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L-Ficolin

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L-ficolin is a serum lectin synthesized (as a ~37 kDa polypeptide) predominantly by the liver, and is one of the key molecules of the innate immune system. It has an amino (N)-terminal cysteine-rich region, a middle stretch of a collagen-like sequence, and a fibrinogen-like domain in the carboxy (C)-terminus. Three identical polypeptides form a structural (triple helical) subunit, with the help of the collagen-like domain. Further oligomerization of this subunit results in different sized L-ficolin molecules (from dimers to tetramers) in circulation. However, the tetrameric form (composed of 12 polypeptides) is the most prevalent structure. The polypeptides in the structural subunit are cross-linked by disulphide bonds in the N-terminal region. The fibrinogen-like domain forms a globular structure. The overall structure of oligomeric L-ficolin closely resembles mannose-binding lectin (MBL). Similar to MBL, L-ficolin also acts as a pattern recognition receptor. It primarily recognizes acetylated sugar residues on the cell surface of different gram-positive and gram-negative bacteria, viruses and other pathogens. There are two pathways by which L-ficolin may participate in a host defense response: 1) It activates the complement lectin pathway, via MBL/ficolin associated serine proteases (MASPs), that converges with the classical complement pathway at the level of complement C4, and 2) it may also act directly as an opsonin, enhancing phagocytosis by binding to cell-surface receptors present on phagocytic cells. M-ficolin and H-ficolin are structurally similar to L-ficolin. However, they differ in their tissue expression and binding affinities to pathogenic ligands.

KEYWORDS
37 kDa elastin-binding protein; Collagen/fibrinogen domain-containing protein 2; EBP-37; FCN2; FCNL; Ficolin (collagen/fibrinogen domain containing lectin) 2 (hucolin); Ficolin B; Ficolin-2; ficolin-2; Ficolin-B; Ficolin-beta; Hucolin; L-ficolin; L-Ficolin; P35; Serum lectin p35

IDENTIFIERS
Molecule Page ID:A004266, Species:Human, NCBI Gene ID: 2220, Protein Accession:NP_004099.2, Gene Symbol:FCN2

PROTEIN FUNCTION
L-ficolin, originally discovered as a corticosteroid binding protein (Edgar 1995) is recognized as an important player in the lectin pathway of complement activation (Ali *et al*. 2012, Kilpatrick and Chalmers 2012). The original finding of the protein was due to the binding of L-ficolin to cyanogen bromide (CNBr)-activated Sepharose and was thus not due to specific binding to the proteins coupled to the beads. Its oligomeric structure closely resembles that of other two ficolins (M-ficolin and H-ficolin), collectins such as MBL and also that of the recognition molecule of the classical pathway, C1q (Garred *et al*. 2010). L-ficolin exhibits a ~37 kDa polypeptide chain with an N-terminal cysteine rich region, a collagenous domain, and a fibrinogen-like domain at the C-terminus (Matsushita *et al*. 1996, Lu and Le 1998). Three polypeptide chains oligomerize through the collagenous region to form the basic structural subunit, a triple helix. L-ficolin circulates in serum as a tetramer of this structural subunit, thus having 12 identical polypeptide chains (Hummeslshoj *et al*. 2007).

Complement activation: The fibrinogen-like domain binds to ligands such as acetylated sugar residues (N-acetylglucosamine, GlcNAc and N-acetylneuraminic acid, NeuNAc) and 1,3 β-D glycan on a variety of pathogens (Garlatti *et al*. 2007, Krarup *et al*. 2004, Ma *et al*. 2004) (see 'Interactions With Ligands and Other Proteins' section). The triple helix formed by the collagenous regions is bound to serine proteases such as MASP-1 and MASP-2 (Gaboriaud *et al*. 2007). Upon binding to pathogen surfaces, MASP-1 and MASP-2 get activated (through proteolysis), which in turn sequentially cleave complement proteins C4 and C2 (Héja *et al*. 2012a, Héja *et al*. 2012b). Thus, the lectin pathway of complement gets activated leading to complement attack on pathogens. Even though, L-ficolin is structurally similar to other collectins, it has unique pathogenic ligands making it an important player in host resistance against pathogens (Krarup *et al*. 2005).

