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Mannose/mannan-binding lectin

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Mannose/mannan-binding lectin (MBL) is a serum lectin synthesized (as a ~32 kDa peptide) by the liver and is one of the key molecules of the innate immune system. Each peptide has an N (amino)-terminal cysteine-rich region, a middle stretch of a collagen-like sequence, and a carbohydrate recognition domain (CRD) in the C (carboxy)-terminus. Three identical peptides form a structural subunit, similar to a collagenous triple helix, which is the basic building block of all circulating molecular forms of MBL. Further oligomerization of these structural subunits by disulphide bonds in the N-terminal region results in MBL molecules of different sizes (from dimers to hexamers), but the hexameric form is probably the most common. MBL-associated serine proteases (MASPs) bind to MBL multimeric forms to stabilize the molecule. MBL is a pattern-recognition receptor and the CRDs of MBL serve to bind to a wide range of pathogens such as bacteria, viruses and protozoa, by recognizing carbohydrate moieties on their surfaces. There are two pathways by which MBL can participate in a host defense response: 1) MBL activates the lectin complement pathway via MASPs, that converges with the classical complement pathway, at the level of complement C4 (C4-A or C4-B), and 2) MBL may also act directly as an opsonin, enhancing phagocytosis by binding to cell-surface receptors present on phagocytic cells.

KEYWORDS
COLEC1; Collectin-1; HSMBPC; Mannan-binding lectin; Mannan-binding protein; Mannose-binding lectin; Mannose-binding lectin (protein C) 2, soluble; Mannose-binding lectin (protein C) 2, soluble (opsonic defect); Mannose-binding lectin 2, soluble (opsonic defect); Mannose-binding protein C; Mannose/mannan-binding lectin; MBL; MBL2; MBL2D; MBP; MBP-C; MBP1

IDENTIFIERS
Molecule Page ID:A004276, Species:Human, NCBI Gene ID: 4153, Protein Accession:NP_000233.1, Gene Symbol:MBL2

PROTEIN FUNCTION
Mannose/mannan-binding lectin (MBL), previously known as mannan-binding protein (MBP) is a (C-type or calcium dependent) serum lectin with primary specificity for sugars such as D-mannose, N-acetylglucosamine (GlcNAc), N-acetylmannosamine (ManNAc) and L-fucose (Kawasaki *et al*. 1983, Sheriff *et al*. 1994). It circulates in serum as tri- to hexameric forms of the structural subunit (see 'Interactions with Ligands and Other Proteins' section) in association with a group of MBL-associated serine proteases (MASPs) (Matsushita and Fujita 1992). Being part of the innate immune system, MBL recognizes pathogens and damaged cells, by binding to carbohydrate moieties on microorganisms and altered self-surfaces. MBL firmly bound to foreign or altered self-surfaces, can participate in host defense response by activation of: the lectin complement pathway, phagocytosis, apoptotic cell clearance and inflammatory processes. As MBL is structurally similar to C1q, MBL can also compete with C1q for binding to altered self-ligands (Oroszlán *et al*. 2007, Agostinis *et al*. 2012).

Complement activation: The lectin pathway of complement activation, initiated through MBL-MASP or Ficolin-MASP cascades, is antibody- and C1q- independent. MBL binds to specific carbohydrate structures found on the surface of a range of microorganisms in association with MASPs and activates the complement system (Ji *et al*. 1993, Thiel *et al*. 1997, Kawasaki *et al*. 1989). On binding to appropriate targets, the MASP-1 activated MASP-2 (both the MASPs are in the MBL-MASP complex) sequentially cleaves complement factors C4 and C2 leading to the formation of C3-convertase (C4b2a) (Thiel *et al*. 1997). The C3-convertase is a complement C3 specific enzyme which cleaves C3, into C3a and C3b fragments. In mice, MBL *via* MASP-1 and MASP-3 has been shown to be essential for activation of complement factor D and the alternative complement pathway (Iwaki *et al*. 2011, Takahashi *et al*. 2010).

