blood level increases significantly in response to infection. The publication of the nucleotide sequence of MBL2 gene revealed several features in the 5′ region that were characteristic of acute phase proteins (Ezekowtiz et al. 1988; Sastry et al. 1989; Taylor et al. 1989). These characteristics included a heat shock consensus element, three glucocorticoid responsive elements, and a sequence with a high degree of homology to amyloid A protein (Turner 1996). In 1992, Thiel et al. confirmed this finding by showing moderate increase in the concentration of MBL in plasma up to three-fold in patients after a major surgery, and in patients suffering a malaria episode (Thiel et al. 1992). Additional measurements from other studies
have also confirmed that MBL is indeed an acute phase protein. However, it should be noted that in comparison with the classical acute phase reactant C-reactive protein, the increase in MBL levels is modest, therefore, MBL can be only characterized as a weak acute phase reactant (Petersen et al. 2001).

MBL circulates in the serum with median levels of about 1.2 μg/mL (Garred et al. 1992); however, it has been observed that the concentration varies greatly between individuals (Turner 1996) from below 50 ng/mL to above 10 μg/mL. This variation between individuals originates primary from some identified polymorphisms in the coding sequence and promoter of the MBL gene (Turner 1996).

**MBL Genetics and Deficiency**

Deficiency of MBL is probably the most common human immunodeficiency and is associated with an increased risk of infections, especially in young children and in immunocompromised individuals (Summerfield et al. 1995; Petersen et al. 2001; Turner 2003). It has been reported that the deficiency may occur in about 15% of the population (Eisen et al. 2008), even though the MBL level cutoff for defining deficiency has not been agreed in the literature. Deficiency has been defined variably as <1000, <500, <200, or <100 ng/mL (Nuytinck and Shapiro 2004; Altorjay et al. 2010). The resolution of the molecular structure of the human MBL2 gene (Sastry et al. 1989; Taylor et al. 1989) revealed the molecular basis of MBL deficiency, which for approximately 20 years was measured functionally as defective yeast opsonization (Turner 1996).

**Organization of the Human MBL2 Gene**

Two human MBL genes have been found, MBL1 and MBL2, where MBL1 is a pseudogene (Guo et al. 1998) and only MBL2 encodes a protein product (Fig. 4); rodents have two distinct functional genes, known as mbl-a and mbl-c encoding two different forms of MBL. The mbl-a and mbl-c genes are located on different chromosomes, 14 and 19, respectively (White et al. 1994). In human the two genes are closely positioned on chromosome 10 (10q11.2-q21) (Sastry et al. 1989; Guo et al. 1998). MBL-2 comprises four exons interrupted by three introns (Fig. 4). Exon 1 encodes the signal peptide, a cysteine-rich domain and seven copies of a repeated Glycine-Xaa-Yaa motif typical for the triple helix formation of collagen structures. Exon 2 encodes the remainder of the collagenous region with 12 Glycine-Xaa-Yaa repeats. Exon 3 encodes a neck region and exon 4 a carbohydrate-binding domain (CRD) (Garred et al. 2006) (Fig. 4).

The promoter sequence of the MBL gene contains various elements which would be expected to enhance MBL transcription (Sastry et al. 1989; Taylor et al. 1989), indicating that MBL is an acute phase protein. The majority of MBL2 transcription
is initiated by a promoter related to exon 1, although it has been found that the MBL2 gene contains an extra alternative promoter region approximately 1 kb upstream of exon 1, which may be responsible for 10–15% of MBL expression (Naito et al. 1999).

**Deficiency**

After resolving the molecular basis of the human MBL gene, mutations were found in the first of the four exons of the human gene (Super et al. 1989; Petersen et al. 2001). Six DNA polymorphisms in MBL2 gene are associated with variation in the expression of MBL, and subsequently in the function of MBL. Three base substitutions have been found in the collagen-like domain and three polymorphisms in promoter 1 (Fig. 4).

