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MASP-2

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MASP-2 (mannose/mannan binding lectin (MBL) associated serine protease-2) is a serum protein predominantly synthesized by the liver as a ~75kDa protein and is one of the key molecules of the innate immune system. It is mainly bound to multimeric protein complexes, such as MBL, the three ficolins (M-ficolin, L-ficolin and H-ficolin) and collectin kidney 1 (CL-K1, alias CL-11). These complexes serve as pathogen receptors, which are further bound to MASP-1, a serine protease. Binding of these complexes to their appropriate pathogenic ligands auto-activates MASP-1. Active MASP-1 in turn acts on its substrate, MASP-2, and thereby activates it. In a cascade of proteolytic cleavage events, MASP-2 activates complement proteins C4 and C2 to form C4b2a (classical C3 convertase), thereby converging the lectin pathway with the classical pathway of complement activation. Further, MASP-2 activity is regulated by several factors, including the serine protease inhibitor C1INH and by interaction with other proteins of the lectin complement pathway.

KEYWORDS
Mannan-binding lectin serine peptidase 1 pseudogene 1; Mannan-binding lectin serine peptidase 2; Mannan-binding lectin serine protease 1 pseudogene 1; Mannan-binding lectin serine protease 2; Mannose-binding protein-associated serine protease 2; MAP19; MASP-2; MASP1P1; MASP2; MBL-associated plasma protein of 19 kD; MBL-associated serine protease 2; Small MBL-associated protein; sMAP

IDENTIFIERS
Molecule Page ID:A004275, Species:Human, NCBI Gene ID: 10747, Protein Accession:NP_006601.2, Gene Symbol:MASP2

PROTEIN FUNCTION
MBL-associated serine protease-2 (MASP-2) was initially discovered in 1997 by Thiel *et al*. MASP-2 has the following domains: two CUB (C1r/C1s/Uegf/bmp1), one epidermal growth factor (EGF)-like, two complement control proteins (CCPs) and a serine protease (which is a chymotrypsin-like protease domain) (Fujita *et al*. 2002).

Activation of complement pathway : MASP-2 in complex with collectins such as mannose/mannan-binding lectin (MBL) or collectin kidney 1 (CL-K1, alias CL-11) and ficolins (M-ficolin, L-ficolin and H-ficolin) activates the complement pathway (Ali *et al*. 2012, Ma *et al*. 2013). Upon binding of collectins or ficolins to its appropriate pathogenic ligands, MASP-2 cleaves C4, followed by binding of C2 to C4b and subsequent cleavage of C2 forming C4b2a (C3 convertase), which cleaves C3 into C3a and C3b (Wallis *et al*. 2007, Vorup-Jensen *et al*. 1998, Matsushita *et al*. 2000). MASP-2 was previously believed to be autoactivated (Vorup-Jensen *et al*. 2000). However, as per current literature another serine protease, MASP-1, bound to MBL or ficolins activates MASP-2 to generate C3 convertase (see 'Regulation of Activity') (Møller-Kristensen *et al*. 2007). MASP-2, in comparison to C1s, has higher efficiency of C4 (~23-fold) and C2 (~3 fold) cleavage, which is attributed to better binding of the substrate through its CCP domains (Rossi *et al*. 2001, Rossi *et al*. 2005). Use of a randomized substrate phage display library revealed MASP-2 to be around 50 times more catalytically active than C1s (Kerr *et al*. 2008). MASP-2 also has very weak C3 cleaving activity (Rossi *et al*. 2001).

Opsonophagocytosis: MASP-2 in complex with MBL and ficolins have been documented to aid in opsonophagocytosis of *Staphylococcus aureus* (Neth *et al*. 2002) and group B streptococci (Aoyagi *et al*. 2005). However, it is not clear if MASP is required or if MBL/ficolins alone are sufficient for this function (Shiratsuchi *et al*. 2008). In mice however, MASP-2 knockout results in increased susceptibility to pneumococcal infection, due to a defect in opsonization of *Streptococcus pneumoniae* (Ali *et al*. 2012).