Opsonophagocytosis: C4 and C2 cleaved by activated L-ficolin-MASP complex form C3-convertase (C4b2a). C3b generated by action of C3-convertase on C3, acts as an opsonin when deposited on pathogen surfaces. L-ficolin can bind calreticulin (CRT,cC1qR) (Lacroix *et al*. 2009), which may aid ficolin-mediated phagocytosis of pathogens such as Salmonella (Matsushita *et al*. 1996), group B streptococci (Aoyagi *et al*. 2005) and *Pseudomonas aeruginosa* (Zhang *et al*. 2009). Apart from phagocytosis of pathogens, L-ficolin can also aid in clearance of late apoptotic and necrotic host cells (Kuraya *et al*. 2005, Jensen *et al*. 2007).

Activation of coagulation system: Active MASP-1 and MASP-2 have been shown to act on coagulation proteins. MASP-1 has thrombin-like activity while MASP-2 has been shown to generate thrombin from prothrombin (Krarup *et al*. 2007, Presanis *et al*. 2004). A more direct evidence of L-ficolin bound MASP-1 and MASP-2 involvement in fibrin clot formation was recently shown (Gulla *et al*. 2010, Hess *et al*. 2012). Importantly such activity was not confirmed when specific inhibition of MASP-1 was analyzed in plasma (Megyeri *et al*. 2013).

REGULATION OF ACTIVITY
The activity of L-ficolin can be primarily regulated at the following levels: serum concentration, efficacy of binding to pathogens and during cleavage of MASP proteins (Skjoedt *et al*. 2010). Serum concentration of L-ficolin is weakly regulated by

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the presence of polymorphisms (see 'Regulation of Concentration' section). Binding to pathogens is also regulated by polymorphisms (see 'Phenotypes' section), capsulation of pathogens such as group B streptococci (Aoyagi *et al*. 2008, Krarup *et al*. 2005) or by presence of adaptor proteins (see 'Interactions With Ligands and Other Proteins' section). Apart from these factors, karilysin, a matrix metalloproteinase-like enzyme produced by periodontal pathogen *Tannerella forsythia*, cleaves L-ficolin along with other complement proteins, thereby inhibiting complement activation (Jusko *et al*. 2012).

INTERACTIONS

Twelve polypeptide chains of L-ficolin (as explained in 'Protein Function' section) oligomerize to form a functional complex. L-ficolin interacts with several host and pathogenic factors:

L-ficolin-MASP Complex: Similar to M-ficolin and H-ficolin, the tetrameric form of L-ficolin is in complex with different MASP proteins *via* its collagen region (Lacroix *et al*. 2009, Gaboriaud *et al*. 2007), as listed below. All the MASP proteins bound to L-ficolin are in homo-dimeric form (Gregory *et al*. 2004, Teillet *et al*. 2008) and the binding is dependent on physiological concentrations of calcium (Cseh *et al*. 2002). MASP-1 and MASP-2 encoded by MASP1 and MASP2 genes respectively, are serine proteases (Matsushita *et al*. 2000, Matsushita and Fujita 1992, Thiel *et al*. 1997). MASP-1 is auto-activated, when in complex with L-ficolin bound to acetylated sugar residues on pathogen surfaces. Activated MASP-1 cleaves and activates MASP-2 (Héja *et al*. 2012a, Héja *et al*. 2012b, Degn *et al*. 2012). MASP-2 sequentially activates C4 and C2 through its serine protease activity. MASP-3 is a splice variant of *MASP1* gene and binds to L-ficolin (Dahl *et al*. 2001, Teillet *et al*. 2008). It has a serine protease domain, but has no known physiological relevant substrates. In mice however, MASP-3 has been shown to be important in alternative pathway of complement activation (Iwaki *et al*. 2011) whereas in humans the presence of MASP-3 is not essential for the alternative pathway (Degn *et al*. 2012). MASP-3 has been shown to compete with MASP-2 to bind to MBL, resulting in down-regulation of lectin pathway activation (Dahl *et al*. 2001). However, the physiological role of MASP-3 binding to L-ficolin is yet to be determined. MAp44, expressed mainly in the heart, is yet another splice variant of *MASP1* gene. It however does not have a serine protease domain and is found in complex with L-ficolin (Skjoedt *et al*. 2011, Skjoedt *et al*. 2010, Degn *et al*. 2009). sMAP (MAp19), a splice variant of *MASP2* gene, also lacks a serine protease domain and binds to L-ficolin (Cseh *et al*. 2002, Gregory *et al*. 2004). Further, MAp44 and sMAP are both able to bind to the parts of the helix formed by the collagen-like regions of MBL and thus compete with MASP-2 for binding and thereby down-regulating complement activation (Degn *et al*. 2009, Iwaki *et al*. 2006). It is therefore very likely that MAp44 and sMAP play a similar role in their interaction with L-ficolin, but it is yet to be demonstrated.