The three mutations are at codon 52 (rs5030737; C>T; Arg>Cys), called D allele, codon 54 (rs1800450; G>A; Gly>Asp), called B allele and codon 57 (rs1800451; G>A; Gly>Glu), called C allele (Fig. 4). B, C and D alleles are referred to collectively as O, while A is the wild-type (Sumiya et al. 1991; Lipscombe et al. 1992; Madsen et al. 1994). The point mutation at codon 54 in exon 1 (B allele) causes a substitution of glycine with aspartic acid (GGC to GAC) (Sumiya et al. 1991). The structural substitution in codon 57 (C allele) causes a glycine to be replaced by glutamic acid (GGA to GAA) (Lipscombe et al. 1992); the third point mutation at codon 52 (D allele) causes a substitution of arginine with cysteine (CGT to TGT) (Madsen et al. 1994) (Fig. 4). Each of these mutations result in a similar phenotype: individuals who are heterozygous, A/B, A/C and A/D, for a mutant allele show a dominant decreasing effect on the functional levels of MBL serum. Specifically, studies have shown that heterozygotes for B and C alleles have an about ten times decrease in median protein concentration (Garred et al. 2003, 2016), while the D allele does not reduce the protein concentration to analogous degree (Garred et al. 2003).
All three variants contain a structural change in the collagen-encoded region of the molecule impairing the assembly and/or stability of the basic MBL structural unit; they do not effectively bind mannan and make probably the protein prone to degradation (Sumiya et al. 1991), resulting in low MBL serum concentration. Furthermore, the absence of a sufficient number of higher orders oligomers leads to inefficient complement-fixing activity of MBL (Yokota et al. 1995; Wallis and Drickamer 1999; Larsen et al. 2004). Specifically, it was suggested that the decreasing effect on the B and C alleles on the MBL serum concentration was due to incorrect assembly of the MBL triple helix, caused by disruption of the Gly-X-Y repeats of the collagenous region (Sumiya et al. 1991; Petersen et al. 2001), while the additional cysteine residue in D allele has been suggested to disrupt oligomer formation by generation of aberrant sulfide bonds (Wallis and Cheng 1999).

Additional to the structural mutation within the MBL2 gene, promoter polymorphisms have been identified. This identification showed that the level of MBL in plasma is also modulated at the transcriptional level (Madsen et al. 1995) and large inter-individual variations that have been observed may be explained by polymorphisms found in the promoter 1 region of MBL2 (Madsen et al. 1994, 1995). Particularly, the promoter polymorphisms that have been identified are: at position −550 (rs11003125; G>C; polymorphism H/L) and −221 (rs7096206; C>G; polymorphism X/Y), 7 and a P/Q variant in a 5′untranslated region at position +4, (C>T, rs7095891) (Madsen et al. 1998) (Fig. 4). Because of a linkage disequilibrium between the polymorphisms present in the promoter and the structural alleles in exon 1 of the MBL2 gene, only seven common haplotypes have been described (HYPA, LYPA, LXPA, LYQA, HYPD, LYPB and LYQC) (Madsen et al. 1998), and thus, there are 28 possible diplotypes, the frequency of which varies among populations (Garred et al. 2006). It has been shown that haplotypes with the wild-type A allele, HYPA and LYQA are related to high MBL levels, whereas LYPA is related to medium to low levels (Madsen et al. 1998; Garred et al. 2003).

Moreover, ethnic differences have also been studied and it has been observed that the occurrence of these haplotypes varies in different human populations (Nuytinck and Shapiro 2004), specifically low MBL level related genotypes exist in 10% of Caucasians and up to 40% of Africans (Madsen et al. 1995; Ezekowitz 2003; Garred 2008). It has been also reported that the B allele is frequent among Caucasians, South Americans and Asians; C allele is only frequent among Africans but is rare elsewhere, and D allele has low frequency among all populations (Garred et al. 2006).