Opsonization and Phagocytosis: MBL can function directly as an opsonin by binding to pathogen, or indirectly by producing opsonins like C3b. These opsonized pathogens/particles are recognized by a number of putative binding proteins/phagocytic receptors including, calreticulin/CD91 (cC1qR/LRP-1) (Ogden *et al*. 2001, Malhotra *et al*. 1990), C1QR1 (C1qRp, CD93) (Tenner *et al*. 1995) and complement receptor type-1 (CR1, CD35) (Ghiran *et al*. 2000). Calreticulin, an endoplasmic reticulum (ER) protein that acts as a chaperone during protein assembly, can be recruited to the cell surface during phagocytic recognition (Gagnon *et al*. 2002). Low levels of serum MBL are associated with defects in C3b opsonization on yeast surfaces and recurrent infections in children, which imply a role for MBL in host defense in humans (Super *et al*. 1989, Turner *et al*. 1981). MBL (from MBL-coated *Salmonella montevideo*) was able to interact directly with cell surface receptors and promoted opsonophagocytosis (Kuhlman *et al*. 1989). MBL can opsonize Human immunodeficiency virus 1 (HIV-1) but does not induce neutralization at the levels at which it is normally present in serum. However, binding and opsonization of HIV by MBL may alter virus trafficking and viral antigen presentation during HIV infection (Ying *et al*. 2004). MBL and C1q (as MBL is structurally similar to C1q), modulate monocyte activation and chemokine responses during the clearance of oxidized (Ox) LDL. MBL has been reported to directly bind OxLDL and enzymatically modified forms of LDL (E-LDL) in OxLDL-loaded monocytes and human monocyte derived macrophages (HMDM) and can therefore enhance cholesterol efflux (Fraser and Tenner 2010).

Recognition and clearance of altered-self: Role for MBL in the

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clearance of apoptotic cells was suggested through antibody blockade studies that showed that inhibition of calreticulin and CD91 blocked collectin mediated uptake of apoptotic cells by macrophages (Ogden *et al*. 2001). MBL was found to bind directly to apoptotic cells that expose terminal sugars of cytoskeletal proteins, thereby permitting their recognition and directly facilitating their phagocytosis by macrophages. However, it is important to note that MBL can also act as an opsonin by mediating uptake not only via collectin receptors but also through the generation of C3 opsonins (C3b and iC3b) that coats the targets and triggers uptake by complement receptor type 3 (CR3,CD18/CD11b) (Ip *et al*. 2009). Changes in cell surface structures during oncogenic transformation appear to promote binding of MBL to cancer cells (Hakomori 2001), wherein the protein can mediate cytotoxic effects including MBL-dependent cell mediated cytotoxicity (Ma *et al*. 1999, Nakagawa *et al*. 2003).

Modulation of inflammation: MBL plays an important role in modulating inflammation, by releasing cytokines and interleukins. MBL is involved in the binding of cryptococcal mannoprotein (MP2) to human peripheral blood mononuclear cells (PBMCs) and the release of tumor necrosis factor-α (TNF-α) (Chaka *et al*. 1997). Likewise, PBMCs from HIV infected patients when bound to MBL, increase cytokine production and viral replication (Huggelund *et al*. 2005). Monocytes secrete higher levels of TNF-α, interleukin-6 (IL6) and IL-1β, when infected with MBL-opsonised *Neisseria meningitides* (Jack *et al*. 2001) or *Leishmania chagasi* promastigotes (Santos *et al*. 2001), as compared to non-opsonized bacteria.

REGULATION OF ACTIVITY

Hepatocyte gene expression and plasma levels of MBL are stimulated by peroxisome proliferator-activated receptor - α (PPARα) and fenofibrate (used to reduce cholesterol levels in humans at risk of cardiovascular disease). This evidence links PPARα to regulation of innate immunity and complement activation in humans, and suggests a possible role of MBL in lipid metabolism (Rakhshandehroo *et al*. 2012). The salivary scavenger and agglutinin (SALSA, gp340), binds to both pathogen surface and MBL. This interaction (when SALSA is bound to the surface) activates the lectin pathway, while soluble SALSA inhibits MBL function (Reichhardt *et al*. 2012). Thus, SALSA can protect host tissues from complement induced damage. MBL binding to biglycan, an extracellular matrix proteoglycan, inhibits the lectin pathway (Groeneveld *et al*. 2005).

