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MASP-1

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MASP-1 (mannose/mannan binding lectin associated serine protease-1) is a serum protein (~79kDa poylpeptide) predominantly synthesized by the liver. It is an important player in the innate immune system and is mainly bound to multimeric pathogen recognition receptors such as mannose/mannan-binding lectin (MBL) and the three ficolins (M-ficolin, L-ficolin and H-ficolin). MASP-1 has two CUB, a calcium-binding EGF-like, a trypsin-like serine protease and two complement control protein (CCP) domains. The serine protease domain is auto-activated upon binding of these receptors to their appropriate pathogenic ligands, generally carbohydrate domains or acetylated sugar residues. MASP-1 is therefore a component of the lectin pathway of complement activation. The primary substrate for MASP-1 activity is MASP-2, another serine protease. MASP-2 in turn cleaves and activates complement proteins C4 and C2, thus converging the lectin pathway with the classical pathway of complement activation. MASP-1 activity is negatively regulated by the presence of alternate splice variants, MASP-3 and MAp44. MASP-1 by virtue of its serine protease activity, also plays a role in the coagulation pathway.

KEYWORDS
Complement-activating component of Ra-reactive factor; CRARF; CRARF1; Mannan-binding lectin serine peptidase 1 (C4/C2 activating component of Ra-reactive factor); Mannan-binding lectin serine protease 1; Mannose-binding lectin-associated serine protease 1; Mannose-binding protein-associated serine protease; MASP; MASP-1; MASP1; PRSS5; Ra-reactive factor serine protease p100; RaRF; Serine protease 5

IDENTIFIERS
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PROTEIN FUNCTION
Complement activation: The complement pathway is one of the important innate immune mechanisms to counter pathagenic attack. The complement pathway is activated by three different routes: classical, alternative and lectin. The lectin pathways is activated upon binding of host receptors such as, collectins (mannose/mannan- binding lectin (MBL) and collectin kidney 1 (CL-K1 or CL-11) and the three ficolins (M-ficolin, L-ficolin and H-ficolin) to their respective pathogenic ligands. MASP-1 activates the lectin pathway of complement activation by co-operating with MASP-2 in generation of C3 convertase (Møller-Kristensen *et al*. 2007). Unlike MASP-2, MASP-1 cannot cleave C4 and can only marginally activate C2 and C3 (Sørensen *et al*. 2005, Héja *et al*. 2012, Matsushita and Fujita 1995, Matsushita *et al*. 1998, Matsushita *et al*. 2000, Chen and Wallis 2004, Rossi *et al*. 2001, Ambrus *et al*. 2003). Studies in a MASP-1 deficient patient, use of inhibitors and structural details all reveal that MASP-1 is responsible for cleavage and thereby activation of MASP-2 (Degn *et al*. 2012, Kocsis *et al*. 2010, Heja *et al*. 2012a, Heja *et al*. 2012b, Megyeri *et al*. 2013). Studies in knockout mice also show similar results and further suggest a role for MASP-1 in activation of complement factor D (fD) and thereby alternative complement pathway (Takahashi *et al*. 2008, Takahashi *et al*. 2010, Banda *et al*. 2011). Further, MASP-1 has been shown to cleave MASP-3 (Iwaki *et al*. 2011, Megyeri *et al*. 2013).

Coagulation pathway: MASP-1 has thrombin-like activity (Presanis *et al*. 2004) and mediates complement cross-talk with the coagulation and the kallikrein (a serine protease) systems, leading to formation of a fibrin clot (Gulla *et al*. 2010, Dobo *et al*. 2011, Takahashi *et al*. 2011, Hess *et al*. 2012). The crystal structure of MASP-1 reveals differences between MASP-1 and other serine proteases such as, MASP-2, C1r and C1s and also specificity for thrombin (Dobo *et al*. 2008, Dobo *et al*. 2009).

Other roles: MASP-1 can cleave protease activated receptor 4 (PAR4) on endothelial cells due to its thrombin-like activity (Megyeri *et al*. 2009). PAR4 cleavage and thereby activation in turn leads to activation of cytokine release, leukocyte rolling and inflammatory pathways, thus linking MASP-1 activity to these physiological phenomena. MBL-MASPs complex aids phagocytosis of *Staphylococcus aureus* (Neth *et al*. 2002). L-ficolin-MASP complex binds to capsular polysaccharide of group B streptococci and aids its opsonophagocytosis (Aoyagi *et al*. 2005). However, it is not clear if MASP is required or MBL alone is sufficient for this function (Shiratsuchi *et al*. 2008).