Interactions with other host factors: L-ficolin can bind to chaperones such as calreticulin and to other recognition molecules, e.g. C-reactive protein (CRP) and pentraxin-3 (PTX3), and all of these interactions enhance complement activation (Lacroix *et al*. 2009, Zhang *et al*. 2009, Ma *et al*. 2009) and thereby increase resistance against pathogens. Binding to CRT or DNA from apoptotic cells also aids clearance of late apoptotic and necrotic cells (Kuraya *et al*. 2005, Jensen *et al*. 2007). However, L-ficolin can also bind to artificially acetylated low-density lipoprotein (ac-LDL) and activate the lectin pathway (Faro *et al*. 2008).

Interactions with pathogens: L-ficolin *via* its fibrinogen-like domain binds to several pathogen surfaces, including 1,3β-D glycan. It primarily recognizes acetylated sugar residues on different gram-positive and gram-negative bacteria (Krarup *et al*. 2004, Krarup *et al*. 2008), including GlcNAc residues on *Salmonella typhimurium* (Taira *et al*. 2000) and *Streptococcus pneumoniae* (Krarup *et al*. 2004). L-ficolin binds to NeuNAc residues on capsulated forms of group B streptococci (GBS), while MBL failed to bind to these capsulated pathogens (Aoyagi *et al*. 2005, Aoyagi *et al*. 2008), implying an important role for L-ficolin in clearance of capsulated pathogens. In fact, L-ficolin exclusively bound to capsulated forms of *Staphylococcus aureus* and *Streptococci pneumoniae* (Krarup *et al*. 2005). Lipoteichoic acid (LTA), found on cell wall of gram-positive bacteria, can bind to L-ficolin (Lynch *et al*. 2004). *Escherichia coli* (Hummelshoj *et al*. 2012) and *Mycobacterium bovis* BCG (Carroll *et al*. 2009) can bind to L-ficolin. Viruses, such as hepatitis C (HCV) and influenza A are bound to L-ficolin. N-glycans of HCV envelope glycoproteins (Liu *et al*. 2009) and glycoproteins hemagglutinin and neuraminadase of influenza A (Pan *et al*. 2012) are L-ficolin ligands. L-ficolin also binds to the surfaces of *Typanosoma cruzi* (pathogen causing Chagas disease) (Cestari *et al*. 2009, Cestari *et al*. 2010) and *Giardia intestinalis* (Evans-Osses et al. 2010), and likely aids in clearance of these pathogens.

CMAP, a complement database, documents the biochemical methods used to identify these interactions (Yang *et al*. 2013).

PHENOTYPES

L-ficolin is produced by expression of ficolin-2 (FCN2) gene, which is located on chromosome 9q34 and consists of eight exons (Endo *et al*. 1996). A large number of single nucleotide polymorphisms (SNPs) are found in both the promoter and coding regions across varied ethnic groups (Herpers *et al*. 2006, Hummelshoj *et al*. 2008). The most common SNPs in Caucasians occur at the following positions: -986, -602, -557, -64, -4 in the promoter region and +2488, +6359, +6424 in the exon region (Herpers *et al*. 2006, Hummelshoj *et al*. 2005). While generally polymorphisms in the promoter and coding regions affect serum concentration and pathogen-binding efficacy respectively, polymorphism at +6424 position (from ATG site) is known to affect both serum levels and binding efficacy (Munthe-Fog *et al*. 2007, Hummelshoj *et al*. 2005). Several studies report association of lower serum levels of L-ficolin (resulting from SNPs) with recurrent respiratory tract infections (RTI) in children (Atkinson *et al*. 2004, Cedzynski *et al*. 2009, Cedzynski *et al*. 2007) and also with pre-mature birth and lower birth weight in Polish neonates (Sweirzko *et al*. 2009). However, a recent study has shown no associations between genotypes and lower birth weight or perinatal infections (Kilpatrick *et al*. 2013). Lower serum levels are also associated with schistosomiasis (Ouf *et al*. 2012), streptococcal infection (Messias-Reason *et al*. 2009) and bronchiectasis (Kilpatrick *et al*. 2009), chronic Chagas disease (Luz *et al*. 2013) and inversely correlated with hereditary angioedema due to C1-inhibitor deficiency (HAE-C1-INH) (Csuka *et al*. 2013). SNP causing Thr236Met substitution at the fibrinogen-like domain of L-ficolin, reduces substrate (pathogen) binding and might contribute to staphylococcal peritonitis (Meijvis *et al*. 2011). This SNP also reduces binding to PTX3 and GlcNAc residues on *Aspergillus fumigatus* surface (Ma *et al*. 2009). In