INTERACTIONS

MBL, a member of the collectin family, is a ~32 kDa peptide with an N-terminal cysteine rich region, a collagenous domain, and a region with multiple carbohydrate recognition domains (CRDs) at the C-terminal (Medzhitov and Janeway 2000). Three peptide chains form a homotrimer through the collagenous region, which is the basic structural subunit of all circulating forms of MBL. This structural homotrimer further forms oligomers ranging from dimers to hexamers; hexamer has 6 structural subunits or 18 identical polypeptide chains of 32 kDa each (Sheriff *et al.* 1994, Hoffmann *et al.* 1999). MBL of higher order oligomers (e.g. tetramers to hexamers) are the effective forms in terms of protein functions, such as carbohydrate recognition and complement activation on microbial surfaces (Lu *et al.* 1990, Yokota *et al.* 1995, Iobst *et al*. 1994). The CRDs on each chain recognize or bind polysaccharide patterns on the surface of many microorganisms and self-components including apoptotic cells, phospholipids, and immune complexes. By recognition of cell surface carbohydrates on apoptotic cells, MBL can play an essential role in controlling not only innate immunity responses but also immune cell homeostasis. The recognition of carbohydrates on aberrant host cells may lead to inflammation and breakdown of homeostasis (van Kooyk and Rabinovich 2008, Ip *et al.* 2009).

MBL-MASP Complex: MBL, as an oligomer (tri- to hexameric), forms complexes with different MASP proteins as listed below. All the MASP proteins bind to MBL in homo-dimeric form (Chen and Wallis 2001, Teillet *et al.* 2008, Thielens *et al.* 2001). However, the stoichiometry of the different components in the MBL-MASP complex is highly variable. MBL binds to MASP *via* its collagen domain (Super *et al.* 1992, Kurata *et al.* 1993).

MASP-1 and MASP-2: MASP-1 and MASP-2 encoded by *MASP1* and *MASP2* genes respectively, are serine proteases (Matsushita *et al.* 2000, Skjoedt *et al.* 2011, Thiel *et al.* 1997), which when activated, sequentially cleave complement proteins C4 and C2. MASP-1 is auto-activated, when in complex with MBL bound to microbial carbohydrates. Activated MASP-1 then activates MBL bound MASP-2 (Sekine *et al.* 2013, Héja *et al.* 2012a, Héja *et al.* 2012b). MASP-1 can cleave complement C3 (weakly as compared to C3-convertase), complement factor D in mice (Takahashi *et al*. 2010) and appears to cleave complement C2 (Matsushita *et al.* 2000).

MASP-3: MASP-3 is a splice variant of *MASP1* gene. It has a serine protease domain, but has no known substrates. It is believed to compete with MASP-2 to bind to MBL and therefore down-regulate lectin pathway activation (Dahl *et al.* 2001). In mice however, MASP-3 has been shown to be important in alternative pathway of complement activation (Iwaki *et al.* 2011). Higher oligomeric structures of MBL (larger than trimeric forms) are shown to be in complex with all the three MASPs (MASP-1, MASP-2 and MASP-3) at the same time (Dahl *et al.* 2001).

MAp44 and sMAP (MAp19): MAp44, expressed mainly in the heart, is yet another splice variant of *MASP1* gene. It however does not have a serine protease domain. It competes with MASP-2 to bind to MBL and down-regulates lectin pathway activation (Skjoedt *et al.* 2010, Degn *et al.* 2009). sMAP, a splice variant of *MASP2* gene, also lacks a serine protease domain and competes with MASP-2 to bind to MBL, thereby down-regulating lectin pathway activation (Stover *et al.* 1999 ,Takahashi *et al.* 1999). It was found to be in complex with MASP-1 and trimeric form of MBL (Tateishi *et al.* 2011).

MBL-Host Interactions: MBL has been shown to bind directly to apoptotic (and necrotic) cells, and facilitate clearance of these cells by phagocytosis (Nauta *et al.* 2003, Ogden *et al.* 2001). The bound MBL on apoptotic cells stimulate ingestion by phagocyte by binding to calreticulin (cC1qR), which in turn is bound to the endocytic receptor protein CD91 (LRP-1, α2-macroglobulin receptor) (Eggleton *et al.* 1994). Direct interaction of MBL and CD91 has also been documnted (Duus *et al.* 2010). MBL can also bind to complement receptor type 1 (CR1, CD35) and C1qR (CD93) receptors present on phagocytes (Ghiran *et al.* 2000, Malhotra *et al.* 1995). Therefore MBL deficiency might lead to the accumulation of apoptotic cells, thereby predisposing the host to systemic autoimmunity. MBL pathway is activated upon interaction with $\alpha_2\beta_1$