The relation between MBL deficiency and several diseases has been reported in a significant amount of publications, where clinical significance of low serum levels of the protein has been described. It has been shown that MBL deficiency influences the susceptibility, and the course of diseases, including numerous types of infectious, autoimmune, cardiovascular diseases and even cancer (Nuytinck and Shapiro 2004).
MBL Associated with Diseases

An abundance of reports has been published which show correlation between MBL and disease. Many reports agree that MBL deficiencies are particularly associated with an increased risk for infections and autoimmune diseases; additionally, influence on the severity and course of several diseases has been shown (Kilpatrick 2002a, b; Eisen and Minchinton 2003; Summerfield 2003; Turner 2003). However, a lot of controversy is found in the literature about MBL’s role in several diseases.

Certainly, MBL plays an important role during early childhood (6–18 months) when the adaptive immune system has not yet matured. In this age children are vulnerable to infection (Koch et al. 2001) and especially those who have been found homozygotic for MBL2 mutations. Immunosuppressed adult patients with autoimmune diseases or malignancies who carry MBL2 mutations have been also shown to have increased susceptibility to various-infectious related diseases (Neth et al. 2001; Schmiegelow et al. 2002; De Benedetti et al. 2007). Patients with co-existing low MBL levels and primary or secondary immune deficits are also prone to develop infectious diseases (Nuytinck and Shapiro 2004). On the other hand, MBL deficiency has been also associated with protection against diseases. MBL2 heterozygotic individuals may be protected against diseases such as tuberculosis (Hoal-Van Helden et al. 1999; Søborg et al. 2003).

The following brief overview will focus on selected examples of diseases that have been investigated for association of MBL deficiency (Table 1).

MBL and Infection

The main function of MBL is probably protection against pathogens which is achieved via opsonization and lysis (Super et al. 1989). MBL deficiency was first recognized as a functional opsonic defect in children with recurrent, unexplained infections (Super et al. 1989). Since then, many studies have been published about MBL’s relation to infectious diseases.

Increased frequencies of MBL variant alleles have been found in patients with infections (Summerfield et al. 1995) and in patients with suspected immunodeficiency (Garred et al. 1995). Also, it has been shown that patients with insufficient MBL levels develop recurrent infections (Summerfield et al. 1995; Kakkanaiah et al. 1998; Garred et al. 2003; De Benedetti et al. 2007).

Acute respiratory tract infections seem to be associated with deficiency of the protein (Eisen 2010) (Table 1). It has been shown that MBL deficiency predisposes to invasive pneumococcal disease (Roy et al. 2002) and low serum levels caused by deficiency of the protein, are associated with increased death in patients with pneumococcal sepsis (Eisen et al. 2008). However, some reports have come to opposite conclusions about MBL’s role in pneumococcal infection (Kronborg et al. 2002; Moens et al. 2006) and this association requires further investigation by
Table 1 Mannose-binding lectin and its association with various diseases

