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MASP-3

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MASP-3 (mannose/mannan binding lectin (MBL) associated serine protease-3) is ~82 kDa protein generated through alternative splicing of the *MASP1* gene. This gene also generates MASP-1 and MAp44 proteins. MASP-3 is bound to multimeric forms of pathogen receptors, such as MBL and the three ficolins. MASP-3 has two CUB, a calcium-binding EGF-like, a trypsin-like serine protease and two complement control protein (CCP) domains. The serine protease domain however, is not known to be active and does not act on substrates of either MASP-1 or MASP-2. Instead, it competes with MASP-1 and MASP-2 to bind to MBL and therefore plays a regulatory role in the lectin pathway of complement activation. In mice however, MASP-3 can activate the alternative complement pathway, by directly activating complement factor D (fD).

KEYWORDS
Complement factor MASP-3; Complement-activating component of Ra-reactive factor; CRARF1; Mannan-binding lectin serine peptidase 1 (C4/C2 activating component of Ra-reactive factor); Mannose-binding lectin-associated serine protease 1; Mannose-binding protein-associated serine protease; MASP; MASP-3; MASP1; MASP3; MBL-associated serine protease-3

IDENTIFIERS
Molecule Page ID:A008391, Species:Human, NCBI Gene ID: 5648, Protein Accession:AAK84071.1, Gene Symbol:MASP1

PROTEIN FUNCTION
MASP-3 (*MASP1* Isoform 2) is an alternate splice product of *MASP1*, which primarily encodes for MASP-1 (*MASP1* Isoform 1) (Dahl *et al*. 2001). Thus, MASP-3 transcript shares some of its exons with MASP-1 (see 'Splice Variants' section). All the three MASP proteins, MASP-1, MASP-2 and MASP-3, have serine protease domains and bind to mannose/mannan-binding lectin (MBL). However, only MASP-1 and MASP-2 exhibit serine protease activity to activate the complement pathway, a key mechanism of the innate immune system to counter-act pathogens (Møller-Kristensen *et al*. 2007). The complement pathway can be activated by three different routes: classical, alternative and lectin. MASP-1 and MASP-2 proteins activate the lectin branch of the complement pathway. In contrast, the serine protease domain of MASP-3 is not activated and hence MASP-3 does not cleave C4, C2 or C3 (Dahl *et al*. 2001, Zundel *et al*. 2004). Instead, MASP-3 competes with MASP-1 and MASP-2 for binding sites on MBL and ficolins. Thereby, upon binding to MBL and ficolins, MASP-3 blocks the generation of C3 convertase and prevents excessive complement activation (Skjoedt *et al*. 2010).

Studies in mice have suggested a role for MASP-3 in activation of the alternative complement pathway by cleavage of complement factor D (fD) (Iwaki *et al*. 2011).

REGULATION OF ACTIVITY
Both MASP-1 and MASP-2 activities are regulated by binding to C1 inhibitor (C1INH). However, MASP-3 does not interact with C1INH (Zundel *et al*. 2004).

INTERACTIONS
MASP-3 forms head-to-tail homodimers with Ca^{2+} binding sites (Telliet *et al*. 2008). MASP-3 can interact with MBL and ficolins (Zundel *et al*. 2004, Matsushita *et al*. 2002) and is found together with other MASPs on larger MBL oligomers (Dahl *et al*. 2001, Terai *et al*. 2003). Similar to MASP-1, C1r/C1s/Uegf/bmp1 (CUB)-1 and CUB-2 domains of MASP-3 interact with Lys55 (residue number corresponds to mature protein) of MBL (Teillet *et al*. 2007, Teillet *et al*. 2008). In fact, MASP-3 competes with calreticulin (CRT) and CD91 [Low density lipoprotein receptor-related protein 1 (LRP1), or alpha-2-macroglobulin receptor (A2MR)] for the same binding site on MBL (Duus *et al*. 2010, Pagh *et al*. 2008). Lys57 of L-ficolin and Lys47 of H-ficolin are important in binding to MASP-3 (Lacroix *et al*. 2009). Based on immunoprecipitation experiments, H-ficolin is the preferred partner for MASP-3 among MBL and ficolins (Skjoedt *et al*. 2010). MASP-3 can also interact with a novel collectin, CL-11 (CL-K1), which circulates in the plasma (Hansen *et al*. 2010).