contrast, SNPs known to cause low serum levels or decreased binding are not associated with pneumococcal disease (Chapman *et al*. 2007). Presence of Ala258Ser variant of L-ficolin in the donor predicts an improved renal transplant outcome, which may be attributed to increased binding to GlcNAc (Eikmans *et al*. 2013). Haplotypes which produce normal levels of L-ficolin offer protection against leprosy (de Messias-Reason *et al*. 2009) while certain ficolin-2 genotypes are associated with leprosy in a specific Chinese population (Zhang *et al*. 2013). Higher levels of L-ficolin due to AGACG (at positions -986, -602, -4, +6359 and +6424) and AAAG (at positions -986, -602, -4, and +6424) haplotypes adversely affect patients with leishmaniasis and hepatitis B infection respectively (Assaf *et al*. 2012, Hoang *et al*. 2011). L-ficolin can also adversely affect host tissue during nephropathy (Roos *et al*. 2006).

MAJOR SITES OF EXPRESSION

L-ficolin is produced by the hepatocytes in liver (Matsushita *et al*. 1996).

SPLICE VARIANTS

L-ficolin, located on chromosome 9q34 consists of eight exons and has no known splice variants (Endo *et al*. 1996).

REGULATION OF CONCENTRATION

Serum levels of L-ficolin have been measured in a number of studies involving a large number of subjects. These studies report median values of L-ficolin in normal healthy individuals to be 4.13 µg/ml, 3.7 µg/ml, 3.3 µg/ml and 3.0 µg/ml respectively (Le *et al*. 1998, Kilpatrick *et al*. 1999, Krarup *et al*. 2005, Gulla *et al*. 2006). Almost all of these studies used ELISA for measurement (Taira *et al*. 2000). Age and gender did not affect serum levels in adults (Kilpatrick *et al*. 1999). However, cord blood samples show much lower levels, with a median of 2.5 µg/ml (Le *et al*. 1998, Kilpatrick *et al*. 1999). Sallenbach *et al*. (2011) reported the levels from various age groups ranging from neonates (2.8 µg/ml), 1> yr (7.08 µg/ml), 1-4 yr (11.3 µg/ml), 4-16 yr (8.66 µg/ml) and adults (3.37 µg/ml). Three polymorphisms in the promoter region were shown to affect serum levels by two-fold increase or decrease (Munthe-Fog *et al*. 2007, Hummelshoj *et al*. 2005). While generally polymorphisms in exon regions have been attributed to binding efficiency, one polymorphism in +6424 position (from ATG start site) results is lower serum concentration (Munthe-Fog *et al*. 2007). Serum levels of L-ficolin are known to increase during acute phase of malaria (Faik *et al*. 2011). Several diseases have been associated with lower serum concentration, which are further discussed in 'phenotypes' section.

ANTIBODIES

The following companies sell antibodies against human L-ficolin: Merck Millipore, Antibodies-online, Novus Biologicals, Thermo Fisher Scientific Inc., Abnova, Abcam, Fitzgerald, Aviva Systems Biology, Biorbyt, Enzo Life Sciences, Nova TeinBio, Abgent and Hycult Biotechnology.