(CD49/CD29) integrin in mast cells (Edelson *et al.* 2006). MBL is responsible for activating complement on endothelial cells following periods of oxidative stress. Oxidative stress increases endothelial cytokeratin-1 (CK1) expression (Collard *et al.* 2001) and CK1 represents a candidate molecule as a MBL ligand under conditions of cell stress and injury (Collard *et al.* 2001, Montalto *et al.* 2001). Aberrant glycosylation patterns, like Lewis A and Lewis B (Lea–Leb), expressed on glycoproteins CD26 and CD98 heavy chain of human tumor cell lines derived from colon adenocarcinoma and colorectal carcinoma respectively (Muto *et al.* 1999, Muto *et al.* 2001), have been identified as ligands for MBL (Kawasaki *et al.* 2009). Furthermore, MBL has been implicated in activating complement by binding to glycosylated immunoglobulin(Ig)G isoforms associated with rheumatoid arthritis (Tenner *et al.* 1995), polymeric forms of IgA (Hisano *et al.* 2001, Roos *et al.* 2001, Terai *et al.* 2006) and certain glycoforms of IgM (Arnold *et al.* 2005).

MBL-Pathogen Interactions: MBL binds multiple bacterial polysaccharides having terminal monosaccharides such as D-mannose, GlcNAc, ManNAc and L-fucose but not galactose and sialic acids (which are present on host cells) (Weis *et al.*1992, Drickamer 1992). In fact, some pathogens use the strategy of producing polysaccharide capsule and sialylation of lipopolysaccharide structures to escape MBL binding (Jack *et al.* 2001, Krarup *et al.* 2005). MBL has been shown to bind to a wide range of bacteria, viruses, fungi and protozoa (Dommett *et al.* 2006). However, the binding of MBL to pathogens differs both between and within species (heterogeneous binding patterns) (Townsend *et al.* 2001, Neth *et al.* 2000).

Teichoic acid of *Staphylococcus aureus*, a cell surface glycopolymer containing GlcNAc residue, has been shown to be a functional ligand of MBL (Park *et al.* 2010). In addition to *Staphylococcal aureus*, several bacterial species have been found to bind to MBL including: *Actinomyces israelii*, *Bifidobacterium bifidum*, *Leptotrichia buccalis*, *Proprionibacterium acnes* (Townsend *et al.* 2001); *Burkholderia cepacia*, *Pseudomonas aeruginosa* (Davies *et al.* 2000); *Chlamydia pneumoniae* (Swanson *et al.* 1998); *Klebsiella aerogenes*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Escherichia coli*, *Haemophilus influenza*, *Neisseria meningitidis*, *Listeria monocytogenes*, (van Emmerik*et al.* 1994, Neth *et al.* 2000); *Mycobacterium avium* (Polotsky *et al.* 1997); *Mycoplasma pneumonia* (Hamvas *et al.* 2005); and *Salmonella montevideo* (Kuhlman *et al.* 1989). Interestingly, other bacteria (anaerobic) that are most commonly implicated in clinical disease such as, Bacteroides and Clostridium, bound little or no MBL. Similarly, the only Veillonella species that causes any appreciable disease, *V. parvula*, bound little or no MBL. In contrast, *Vitellariopsis dispar*, *Bifidobacterium bifidum*, *Propionibacterium acnes*, *Leptotrichia buccalis*, which very rarely cause significant infections, bound to MBL. Also, Fusobacterium, a rarely isolated organism is bound to measurable amounts of MBL. This suggests that there may be an inverse relationship between pathogenicity and the level of MBL binding (Townsend *et al.* 2001). MBL can bind to viruses such as, influenza A, HIV (Hartshorn *et al.* 1993, Saifuddin *et al.* 2000, Hart *et al.* 2002, Ji *et al.* 2005), and severe acute respiratory syndrome (SARS) coronavirus (CoV) (Ip *et al.* 2005). A number of clinical studies have suggested that deficiency of MBL is a risk factor for acquiring HIV infection. MBL can bind to purified HIV-gp120 which is likely the target of HIV (Ezekowitz *et al.* 1989). MBL can also bind to *Aspergillus fumigatus*, *Candida albicans* (Neth *et al.* 2000) and protozoans such as *Cryptosporidium parvum* (Kelly *et al.* 2000); *Plasmodium falciparum* (Klabunde *et al.* 2002) and *Trypanosoma cruzi* (Kahn *et al.* 1996), to prevent infection.