REGULATION OF ACTIVITY
C1 inhibitor (C1INH), an inhibitor for C1r and C1s, formed equimolar complexes with MASP-1 and MASP-2 and inhibited their proteolytic activities (Matsushita *et al*. 2000, Ambrus *et al*. 2003, Presanis *et al*. 2004). Alpha 2-macroglobulin was also shown to inhibit MASP-1 proteolytic activity (Ambrus *et al*. 2003). Among the thrombin inhibitors, boroMpg could inhibit MASP-1, while anti-thrombin III required presence of heparin to inhibit MASP-1 (Presanis *et al*. 2004). Both the splice variants of *MASP1*, MASP-3 and MAp44, can compete with MASP-1 to bind to MBL and ficolins and thereby down-regulate complement activation (Dahl *et al*. 2001, Degn *et al*. 2013, Skjoedt *et al*. 2010). MASP-1/3 promoter activity was increased in the presence of interleukin (IL)-1β. However, this increase is nullified in the presence of IL-6. Further, promoter activity is also down-regulated by interferon (IFN)γ (Endo *et al*. 2002).

INTERACTIONS
With MBL and ficolins: MASP-1 forms head to tail homo-

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dimers (Thielens *et al*. 2001, Teillet *et al*. 2008). The homodimers then go on to interact with MBL in a Ca^{2+} dependent manner (Matsushita and Fujita 1992, Thiel *et al*. 2000, Thielens *et al*. 2001). Gly54 and Lys55 of MBL (residue numbers correspond to the mature protein) are important in binding to MASP-1 (Matsushita *et al*. 1995, Teillet *et al*. 2007, Teillet *et al*. 2008). MASP-1 interacts with higher forms of MBL (Terai *et al*. 2003) and the oligomerization state of MBL has no influence on the binding affinities for MASPs (K_D values are similar for binding to a trimer or tetramer) (Teillet *et al*. 2005).

MASP-1 can interact with L-ficolin and H-ficolin (Matsushita *et al*. 2002, Ma *et al*. 2004, Matsushita and Fujita 2001, Cseh *et al*. 2002) to activate the complement pathway. Lys57 and Lys47 of L-ficolin and H-ficolin respectively (residue numbers correspond to the mature proteins) are important in binding to MASP-1 (Lacroix *et al*. 2009). MASP-1 also interacts with a novel collectin, collectin kidney 1 (CL-K1 or CL-11), which leads to complement pathway activation (Hansen *et al*. 2010, Ali *et al*. 2013, Ma *et al*. 2013).

With other MASPs: MASP-1 has been shown to interact with MASP-2, which can be disrupted by MAp44 (Degn *et al*. 2013). Complexes such as MBL-MASP and ficolin-MASP, interact with MASP-1, along with other MASPs such as MASP-2, sMAP (a splice variant of *MASP2*) and MASP-3 (Matsushita *et al*. 2000, Takahashi *et al*. 1999, Tateishi *et al*. 2011, Cseh *et al*. 2002, Dahl *et al*. 2001).

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

PHENOTYPES

MBL-MASP-1 activity can result in glomerular deposition of fibrinogen, which in turn may contribute to the development of advanced glomerular injuries, such as post-streptococcal acute glomerulonephritis (PSAGN) (Hisano *et al*. 2007) and prolonged urinary abnormalities in patients with Henoch-Schonlein purpura nephritis (HSPN) (Hisano *et al*. 2005). Increased activity of MBL-MASP-1 complex is also associated with severe fibrosis in hepatitis C virus-infected patients (Brown *et al*. 2007). A non-sense mutation (W290X) results in a phenotype resembling 3MC (Carnevale, Mingarelli, Malpuech, and Michels) syndrome (Sirmaci *et al*. 2010). An allele found in some Caucasians, resulting in G54A substitution, is unable to activate the complement pathway (Matsushita *et al*. 1995).One single nucleotide polymorphism (SNP) for MASP-1 has been documented at position +50074 (relative to the transcription start site, in the second complement control protein (CCP) domain), which results in substitution of glycine with glutamic acid residue (Weiss *et al*. 2007).