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

PHENOTYPES
A MASP-3 single nucleotide polymorphism (SNP) is associated with early chronic colonization of *Pseudomonas aeruginosa* in cystic fibrosis patients (Haerynck *et al*. 2012). However, this SNP at rs850312 does not cause amino acid substitution (L617L). Three homozygous mutations in exon 12 of *MASP1* (which encodes for serine protease domain in MASP-3), H497Y, C630R and G666D, have been associated with 3MC (Carnevale, Mingarelli, Malpuech, and Michels) syndrome, a spectrum of developmental disorders (Rooryk *et al*. 2011). Also, G687R mutation has been associated with 3MC syndrome (Sirmaci *et al*. 2010).

MAJOR SITES OF EXPRESSION
MASP-3 is mainly expressed in the liver (Endo *et al*. 2002). However, its expression in other tissues such as colon and heart is more ubiquitous than MASP-1 and MASP-2 (Seyfarth *et al*. 2006).

SPLICE VARIANTS
MASP-3 is an alternative splice variant of *MASP1* gene. *MASP1* encodes for three proteins, MASP-1 (*MASP1* isoform 1), MASP-3 (*MASP1* isoform 2) and MAp44 (*MASP1* isoform 3) (Dahl *et al*. 2001, Degn *et al*. 2009). *MASP1* encodes for six domains: two C1r/C1s/Uegf/bone morphogenetic protein 1

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(CUB), 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, while the serine protease domain forms the light (or 'B') chain (Fujita *et al*. 2002). *MASP1* is alternatively spliced after exon 11 to result in MASP-3. MASP-3 shares the heavy chain sequence with MASP-1. However, the sequence of the serine protease domain in MASP-3 is different, as it is produced by an exon distinct from the exons coding for the protease domain in MASP-1 (Dahl *et al*. 2001). MAp44 is formed by alternative splicing in the ninth exon of *MASP1*. MAp44 has two CUB domains, EGF, one CCP domain, a unique C-terminal domain of 17 a.a and importantly lacks the serine protease domain (Degn *et al*. 2009, Skjoedt *et al*. 2010). Please refer to MASP-1 and MAp44 Molecule Pages at www.signalinggateway.org for more information.

REGULATION OF CONCENTRATION

MASP1/3 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). Using samples from 100 Danish blood donors, the serum levels of MASP-3 was found to be 6.4 µg/ml (range: 2-12.9 µg/ml). Moreover, MASP-3 was primarily found in complex with H-ficolin, rather than in complex with MBL or other ficolins (Skjoedt *et al*. 2010).

ANTIBODIES

MASP-3 antibodies are available from: Santa Cruz Biotechnology, Abcam, LifeSpan Biosciences, Hycult Biotech and Abnova.

Table 1: Functional States

STATE DESCRIPTION	LOCATION	REFERENCES
MASP-3	extracellular space	
2(MASP-3)	extracellular space	Teillet F *et al.* 2008
2(MASP-3)/4(3MBL)/2(MASP-1)/2(MASP-2)	extracellular space	Dahl MR *et al.* 2001
2(MASP-3)/5(3MBL)/2(MASP-1)/2(MASP-2)	extracellular space	Dahl MR *et al.* 2001
2(MASP-3)/6(3MBL)/2(MASP-1)/2(MASP-2)	extracellular space	Dahl MR *et al.* 2001
2(MASP-3)/6(3MBL)/active2(MASP-1)/2(MASP-2)	extracellular space	Fujita T *et al.* 2002
2(MASP-3)/6(3MBL)/active MASP-1/active MASP-2	extracellular space	Héja D *et al.* 2012; Dahl MR *et al.* 2001
2(MASP-3)/L-FCN	extracellular space	Dahl MR *et al.* 2001; Lacroix M *et al.* 2009
2(MASP-3)/H-FCN	extracellular space	Teillet F *et al.* 2008
2(MASP-3)/CL-K1	extracellular space	Hansen S *et al.* 2010

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SUPPLEMENTARY

Supplementary information is available online.

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This molecule exists in 10 states , has 9 transitions between these states and has 0 enzyme functions.(Please zoom in the pdf file to view details.)