PHENOTYPES

MBL2 gene (which encodes human MBL protein), along with other collectins, is a part of tightly linked cluster of genes found on the chromosome 10 (Guo *et al.* 1998). MBL deficiency is inherited in an autosomal co-dominant manner (Pettigrew *et al.* 2009), with heterozygotes having about 10% of the normal functional level of MBL and homozygotes having less than 1% functional levels of MBL (Hibberd *et al.* 1999) and affect the serum concentration (Madsen *et al.* 1995, Madsen *et al.* 1998). The point mutations (single nucleotide polymorphisms, SNPs), three in exon 1 and two in promoter region of the MBL gene, lead to a dramatic decrease in the serum concentration of MBL. The transcription of *MBL2* is regulated by two alternative promoters (named 0 and 1) where promoter 0 derived transcripts include an additional 5′ untranslated region (5'UTR) encoded by an extra exon (exon 0). Low extra-hepatic levels of *MBL2* mRNA were predominantly found in small intestine and testis tissue, and were quantitatively dominated by promoter 1 transcripts. Moreover, these transcripts varied due to the use of alternative acceptor splice sites positioned inside exon 1 (Seyfarth *et al.* 2006).

Polymorphisms in Exon 1: The exon 1 mutations on the protein product are believed to impair oligomerization and lead to a functional deficiency. These point mutations are (now commonly referred to as B, C and D alleles) collectively denoted by ‘O’, with variant A indicating the wild type.

Variant B: A reported exon 1 mutation is at codon 54 in which glycine is replaced by aspartic acid (GGC to GAC) when studying a Eurasian population with frequency of approximately 25% (Sumiya *et al.* 1991). This mutation was associated with (most) low MBL serum levels, opsonization defect and recurrent bacterial infections.

Variant C: This exon 1 mutation is at codon 57 in which glycine is replaced by glutamic acid (GGA to GAA), in a sub-Saharan African population with frequencies of 50%–60% (Lipscombe *et al.* 1992).

Variant D: This exon 1 mutation is at codon 52 in which arginine is replaced by cysteine (CGT to TGT) (Madsen *et al.* 1994). This extra cysteine has been proposed to cause formation of adventitious disulphide bonds that hinder higher oligomer formation (Wallis and Drickamer 1999).

Polymorphisms in promoter region: Since exon 1 polymorphisms did not explain variations of MBL serum levels sufficiently, inter-individual variation in serum MBL levels revealed two polymorphisms (H/L and X/Y, at positions −550 and −221 respectively to transcription start site, TSS) in the upstream promoter region of the *MBL2* (Madsen *et al.* 1995). The different combinations of these promoter polymorphisms result in different haplotypes, HY, LY, and LX, with high, medium, and low levels of MBL serum concentrations, respectively. Later a polymorphism, P/Q variant, at 5′UTR of the gene (part of Exon 1) was also identified (Madsen *et al.* 1998) which is also associated with low levels of serum MBL. Promoter polymorphisms and the exon 1 mutations cluster in a pattern of linkage disequilibrium (Garred 2008, Verdu *et al.*

2006, Bernig *et al.* 2004).

The impact of the variations in MBL genotypes or serum concentrations on different human diseases has been intensively studied (disease association studies) (Sumiya *et al.* 1991, Kilpatrick 2002, Eisen and Minchinton 2003, Turner 2003). MBL deficiency is associated with an increased susceptibility to infection with *Neisseria meningitidis* (Bathum *et al.* 2006), and severity of atherosclerotic disease (Madsen *et al*. 1998). The recent findings have shown a correlation between MBL deficiency and *Pseudomonas* infections in cystic fibrosis patients, suggesting that MBL is inherently involved in clearance of potential pathogens in the body. MBL binding may facilitate the uptake of *Mycobacterium* by macrophages, thereby promoting infection. In contrast, presence of mutant alleles, which may lead to MBL deficiency, may convene a protective role against tuberculosis (TB) (Cosar *et al*. 2008, Thye *et al.* 2011, Singla *et al.* 2012). However, certain polymorphisms in *MBL2* contribute to development of TB in HIV patients (Raghavan *et al.* 2012, Alagarasu *et al.* 2007). MBL polymorphisms may also lead to systemic lupus erythematosus (Davies *et al*. 1995), Alzheimer's disease (Sjölander *et al*. 2013) and pulmonary disease in cystic fibrosis (Gabodle *et al*. 1999). MBL function may play a role in survival of kidney graft patients (Bay *et al*. 2013, Damman and Seelen 2013).