Other roles: MASP-2 has been shown to activate coagulation (Krarup *et al*. 2007) and studies in mice have shown MASP-2 to be involved in ischemia-reperfusion injury (Schwaeble *et al*. 2011). sMAP (also known as MAp19) is a splice variant of *MASP2* (see 'Splice Variants' section) with no enzymatic activity. Hence unlike MASP-2, sMAP cannot cleave C4 and C2.

REGULATION OF ACTIVITY
MASP-2 is synthesised as single chain proenzyme and activation proceeds through the cleavage of a single Arg-Ile bond, generating two disulfide-linked chains, A (N-terminal) and B (C-terminal serine protease domain). Isolated rat and human recombinant MASP-2 undergo autoactivation, which is enhanced by binding to target-bound MBL or ficolins (Chen and Wallis 2004, Gal *et al*. 2005). MBL was also proposed to occlude the C4 binding site on MASP-2, till activation occurs (Chen and Wallis 2004). Recent studies, including in a MASP-1 deficient patient and MASP-1 knockout mice, structural details and use of inhibitors demonstrate that MASP-1 cleaves and thereby activates MASP-2 (Degn *et al*. 2012, Megyeri *et al*. 2013, Kocsis *et al*. 2010, Heja *et al*. 2012a, Heja *et al*. 2012b, Takahashi *et al*. 2008).

MASP-2 activity is inhibited by C1 inhibitor (C1INH), an inhibitor for C1r, C1s and MASP-1. C1INH forms equimolar complexes with both MASP-1 and MASP-2 (Matsushita *et al*. 2000, Rossi *et al*. 2001, Ambrus *et al*. 2003, Presanis *et al*. 2004) and can inhibit MASP-2 fifty-fold faster than C1s, implying MASP-2 to be a major physiological target of C1INH (Kerr *et al*. 2008). Also, anti-thrombin III could inhibit activity in the presence of heparin (Presanis *et al*. 2004, Paréj *et al*. 2013). MASP-3 (a splice variant of *MASP1*) and sMAP have been shown to down-regulate C4 deposition, most likely by

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competing with MASP-2 binding to MBL or ficolins (Dahl *et al*. 2001, Møller-Kristensen *et al*. 2007, Iwaki *et al*. 2006, Skjoedt *et al*. 2010a). However, results obtained *in vitro* with human proteins suggest that sMAP has no inhibitory activity on MASP-2 mediated activation of the lectin pathway (Degn *et al*. 2011). Also, MAp44 (also known as MAP-1), another splice variant of *MASP1*, can disrupt heterodimer interaction of MASP-1 and MASP-2 and thereby inhibit MASP-2 activity (Degn *et al*. 2013, Degn *et al*. 2009, Skjoedt *et al*. 2010b, Pavlov *et al*. 2012).

INTERACTIONS

Collectins and ficolins: Both MASP-2 and sMAP form homodimers in human and rat (Chen and Wallis 2001, Thielens *et al*. 2001, Feinberg *et al*. 2003) in a Ca^{2+} dependent manner. The homodimers then go on to interact with MBL and L-ficolin through its CUB1 domain in a Ca^{2+} dependent manner (Thielens *et al*. 2001, Gregory *et al*. 2004). Comparison of K_D values between MASP-2 and sMAP suggest MASP-2 to bind more efficiently to MBL (0.8 nM vs 13 nM). MASP-2 and sMAP bind to Lys55 (residue number corresponds to the mature protein) of MBL in presence of Ca^{2+} (Thiel *et al*. 2000, Teillet *et al*. 2007). Further, MASP-2 and sMAP compete with calreticulin (CRT) for the same binding site on MBL (Pagh *et al*. 2008). The oligomerization state of MBL has no influence on the interaction with the MASPs (similar K_D values for trimer and tetramer) (Teillet *et al*. 2005). MASP-2 interaction with L-ficolin and H-ficolin also requires Ca^{2+} (Ma *et al*. 2004, Matsushita and Fujita 2001, Cseh *et al*. 2002, Zacho *et al*. 2012, Csuka *et al*. 2013). Lys57 and Lys47 of L-ficolin and H-ficolin respectively (residue numbers correspond to the mature proteins) are important in binding to MASP-2 (Lacroix *et al*. 2009). M-ficolin was shown to mediate activation of the lectin pathway, which strongly suggests that, similarly to L- and H-ficolins, M-ficolin interacts with MASP-2 (Liu *et al*. 2005). MASP-2 can also interact with a novel collectin, CL-11 (CL-K1) to activate the complement pathway (Ali *et al*. 2012, Ma *et al*. 2013).