Table 1: Functional States

STATE DESCRIPTION	LOCATION	REFERENCES
L-FCN (native)	extracellular region	
L-FCN triple helix	extracellular region	Hummelshoj T *et al.* 2007
L-FCN dodecamer	extracellular region	Hummelshoj T *et al.* 2007
L-FCN/MASP-1	extracellular region	Cseh S *et al.* 2002; Lacroix M *et al.* 2009
L-FCN/MASP-2	extracellular region	Lacroix M *et al.* 2009; Cseh S *et al.* 2002
L-FCN-NeuNAc	extracellular region	Aoyagi Y *et al.* 2008
L-FCN-acetyl groups	extracellular region	Krarup A *et al.* 2004; Krarup A *et al.* 2008; Lacroix M *et al.* 2009
L-FCN-LTA	extracellular region	Lynch NJ *et al.* 2004
L-FCN/Hemagglutinin	extracellular region	Pan Q *et al.*
L-FCN/Neuraminidase	extracellular region	Pan Q *et al.*
L-FCN-GlcNAc	extracellular region	Krarup A *et al.* 2008; Krarup A *et al.* 2004; Taira S *et al.* 2000
L-FCN/MASP-1/MASP-2/sMAP	extracellular region	Lacroix M *et al.* 2009; Matsushita M *et al.* 2000; Cseh S *et al.* 2002
L-FCN/CRT	extracellular region	Lacroix M *et al.* 2009; Kuraya M *et al.*
L-FCN/MASP-3	extracellular region	Dahl MR *et al.* 2001; Lacroix M *et al.* 2009
L-FCN/sMAP	extracellular region	Gregory LA *et al.* 2004; Lacroix M *et al.* 2009; Takahashi M *et al.* 1999; Cseh S *et al.* 2002
L-FCN/MAp44	extracellular region	Skjoedt MO *et al.* 2011; Skjoedt MO *et al.* 2010; Degn SE *et al.* 2009
L-FCN/PTX3	extracellular region	Ma YJ *et al.* 2009
L-FCN/CRP	extracellular region	Zhang J *et al.* 2009
L-FCN/LDL-Ac	extracellular region	Faro J *et al.* 2008
L-FCN-DNA	extracellular region	Jensen ML *et al.* 2007
L-FCN/MASP-1/MASP-2	extracellular region	Héja D *et al.* 2012; Héja D *et al.* 2012
L-FCN/MASP-1(active)/MASP-2	extracellular region	Héja D *et al.* 2012
L-FCN/MASP-1(active)/MASP-2(active)	extracellular region	Héja D *et al.* 2012

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SUPPLEMENTARY

Supplementary information is available online.

REFERENCES

Ali YM, Lynch NJ, Haleem KS, Fujita T, Endo Y, Hansen S, Holmskov U, Takahashi K, Stahl GL, Dudler T, Girija UV, Wallis R, Kadioglu A, Stover CM, Andrew PW, Schwaeble WJ (2012). The lectin pathway of complement activation is a critical component of the innate immune response to pneumococcal infection. *PLoS Pathog*, 8, 7.

Aoyagi Y, Adderson EE, Min JG, Matsushita M, Fujita T, Takahashi S, Okuwaki Y, Bohnsack JF (2005). Role of L-ficolin/mannose-binding lectin-associated serine protease complexes in the opsonophagocytosis of type III group B streptococci. *J Immunol*, 174, 1.

Aoyagi Y, Adderson EE, Rubens CE, Bohnsack JF, Min JG, Matsushita M, Fujita T, Okuwaki Y, Takahashi S (2008). L-Ficolin/mannose-binding lectin-associated serine protease complexes bind to group B streptococci primarily through N-acetylneuraminic acid of capsular polysaccharide and activate the complement pathway. *Infect Immun*, 76, 1.

Assaf A, Hoang TV, Faik I, Aebischer T, Kremsner PG, Kun JF, Velavan TP (2012). Genetic evidence of functional ficolin-2 haplotype as susceptibility factor in cutaneous leishmaniasis. *PLoS One*, 7, 3.

Atkinson AP, Cedzynski M, Szemraj J, St Swierzko A, Bak-Romaniszyn L, Banasik M, Zeman K, Matsushita M, Turner ML, Kilpatrick DC (2004). L-ficolin in children with recurrent respiratory infections. *Clin Exp Immunol*, 138, 3.