| Disease field            | Disease subtype/subgroup | Outcome                                                                 | Refs.                          |
|--------------------------|--------------------------|------------------------------------------------------------------------|--------------------------------|
| Respiratory Tract Infection | Pneumococcal disease   | O/O MBL2 genotype predispose to invasive pneumococcal disease          | Roy et al. (2002)              |
| Respiratory Tract Infection | Pneumococcal disease   | MBL deficiency doesn’t seem to play a role in the outcome of invasive pneumococcal infection | Kronborg et al. (2002); Moens et al. (2006) |
| Respiratory Tract Infection | Pneumococcal disease   | Low MBL levels were associated with increased death due pneumococcal infection | Eisen et al. (2008)           |
| Respiratory Tract Infection | Pneumococcal disease   | MBL2 genotypes are not involved in susceptibility to either P-CAP\(a\) or IPD\(b\) | García-Laorden et al. (2013) |
| Respiratory Tract Infection | Pneumococcal disease   | Role of MBL deficient genotypes in PM\(c\) (caused by \(S.\) pneumoniae). Children (<2 years) with MBL deficiency are in higher risk for PM | Bautista-Rodriguez et al. (2017) |
| Bacterial infection      | Pneumococcal infection | MBL does not drive lectin pathway activation on the surface of \(S.\) pneumoniae | Ali et al. (2012)              |
| Respiratory Tract Infection | Pneumococcal disease   | Low MBL production could be associated with IPD in children <2 years     | Muñoz-Almagro et al. (2014)   |
| Viral infection          | Influenza A viral infection | \textit{In vivo} studies on mice about protection of MBL from IAV infection. Suggesting MBL deficiency as a risk factor for IAV infection | Chang et al. (2010)           |
| Viral infection          | Influenza virus-related critical illness | MBL deficiency is not a risk factor for severe influenza infection in children and young adults | Levy et al. (2019)           |
| Viral infection          | HIV                      | There is an association between undetectable serum MBL concentrations and susceptibility to HIV infection. But the course of HIV infection does not seem to be influenced by the level of MBL | Nielsen et al. (1995)         |
| Viral infection          | HIV                      | Homozygous carriers of MBL alleles are at increased risk of HIV infection | Garred et al. (1997)          |
| Autoimmune diseases      | Systemic lupus erythematosus | Increased frequency of MBL allele (codon 54) in patients with SLE, but it represents a minor risk factor for this disease. Studies in British SLE patients | Davies et al. (1995)          |
| Autoimmune diseases      | Systemic lupus erythematosus | MBL allele represents a risk factor for SLE in Spanish population and may affect susceptibility in an additive way with C4 null alleles | Davies et al. (1997)          |

(continued)
Table 1 (continued)

| Disease field | Disease subtype/ subgroup | Outcome | Refs. |
|---------------|---------------------------|---------|-------|
| Autoimmune diseases | Systemic lupus erythematosus | MBL mutation on codon 54 may seem to be a minor risk factor for SLE. Study on SLE Chinese patients | Lau et al. (1996) |
| Autoimmune diseases | Systemic lupus erythematosus | Deficiencies of MBL predispose individuals to SLE. Study in SLE black patients | Sullivan et al. (1996) |
| Autoimmune diseases | Systemic lupus erythematosus | Not a significant association between MBL deficiency and SLE | García-Laorden et al. (2003) |
| Autoimmune diseases | Systemic lupus erythematosus | Patients with low MBL-producing genotype have a predisposition to develop SLE. Study in Indian females | Panda et al. (2013) |
| Autoimmune diseases | Systemic lupus erythematosus | A tendency of higher frequency of the B allele was observed in Spanish patients with SLE | Losada López et al. (2016) |
| Autoimmune diseases | CVD and SLE | MBL variant alleles are associated with an increased risk of arterial thrombosis. Study in Danish patients with SLE | Øhlenschläger et al. (2004) |
| Autoimmune diseases | CVD and SLE | MBL deficiency is not determinant of CVD in SLE patients, independent of other risk factors | Kieninger-Gräfitsch et al. (2020) |
| Virus infection | Influenza | MBL doesn’t increase susceptibility to severe influenza infection in pediatric patients | Levy et al. (2019) |
| Bacterial infection | Pulmonary tuberculosis | MBL-2 gene polymorphisms may be involved in the pathogenesis of PTB (pulmonary tuberculosis) and serum may be a biomarker for the diagnosis of PTB | Tong et al. (2019) |
| Autoimmune diseases | RA | MBL2 polymorphisms at codon 52, 54 and 57, as well as at promoter position −220, were not associated with increased risk to RA. (Meta-analysis) | Epp Boschmann et al. (2016) |
| Neonatal sepsis | | MBL is protective toward the development of neonatal sepsis and low MBL levels at birth are associated with an increased risk of hospital-acquired sepsis in infants | De Benedetti et al. (2007) |
| Neonatal sepsis | | Low MBL levels were not associated neither with gestational age or sepsis in infants | Hartz et al. (2018) |
| Sepsis | | MBL2 exon polymorphisms with low serum levels of MBL increase the risk of sepsis infection and septic shock in pediatric patients | Fidler et al. (2004) |

(continued)
performing clinical studies, particularly on MBL’s contribution to the phagocytosis of *Streptococcus pneumoniae* and *S. aureus* (Eisen 2010).