MASPs and other proteins: MASP-3 was found together with MASP-2 on large MBL oligomers whereas MASP-1 and sMAP were found on lower MBL oligomers, but no direct evidence of heterodimerization was provided (Thiel *et al*. 2000, Dahl *et al*. 2001, Tateishi *et al*. 2011). A recent study documents heterodimer formation between MASP-1 and MASP-2, which can be disrupted by MAp44 (Degn *et al*. 2013). The CCP domains of MASP-2 positively co-operate with the active site to ensure effective binding to C4 and C4b (Duncan *et al*. 2012, Kidmose *et al*. 2012). The exosite contributed by both CCP domains of MASP-2 recognizes the C345C domain of C4.

The experimental methods used to characterize these interactions are documented in CMAP, a complement map database (Yang *et al*. 2013).

PHENOTYPES

Most inherent differences in the protein levels arise from single nucleotide polymorphisms (SNPs), several of which (D120G, R99N, V377A, R439H) have been documented in the recent years.

p.D120G: The SNP resulting in D120G substitution, found in Caucasians and Inuits from West-Greenland (Thiel *et al*. 2007) shows very low serum levels (5% and 45% of wild-type in homozygous and heterozygous mutants respectively) (Stengaard-Pedersen *et al*. 2003). A cystic fibrosis patient with homozygous D120G mutation was found to have a severe lung disease (Olesen *et al*. 2006). Further studies showed that MASP-2 with D120G substitution could not bind to MBL and hence could not activate the complement pathway (Thiel *et al*. 2009). The same mutation, when introduced in MAp19, also abolished its interaction with MBL and L-ficolin (Gregory *et al*. 2004).

p.R99Q: This SNP isolated in the CUB1 domain is generally found in African and Amerindian populations (Lozano *et al*. 2005, Thiel *et al*. 2007). MASP-2 with p.R99Q could cleave C4 as efficiently as wild-type (Thiel *et al*. 2009).

p.P126L: This SNP, similar to R99N, is isolated in CUB1 domain and generally found in African and Amerindian populations (Lozano *et al*. 2005, Thiel *et al*. 2007). Individuals with homozygous p.126L showed non-functional MASP-2 (Thiel *et al*. 2007), while the isolated protein could cleave C4 efficiently (Thiel *et al*. 2009). p.126L has also been linked to Crohn's disease haplotype with reduced MASP-2 levels and associated with chagasic cardiomyopathy (Boldt *et al*. 2011).

p.V377A: Similar to p.126L, p.V377A also shows reduced MASP-2 levels, is linked to Crohn's disease haplotype and associated with chagasic cardiomyopathy (Boldt *et al*. 2011). However, the V377A protein (similar to wild type and p.126L) has a normal enzymatic activity and can cleave C4 (Thiel *et al*. 2007, Thiel *et al*. 2009).

p.R439H: This variant, common in Sub-Saharan Africans with a gene frequency of 10%, binds normally to MBL but is deficient in enzymatic activity (Thiel *et al*. 2009).

p.156-159 dupCHNH: This four amino-acid tandem duplication polymorphism, which results in poor secretion of the protein is found only in Chinese population with a gene frequency of 0.26%. It does not bind to MBL and hence does not result in deposition of C4 (Thiel *et al*. 2007, Thiel *et al*. 2009).