MAJOR SITES OF EXPRESSION

MASP-1 is mainly expressed in the liver (Endo *et al*. 2002), with smaller amounts (~100 fold less compared to liver) found in the small intestine and kidney (Seyfarth *et al*. 2006).

SPLICE VARIANTS

MASP1 has two known splice variants, MASP-3 (Dahl *et al*. 2001) and MAp44 (Degn *et al*. 2009). *MASP1* encodes for six domains: two C1r/C1s/Uegf/bmp1 (CUB) domains, an epidermal growth factor (EGF)-like, two complement control proteins (CCPs) and a serine protease domain. The first five domains together form the heavy (or 'A') chain (encoded by exons 1-11), while the serine protease domain forms the light (or 'B') chain (Sato *et al*. 1994, Fujita *et al*. 2002). *MASP1* is alternatively spliced after exon 11 to result in MASP-3. Thus, the heavy chain sequence is similar between MASP-1 and MASP-3. However, the serine protease domain sequences are different, as exons 13-18 encode this domain in MASP-1, while exon 12 encodes the protease domain in MASP-3 (Dahl *et al*. 2001). MAp44 is formed by alternative splicing in the ninth exon of *MASP1*. MAp44 has two CUB domains, EGF and one CCP domain and an unique C-terminal domain of 17 a.a (Degn *et al*. 2009, Skjoedt *et al*. 2010). Please refer to MASP-3 and MAp44 Molecule Pages at www.signalinggateway.org for more information.

REGULATION OF CONCENTRATION

MASP-1 concentration in serum was found to be ~ 11 µg/ml (range 4-30 µg/ml) (Thiel *et al*. 2012) and is present in excess molar amounts over MBL (Vorup-Jensen *et al*. 1998). Further, over 95% of the total MASP-1 in serum is not in complex with MBL (Thiel *et al*. 2000). MASP-1 concentration is highest in the cord blood and in 3-9 year-olds and is fairly stable in adults (Terai *et al*. 1997).

ANTIBODIES

MASP-1 antibodies are available from: Santa Cruz Biotechnology, Abcam, Novus Biologicals, Sigma Aldrich, Hycult Biotech and Abnova.

Table 1: Functional States

STATE DESCRIPTION	LOCATION	REFERENCES
MASP-1	extracellular region	
MASP-1/C1INH	extracellular region	Rossi V *et al.* 2001; Matsushita M *et al.* 2000
2(MASP-1)	extracellular region	Teillet F *et al.* 2008; Thielens NM *et al.* 2001
active 2(MASP-1)	extracellular region	
3(3MBL)/2(MASP-1)/2(sMAP)	extracellular region	Tateishi K *et al.* 2011
4(3MBL)/2(MASP-1)/2(MASP-2)/2(MASP-3)	extracellular region	Thielens NM *et al.* 2001; Teillet F *et al.* 2005
5(3MBL)/2(MASP-1)/2(MASP-2)/2(MASP-3)	extracellular region	Teillet F *et al.* 2008; Teillet F *et al.* 2005
6(3MBL)/2(MASP-1)/2(MASP-2)/2(MASP-3)	extracellular region	Teillet F *et al.* 2005; Teillet F *et al.* 2008
L-FCN/2(MASP-1)/2(MASP-2)	extracellular region	Lacroix M *et al.* 2009; Cseh S *et al.* 2002
L-FCN/2(MASP-1)/2(MASP-2)/2(sMAP)	extracellular region	Cseh S *et al.* 2002; Lacroix M *et al.* 2009
CL-K1/2(MASP-1)/2(MASP-2)	extracellular region	Ma YJ *et al.*
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
MASP-1/α2M	extracellular region	Ambrus G *et al.* 2003
MBL,ficolins/active2(MASP-1)/2(MASP-2)	extracellular region	Fujita T *et al.* 2002
MBL,ficolins/active2(MASP-1)/active2(MASP-2)	extracellular region	Héja D *et al.* 2012; Héja D *et al.* 2012

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SUPPLEMENTARY

Supplementary information is available online.

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This molecule exists in 15 states , has 20 transitions between these states and has 3 enzyme functions.(Please zoom in the pdf file to view details.)