Carroll MV, Lack N, Sim E, Krarup A, Sim RB (2009). Multiple routes of complement activation by Mycobacterium bovis BCG. *Mol Immunol*, 46, 16.

Cedzynski M, Atkinson AP, St Swierzko A, MacDonald SL, Szala A, Zeman K, Buczylko K, Bak-Romaniszyn L, Wiszniewska M, Matsushita M, Szemraj J, Banasik M, Turner ML, Kilpatrick DC (2009). L-ficolin (ficolin-2) insufficiency is associated with combined allergic and infectious respiratory disease in children. *Mol Immunol*, 47, 2-3.

Cedzynski M, Nuytinck L, Atkinson AP, St Swierzko A, Zeman K, Szemraj J, Szala A, Turner ML, Kilpatrick DC (2007). Extremes of L-ficolin concentration in children with recurrent infections are associated with single nucleotide polymorphisms in the FCN2 gene. *Clin Exp Immunol*, 150, 1.

Cestari I, Ramirez MI (2010). Inefficient complement system clearance of Trypanosoma cruzi metacyclic trypomastigotes enables resistant strains to invade eukaryotic cells. *PLoS One*, 5, 3.

Cestari Idos S, Krarup A, Sim RB, Inal JM, Ramirez MI (2009). Role of early lectin pathway activation in the complement-mediated killing of Trypanosoma cruzi. *Mol Immunol*, 47, 2-3.

Chapman SJ, Vannberg FO, Khor CC, Segal S, Moore CE, Knox K, Day NP, Davies RJ, Crook DW, Hill AV (2007). Functional polymorphisms in the FCN2 gene are not associated with invasive pneumococcal disease. *Mol Immunol*, 44, 12.

Cseh S, Vera L, Matsushita M, Fujita T, Arlaud GJ, Thielens NM (2002). Characterization of the interaction between L-ficolin/p35 and mannan-binding lectin-associated serine proteases-1 and -2. *J Immunol*, 169, 10.

Dahl MR, Thiel S, Matsushita M, Fujita T, Willis AC, Christensen T, Vorup-Jensen T, Jensenius JC (2001). MASP-3 and its association with distinct complexes of the mannan-binding lectin complement activation pathway. *Immunity*, 15, 1.

Degn SE, Hansen AG, Steffensen R, Jacobsen C, Jensenius JC, Thiel S (2009). MAp44, a human protein associated with pattern recognition molecules of the complement system and regulating the lectin pathway of complement activation. *J Immunol*, 183, 11.

Degn SE, Jensen L, Hansen AG, Duman D, Tekin M, Jensenius JC, Thiel S (2012). Mannan-binding lectin-associated serine protease (MASP)-1 is crucial for lectin pathway activation in human serum, whereas neither MASP-1 nor MASP-3 is required for alternative pathway function. *J Immunol*, 189, 8.

Edgar PF (1995). Hucolin, a new corticosteroid-binding protein from human plasma with structural similarities to ficolins, transforming growth factor-beta 1-binding proteins. *FEBS Lett*, 375, 1-2.

Eikmans M, de Canck I, van der Pol P, Baan CC, Haasnoot GW, Mallat MJ, Vergunst M, de Meester E, Roodnat JI, Anholts JD, van Thielen M, Doxiadis II, de Fijter JW, van der Linden PJ, van Beelen E, van Kooten C, Kal-van Gestel JA, Peeters AM, Weimar W, Roelen DL, Rossau R, Claas FH (2012). The functional polymorphism Ala258Ser in the innate receptor gene ficolin-2 in the donor predicts improved renal transplant outcome. *Transplantation*, 94, 5.

Endo Y, Sato Y, Matsushita M, Fujita T (1996). Cloning and characterization of the human lectin P35 gene and its related gene. *Genomics*, 36, 3.

Evans-Osses I, Ansa-Addo EA, Inal JM, Ramirez MI (2010). Involvement of lectin pathway activation in the complement killing of Giardia intestinalis. *Biochem Biophys Res Commun*, 395, 3.

Faik I, Oyedeji SI, Idris Z, de Messias-Reason IJ, Lell B, Kremsner PG, Kun JF (2011). Ficolin-2 levels and genetic polymorphisms of FCN2 in malaria. *Hum Immunol*, 72, 1.