It has been shown that MBL is able to protect from certain viral infections. MBL binds to microbial surface glycosylation residues and targets influenza A virus via direct neutralization in an complement independent-manner (Kase et al. 1999). Studies have shown MBL’s protection also *in vivo* and it has been suggested that MBL deficiency may be a risk factor for influenza A virus infection (Chang et al. 2010). Nevertheless, in a recent report where 420 patients with confirmed influenza-critical illness were studied, MBL deficiency was not found to be a risk factor for very severe influenza infection in children and adolescents (Levy et al. 2019) (Table 1).

The role of MBL in HIV-1 infection has been studied extensively and many clinical studies have reported that MBL serum levels increase during infection. MBL recognizes the HIV-1 via the gp120 surface glycoprotein of the virus (Ying et al. 2004) and it has been reported that MBL’s insufficiency predisposes to susceptibility to HIV-1 infection (Nielsen et al. 1995; Garred et al. 1997) (Table 1).

### Neonatal Sepsis

Due to the immature immune system of newborns and lack of experience of their maturing adaptive immune system, the innate immune response represents a vital first-line defense mechanism against infections in newborns. Therefore, genetic and/or developmental variations in the innate immune system are probably of high importance in modulating the predisposition to invasive infections (De Benedetti et al. 2007).

Numerous studies have investigated the role of MBL in sepsis, the majority of them indicate an increased risk of sepsis in MBL deficient infants (Table 1). In particular, MBL2 gene mutation, which leads to reduced serum levels and functional impairment of the protein, has been shown to be associated with this condition (Gordon et al. 2006). However, it should be pointed out that not all studies confirm

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**Table 1** (continued)

| Disease field     | Disease subtype/subgroup | Outcome                                                                 | Refs.                  |
|-------------------|--------------------------|-------------------------------------------------------------------------|------------------------|
| Neonatal sepsis   | MBL levels below 400 ng/mL increase the chances of developing sepsis | Dzwonek et al. (2008)   |
| Neonatal sepsis   | No major impact on sepsis risk unless in infants between 32–36 gestational age | Hartz et al. (2017)     |
| Neonatal sepsis   | The B allele of MBL2 exon 1 gene is an important risk factor for development of sepsis in premature infants | Özkan et al. (2012)     |

*P-CAP pneumococcal community-acquired pneumonia
*IPD invasive pneumococcal disease
*PM pneumococcal meningitis
this association (Hartz et al. 2017, 2018). (Table 1). An explanation of this discrepancy may be methodological differences, such as variation in definitions of infection, the sample size which was small in most of the studies, differences in definitions of MBL deficiency, and finally different average of gestational age (Keizer et al. 2014a, b). Studies have shown that serum MBL levels are strongly correlated with gestational age and show a postnatal increase, similar to ficolins and other complement proteins (Schlapbach et al. 2010; Sallenbach et al. 2011). However, this has not been verified by a recent study where it was shown that gestational age had no major influence on MBL and MASP-2 levels most probably due to different inclusion criteria (Hartz et al. 2018).

In summary, the majority of the available evidence indicates that reduced MBL levels are a risk factor for sepsis in neonatal age group. The importance of this condition is not debatable; therefore, further research is needed to identify patients at high risk achieving early diagnosis and treatment of sepsis.