MAJOR SITES OF EXPRESSION

MBL is synthesized in the liver and circulates in the serum (Wild *et al.* 1983). However, extra-hepatic expression of MBL also observed (Nonaka *et al*. 2007). The expression of functional MBL peptide is largely genetically determined (see 'Phenotypes' section). MBL is considered as an acute phage reactant protein (serum levels increases during inflammation) (Ezekowitz *et al.* 1988) (see 'Regulation of Concentration' section). However,unlike other lectin proteins which increase drastically, MBL increases only 2-3 fold.

SPLICE VARIANTS

MBL2 gene (which encodes MBL protein) is located on chromosome 10 (q11.2-q21) (Guo *et al.* 1998) with four exons and three introns. The gene encodes two major transcripts by alternative transcription, resulting in different lengths of mRNA transcripts. Transcription may initiate either at exon 1 or at an additional, non-coding 1kb upstream located, exon 0 (Naito *et al.* 1999, Sastry *et al.* 1989, Taylor *et al.* 1989). It is assumed that 10–15% of MBL in serum derives from exon '0' transcription (Heitzeneder *et al.* 2012). Exon 1 encodes the signal peptide, a cysteine-rich region and part of the glycine-rich collagenous region, exon 2 encodes the remainder of the collagenous region, exon 3 encodes an α-helical coiled-coil structure, which is known as the 'neck' region, and exon 4 encodes the CRD, which adopts a globular configuration (Wallis *et al*. 2004, Madsen *et al.* 1995, Weis *et al.* 1992, Wallis 2007). The promoter region of the MBL gene contains a number of regulatory elements, which affect transcription of the protein (Dommett *et al.* 2006). Both, exon '0' and exon 1, promoter regions possess a TATA box for transcription initiation. In both, the binding sites for transcription factors include response elements to IL-6 . This finding was assumed to underlie the regulation of MBL synthesis as an acute phase protein. In addition, the promoter region of exon 1 comprises a glucocorticoid responsive element (Gabolde *et al.* 1999). However, human *MBL1* gene is a pseudogene.

REGULATION OF CONCENTRATION

MBL serum levels are relatively constant in an individual and may increase 2–3 folds upon infections and inflammatory challenges (Thiel *et al.* 1992). The level of MBL in plasma is genetically determined, and deficiency is associated with frequent infections in childhood, and possibly also in adults (Turner 1996). Large molecular mass complexes (200–700 kDa) of MBL circulate in serum, which are probably stabilized by interaction through the cysteine-rich, amino-terminal regions of adjacent trimeric subunits (Lipscombe *et al.* 1995). The serum concentration of MBL varies, from 0 to 10 μg/ml with a median around 1 μg/ml (Saevarsdottir *et al.* 2001, Steffensen *et al.* 2000, Minchinton *et al.* 2002). Recently, using antibodies of human collectin kidney 1 (COLEC11) (Yoshizaki *et al.* 2012) the MBL concentration in blood was established as 1.72 ± 1.51 μg/ml. Enzyme-linked immunosorbent Assays (ELISAs) was used to measure MBL concentration in cerebrospinal fluid was found to be 0.0016-0.056 μg/ml (Kwok *et al.* 2012). Low levels of MBL (< 1 μg/ml) are mostly caused by three point mutations in exon 1 of the MBL gene (in codons 52, 54, and 57) that disrupt the assembly of the oligomers, and also by a promoter polymorphism that is associated with low MBL production (see 'Phenotypes' section). The combination of structural gene and promoter polymorphisms results in a dramatic variation in MBL concentration in apparently healthy individuals of up to 1000-fold (Ezekowitz *et al.* 1988). Non-genetic factors affecting MBL serum levels include age and hormones. MBL levels vary with age, increase within the first months of life and subsequently decline (Aittoniemi *et al.* 1996, Sallenbach *et al.* 2011, Lau *et al*. 1995, Sørensen *et al*. 2006). Thyroid and growth hormones have a significant effect on regulating MBL synthesis (Frakking *et al.* 2006, Riis *et al*. 2005). Human population studies have shown that high levels of MBL (>1 mg/ml) were associated with a greatly decreased risk of myocardial infraction (MI) in hypercholesteromic individuals (Saevarsdottir *et al.* 2005).

ANTIBODIES

MBL antibodies are available from the following companies: EMD Millipore Corporation, R&D Systems, Inc., OriGene Technologies, Inc., GenScript USA Inc., Novus Biologicals, Epitomics Inc., Uscn Life Science Inc., Hycult Biotech etc.