Additonally, p.D371Y is associated with susceptibility to hepatitis C virus infection (Tulio *et al*. 2011). Polymorphisms flanking MAp19 exon 5 and MASP2 haplotypes generating low MASP-2 levels were associated with susceptibility to leprosy (Boldt *et al*. 2013). MASP-2 levels and thereby activity have been associated with several diseases, including schizophrenia and septic shock induced mortality (Mayilyan *et al*. 2006, Charchaflieh *et al*. 2012). MASP-2 deficiency lead to increased risk of fever and neutropenia in pediatric cancer patients (Schlapbach *et al*. 2007), while higher MASP-2 level was associated with better event free survival in pediatric patients with hematologic malignancies, especially lymphoma (Zehnder *et al*. 2009). A study showed neonates with very low MASP-2 levels (below 42 ng/ml) to have a shorter mean gestational age and a higher incidence of premature and low birthweight babies. In contrast, babies with infections had higher MASP-2 concentrations (St Swierzko *et al*. 2009). Pre-mature infants with higher MASP-2 cord blood levels compared with controls developed necrotizing enterocolitis at a later stage (Schlapbach *et al*. 2008). Colorectal cancer patients showed higher MBL-MASP activity as compared to controls (Ytting *et al*. 2004) and high MASP-2 levels are significantly correlated with recurrent cancer disease and poor survival (Ytting *et al*. 2005, Ytting *et al*. 2008). MASP-2 levels are also increased in patients with acute lymphoblastic leukaemia, non-Hodgkin lymphoma, central nervous system (CNS) tumors (Fisch *et al*. 2011),

hematological infections (0.53 µg/ml compared to patients without infections 0.37 µg/ml) (Ameye *et al*. 2012).

MAJOR SITES OF EXPRESSION

MASP-2 is mainly expressed in the liver (Endo *et al*. 2002), with smaller amounts (~100-500 fold less compared to liver) found in the small intestine and testis (Seyfarth *et al*. 2006). MASP-2-specific mRNA expression, which is generally absent in healthy ovary tissues, was detected in the ovary tissues of patients with malignant reproductive disease (Swierzko *et al*. 2007). Increased MASP-2 expression was observed in esophageal squamous cancer cells in premalignant condition, dysplasia in comparison with the normal tissues and is associated with late clinical stage and nodal metastasis (Verma *et al*. 2006). The promoter activity of the MASP-2 gene was increased in the presence of IL-1β. However, this increase is nullified in the presence of IL-6 (Endo *et al*. 2002). MASP-2 gene expression is positively regulated by binding of Stat3 to its promoter region (Unterberger *et al*. 2007).

SPLICE VARIANTS

MASP2 located on chromosome 1p36.2–3 has one splice variant, MAp19 or sMAP, which is 19 kDa in size (Stover *et al*. 1999, Takahashi *et al*. 1999). *MASP2* encompasses 12 exons (Stover *et al*. 2004), among which 11 encode the six domains of MASP-2: two CUB, an epidermal growth factor (EGF)-like, two complement control proteins (CCPs) and a serine protease domain (Fujita *et al*. 2002). Alternative splicing at exon 5 results in MAp19, which shares 4 exons with MASP-2 (encoding the N-terminal CUB and EGF domains) whereas exon 5 encodes a unique C-terminal extension of 4 a.a. (Schwaeble *et al*. 2002). MAp19 is enzymatically inactive (as it lacks the serine protease domain) and is believed to down-regulate lectin pathway in mice (Iwaki *et al*. 2006). However contradictory results were obtained *in vitro* using human proteins (Degn *et al*. 2011).

REGULATION OF CONCENTRATION

MASP-2 concentrations differ among the diverse populations. Africans from Zambia show the lowest levels of 0.196 µg/ml, while Hong Kong Chinese, Amerindians and Danish Caucasians show 0.262 µg/ml, 0.29 µg/ml and 0.416 µg/ml respectively (Thiel *et al*. 2007). Another study showed the levels in a danish donor population to be 0.534 µg/ml (Møller-Kristensen *et al*. 2003). It is likely that higher MASP-2 concentrations in individuals from a UK population, compared to Armenians, leads to 2-fold higher MBL-MASP-2 activity (Mayilyan *et al*. 2006b). The concentration of MAp19 was detected to be 0.217 µg/ml, (11nM, compared to the 7nM of MASP-2) (Degn *et al*. 2011). Both MASP-2 and MAp19 are generally found in complex with other proteins such as MBL and ficolins in serum (Thiel *et al*. 2000, Møller-Kristensen *et al*. 2003).

Serum levels of MASP-2 also differ with age. Cord sera shows a value of 0.093 µg/ml (St Swierzko *et al*. 2009), while newborns show serum levels of 0.126 µg/ml. The levels increase with age and peak at adulthood (0.416 µg/ml) (Sallenbach *et al*. 2011). However, the levels are stable over time in healthy adults, which makes them potential biomarkers (Ytting *et al*. 2007). Patients with hereditary angiodema, which is the clinical manifestation of C1INH deficiency, showed decreased MASP-2 levels (Varga *et al*. 2008).