Autoimmune Diseases

Several studies have indicated an association of MBL deficiency with susceptibility to autoimmune diseases (Monticielo et al. 2008). Particularly, numerous studies reported an increased frequency of mutant MBL alleles or low levels of the protein in patients with SLE in different ethnicities (Davies et al. 1995, 1997; Lau et al. 1996; Sullivan et al. 1996; Panda et al. 2013) (Table 1). Nevertheless, data remains controversial; the precise effects of MBL deficiency in relation to the development of SLE and disease progression, as well as the role of MBL as a biomarker in assessing SLE activity remain unclear (Losada López et al. 2016). A study about association of MBL deficiency in SLE Spanish patients revealed that there is only a tendency to a greater frequency of the B allele (Losada López et al. 2016), while another study shows that there is not a significant association between SLE and MBL deficiency (García-Laorden et al. 2003) (Table 1). The major cause of death in SLE is cardiovascular disease (CVD). This disease has also been reported to be associated with MBL deficiency (Ohlenschlager et al. 2004; Font et al. 2007) (Table 1). On the other hand, several reports are showing that there is no such link (Larsen et al. 2018) (Table 1). Also, a recent publication that studied whether MBL deficiency, based on the blood concentrations (<1000 ng/mL), is associated with an increased incidence of CVD in SLE patients, showed that this is not the case (Kieninger-Gráfitsch et al. 2020) (Table 1). Large prospective studies with long follow-ups would be required to exclude definitely a role of MBL in SLE-associated CVD, as also for SLE.
MBL Replacement Therapy

For the past 30 years, MBL replacement therapies have been under development, using either plasma derived MBL (pdMBL) or recombinant MBL (rMBL). Some small case studies with pdMBL on MBL-deficient patients in the past years showed that opsonic activity was restored after receipt of MBL infusion (Valdimarsson et al. 1998; Garred et al. 2002). However, these case reports were performed with modest numbers of patients and a conclusion could not be drawn about the significant effect of pMBL. Nevertheless, phase I and early phase II studies have been performed with pdMBL which have established the plasma derived MBL infusions’ safety and efficacy in MBL-deficient individuals (Valdimarsson 2003; Valdimarsson et al. 2004; Brouwer et al. 2009; Frakking et al. 2009).

Phase I studies have been also performed with rMBL (Petersen et al. 2006), which seems to preserve full restoration of functionality of the lectin pathway (Keizer et al. 2018), contrary to pdMBL (Keizer et al. 2014a, b), and therefore it has been proposed to consider new clinical substitution studies using rMBL instead (Keizer et al. 2018).

Conclusions and Perspectives

Unquestionably, MBL is a major component of the innate immunity, taking part in very important functions of the immune system. Therefore, it is reasonable that its deficiency has been associated with numerous different diseases. Association with increased susceptibility to certain infections and autoimmune diseases has been found in individuals who carry MBL2 allelic variants which predispose to low MBL serum levels; these individuals have either an unmatured immune system, carry a coexisting primary or secondary immune deficiency, or are immunocompromised. In those cases, low serum levels of MBL could be a potential biomarker and could be used to identify individuals at increased risk of developing disease. However, more research is needed to standardize MBL measurements (Kilpatrick 2003); this could be achieved by better understanding of the relation between genetic variants and MBL serum levels and determination when MBL serum concentration is associated with clinical relevance (Eisen et al. 2004).

Additionally, the role of MBL in the susceptibility to various diseases is often controversial. Potential reasons of inconsistencies among studies are the focus on the MBL2 gene polymorphisms, the relatively small study populations and the choice of controls (Keizer et al. 2014a, b). It has been observed that the frequencies of MBL polymorphisms show some variability within different populations or ethnicities, hence the selection of the control population is a crucial point. Generally, further cohort studies have to been performed with consistent parameters and greater number of study populations. Moreover, the number of clinical studies is still reduced and the majority of the past clinical studies that have been reported used a modest number of patients. Therefore, larger well-designed trials are necessary.
Finally, MBL replacement therapy may be an important application for the future to reduce the risk of certain diseases in children or immunosuppressed patients. For the better development of effective therapies, a better understanding of the structure of MBL, oligomerization and structural association with its serine proteases is important (Miller et al. 2012).

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