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Authors
Dinasarapu, Ashok Reddy
Chandrasekhar, Anjana
Fujita, Teizo
et al.

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Mannose/mannan-binding lectin

Ashok Reddy Dinasarapu¹, Anjana Chandrasekhar¹, Teizo Fujita², Shankar Subramaniam³

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 lectin protein C; Mannose/mannan-binding lectin; MBL; MBL2; MBL2D; MBP; MBP-C; MBP1

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, Agostini 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

¹Department of Bioengineering, University of California, San Diego, CA 92093, US.
²Dept. of Immunology, Fukushima Medical University, 960-1295, JP.
³Department of Bioengineering, University of California at San Diego, CA 92093, US.
Correspondence should be addressed to Ashok Reddy Dinasarapu: adinasarapu@ucsd.edu
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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 mannanprotein (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 (Reichardt 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, Ilobst 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 homodimeric 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).

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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 (Seke 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 MASP3s (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 (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 MASP3s (MASP-1, MASP-2 and MASP-3) at the same time (Dahl et al. 2001).

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. 1999). Direct interaction of MBL and CD91 has also been documented (Duus et al. 2010). MBL can also bind to complement receptor type 1 (CR1, CD35) and C1qR (CD93) receptors present on phagocytes (Ghirton 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 α2β1.
(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 cytokeatin-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, Propionibacterium 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 influenzae, Neisseria meningitidis, Listeria monocytogenes, (van Emmerik et al. 1994, Neth et al. 2000); Mycobacterium avium (Polotsky et al. 1997); Mycoplasma pneumoniae (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, Veillonellopsis 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 (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 GAC) when studying 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 TGG) (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. 2009).
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 convey 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 phase 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 (COLE11) (Yoshizaki et al. 2012) the MBL concentration in blood was established as 1.72 ± 1.51 μg/ml. Enzyme-linked immunosorbert 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, Sellenbach 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 infarction (MI) in hypercholesteromic individuals (Saevarsdottir et al. 2005).

ANTIBODIES

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<td>Reichhardt MP et al.</td>
</tr>
<tr>
<td>6(3MBL)/(Decorin/Biglycan)</td>
<td>extracellular region</td>
<td>Groeneveld TW et al. 2005</td>
</tr>
<tr>
<td>6(3MBL)/CD45</td>
<td>plasma membrane</td>
<td>Baldwin TA and Ostergaard HL 2001</td>
</tr>
<tr>
<td>6(3MBL)/CD26</td>
<td>plasma membrane</td>
<td>Kawasaki N et al. 2009</td>
</tr>
<tr>
<td>6(3MBL)/M3p-1(active)/M3p-2/M3p-3</td>
<td>extracellular region</td>
<td>Fujita T et al. 2002</td>
</tr>
<tr>
<td>6(3MBL)/M3p-1(active)/M3p-2(active)/M3p-3</td>
<td>extracellular region</td>
<td>Héja D et al. 2012</td>
</tr>
</tbody>
</table>
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SUPPLEMENTARY
SUPPLEMENTARY information is available online.

REFERENCES


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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.)