ANTIBODIES

MASP-2 antibodies are available from: Santa Cruz Biotechnology, Abcam, Novus Biologicals, Sigma Aldrich, Hycult Biotech, Biorbyt, LifeSpan Biosciences, Atlas Antibodies, Aviva, Geneway Biotech, GenTex, My BioSource.com, Origene Technologies, Antibodies-online, Abnova, Creative Biomart, Bioss Inc, USCN Life Science and Fitzgerald industries. MASP-2 antibody has been used as a therapeutic intervention in mice to prevent injury by gastrointestinal post-ischemic reperfusion (Schwaeble *et al*. 2011).

Table 1: Functional States

STATE DESCRIPTION	LOCATION	REFERENCES
MASP-2	extracellular region	
MASP-2/C1INH	extracellular region	Kerr FK *et al.* 2008; Matsushita M *et al.* 2000
MASP-2/C4	extracellular region	Duncan RC *et al.* 2012; Kidmose RT *et al.* 2012
MASP-2/C4b	extracellular region	Wallis R *et al.* 2007
2(MASP-2)	extracellular region	Chen CB and Wallis R 2001; Gregory LA *et al.* 2004; Thielens NM *et al.* 2001
sMAP	extracellular region	Stover CM *et al.* 1999; Takahashi M *et al.* 1999
2(sMAP)	extracellular region	Chen CB and Wallis R 2001; Cseh S *et al.* 2002; Gregory LA *et al.* 2004; Thielens NM *et al.* 2001
3(3MBL)/ 2(MASP-1) / 2(sMAP)	extracellular region	Dahl MR *et al.* 2001; Degn SE *et al.* 2011; Gregory LA *et al.* 2004; Tateishi K *et al.* 2011; Teillet F *et al.* 2005
L-FCN/ 2(MASP-1)/ 2(MASP-2) /2(sMAP)	extracellular region	Lacroix M *et al.* 2009; Cseh S *et al.* 2002; Matsushita M *et al.* 2000; Ma YG *et al.* 2004
H-FCN/ 2(sMAP)	extracellular region	Lacroix M *et al.* 2009; Zacho RM *et al.* 2012; Csuka D *et al.* 2013
4(3MBL)/ 2(MASP-1)/ 2(MASP-2)/ 2(MASP-3)	extracellular region	Dahl MR *et al.* 2001; Sekine H *et al.* ; Teillet F *et al.* 2005; Thielens NM *et al.* 2001
5(3MBL)/ 2(MASP-1)/ 2(MASP-2)/ 2(MASP-3)	extracellular region	Dahl MR *et al.* 2001; Sekine H *et al.* ; Teillet F *et al.* 2005; Thielens NM *et al.* 2001; Wallis R *et al.* 2007
6(3MBL)/ 2(MASP-1)/ 2(MASP-2)/ 2(MASP-3)	extracellular region	Sekine H *et al.* ; Teillet F *et al.* 2005; Thielens NM *et al.* 2001; Dahl MR *et al.* 2001; Wallis R *et al.* 2007
L-FCN/ 2(MASP-1)/ 2(MASP-2)	extracellular region	Cseh S *et al.* 2002; Lacroix M *et al.* 2009
H-FCN/ 2(MASP-1)/ 2(MASP-2)	extracellular region	Csuka D *et al.* 2013; Lacroix M *et al.* 2009; Zacho RM *et al.* 2012
CL-K1/ 2(MASP-1)/ 2(MASP-2)	extracellular region	Ali YM *et al.* ; Ma YJ *et al.*
MBL,ficolins/active2(MASP-1)/ 2(MASP-2)	extracellular region	Fujita T *et al.* 2002; Héja D *et al.* 2012; Héja D *et al.* 2012
MBL,ficolins/ active2(MASP-1)/active2(MASP-2)	extracellular region	Héja D *et al.* 2012; Héja D *et al.* 2012; Megyeri M *et al.* 2013

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SUPPLEMENTARY

Supplementary information is available online.

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This molecule exists in 18 states , has 21 transitions between these states and has 2 enzyme functions.(Please zoom in the pdf file to view details.)