Table 1: Functional States

STATE DESCRIPTION	LOCATION	REFERENCES
MBL (native)	extracellular region	
3MBL (structural, monomer)	extracellular region	Sheriff S *et al.* 1994; Lu JH *et al.* 1990
2(3MBL) (dimer)	extracellular region	Dahl MR *et al.* 2001; Sheriff S *et al.* 1994
3(3MBL) (trimer)	extracellular region	Dahl MR *et al.* 2001; Sheriff S *et al.* 1994
3(3MBL)/MASP-1/sMAP	extracellular region	Stover CM *et al.* 1999; Takahashi M *et al.* 1999; Tateishi K *et al.* 2011; Gregory LA *et al.* 2004
3(3MBL)/MAp44	extracellular region	Skjoedt MO *et al.* 2010; Skjoedt MO *et al.* 2012; Degn SE *et al.* 2009; Skjoedt MO *et al.* 2011
4(3MBL) (tetramer)	extracellular region	Dahl MR *et al.* 2001
4(3MBL)/MASP-1/MASP-2/MASP-3	extracellular region	Dahl MR *et al.* 2001; Sekine H *et al.* ; Wallis R *et al.* 2007
5(3MBL) (pentamer)	extracellular region	Dahl MR *et al.* 2001
5(3MBL)-Zymosan	extracellular region	Lu JH *et al.* 1990
5(3MBL)/MASP-1/MASP-2/MASP-3	extracellular region	Dahl MR *et al.* 2001; Sekine H *et al.* ; Wallis R *et al.* 2007
6(3MBL) (hexamer)	extracellular region	Dahl MR *et al.* 2001
6(3MBL)/cC1qR	extracellular region	Eggleton P *et al.* 1994; Ogden CA *et al.* 2001
6(3MBL)/CD91	plasma membrane	Duus K *et al.* 2010
6(3MBL)/cC1qR/CD91	plasma membrane	Eggleton P *et al.* 1994; Ogden CA *et al.* 2001
6(3MBL)/α2β1	plasma membrane	Edelson BT *et al.* 2006
6(3MBL)/CR1	plasma membrane	Ghiran I *et al.* 2000
6(3MBL)/CK1	extracellular region	Collard CD *et al.* 2001
6(3MBL)/CD93	plasma membrane	Tenner AJ *et al.* 1995
6(3MBL)/IgA	extracellular region	Roos A *et al.* 2001; Royle L *et al.* 2003; Terai I *et al.* 2006
6(3MBL)/IgG	extracellular region	Malhotra R *et al.* 1995
6(3MBL)/IgM	extracellular region	Arnold JN *et al.* 2005; McMullen ME *et al.*
6(3MBL)/LDL	extracellular region	Fraser DA and Tenner AJ 2010
6(3MBL)-GlcNAc	extracellular region	Weis WI *et al.* 1992; Drickamer K *et al.* 1992
6(3MBL)-LTA	extracellular region	Park KH *et al.* 2010
6(3MBL)/SALSA(gp340)	extracellular region	Reichhardt MP *et al.*
6(3MBL)/(Decorin/Biglycan)	extracellular region	Groeneveld TW *et al.* 2005
6(3MBL)/gp120 (HIV)	extracellular region	Haurum JS *et al.* 1993; Ji X *et al.* 2005; Hart ML *et al.* 2002; Senaldi G *et al.* 1995; Saifuddin M *et al.* 2000
6(3MBL)/CD45	plasma membrane	Baldwin TA and Ostergaard HL 2001
6(3MBL)/CD26	plasma membrane	Kawasaki N *et al.* 2009
6(3 MBL)/MASP-1/MASP-2/MASP-3	extracellular region	Héja D *et al.* 2012; Héja D *et al.* 2012; Sekine H *et al.* ; Wallis R *et al.* 2007; Dahl MR *et al.* 2001
6(3MBL)/MASP-1(active)/MASP-2/MASP-3	extracellular region	Fujita T *et al.* 2002
6(3MBL)/MASP-1(active)/MASP-2(active)/MASP-3	extracellular region	Héja D *et al.* 2012

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SUPPLEMENTARY

Supplementary information is available online.

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This molecule exists in 33 states , has 32 transitions between these states and has 2 enzyme functions.(Please zoom in the pdf file to view details.)