Faro J, Chen Y, Jhaveri P, Oza P, Spear GT, Lint TF, Gewurz H (2008). L-ficolin binding and lectin pathway activation by acetylated low-density lipoprotein. *Clin Exp Immunol*, 151, 2.

Gaboriaud C, Teillet F, Gregory LA, Thielens NM, Arlaud GJ (2007). Assembly of C1 and the MBL- and ficolin-MASP complexes: structural insights. *Immunobiology*, 212, 4-5.

Garlatti V, Belloy N, Martin L, Lacroix M, Matsushita M, Endo Y, Fujita T, Fontecilla-Camps JC, Arlaud GJ, Thielens NM, Gaboriaud C (2007). Structural insights into the innate immune recognition specificities of L- and H-ficolins. *EMBO J*, 26, 2.

Garred P, Honoré C, Ma YJ, Rørvig S, Cowland J, Borregaard N, Hummelshøj T (2010). The genetics of ficolins. *J Innate Immun*, 2, 1.

Gregory LA, Thielens NM, Matsushita M, Sorensen R, Arlaud GJ, Fontecilla-Camps JC, Gaboriaud C (2004). The X-ray structure of human mannan-binding lectin-associated protein 19 (MAp19) and its interaction site with mannan-binding lectin and L-ficolin. *J Biol Chem*, 279, 28.

Gulla KC, Gupta K, Gupta RK, Vyas V, Hajela K (2006). Development of a fluorescence assay for the detection of L-ficolin-MASP in serum or purified samples. *J Biochem Biophys Methods*, 66, 1-3.

Gulla KC, Gupta K, Krarup A, Gal P, Schwaeble WJ, Sim RB,

O'Connor CD, Hajela K (2010). Activation of mannan-binding lectin-associated serine proteases leads to generation of a fibrin clot. *Immunology*, 129, 4.

Herpers BL, Immink MM, de Jong BA, van Velzen-Blad H, de Jongh BM, van Hannen EJ (2006). Coding and non-coding polymorphisms in the lectin pathway activator L-ficolin gene in 188 Dutch blood bank donors. *Mol Immunol*, 43, 7.

Hess K, Ajjan R, Phoenix F, Dobó J, Gál P, Schroeder V (2012). Effects of MASP-1 of the complement system on activation of coagulation factors and plasma clot formation. *PLoS One*, 7, 4.

Hoang TV, Toan NL, Song le H, Ouf EA, Bock CT, Kremsner PG, Kun JF, Velavan TP (2011). Ficolin-2 levels and FCN2 haplotypes influence hepatitis B infection outcome in Vietnamese patients. *PLoS One*, 6, 11.

Hummelshoj T, Munthe-Fog L, Madsen HO, Fujita T, Matsushita M, Garred P (2005). Polymorphisms in the FCN2 gene determine serum variation and function of Ficolin-2. *Hum Mol Genet*, 14, 12.

Hummelshoj T, Thielens NM, Madsen HO, Arlaud GJ, Sim RB, Garred P (2007). Molecular organization of human Ficolin-2. *Mol Immunol*, 44, 4.

Hummelshøj T, Ma YJ, Munthe-Fog L, Bjarnsholt T, Moser C, Skjoedt MO, Romani L, Fujita T, Endo Y, Garred P (2012). The interaction pattern of murine serum ficolin-A with microorganisms. *PLoS One*, 7, 5.

Hummelshøj T, Munthe-Fog L, Madsen HO, Garred P (2008). Functional SNPs in the human ficolin (FCN) genes reveal distinct geographical patterns. *Mol Immunol*, 45, 9.

Héja D, Harmat V, Fodor K, Wilmanns M, Dobó J, Kékesi KA, Závodszky P, Gál P, Pál G (2012). Monospecific inhibitors show that both mannan-binding lectin-associated serine protease-1 (MASP-1) and -2 Are essential for lectin pathway activation and reveal structural plasticity of MASP-2. *J Biol Chem*, 287, 24.

Héja D, Kocsis A, Dobó J, Szilágyi K, Szász R, Závodszky P, Pál G, Gál P (2012). Revised mechanism of complement lectin-pathway activation revealing the role of serine protease MASP-1 as the exclusive activator of MASP-2. *Proc Natl Acad Sci U S A*, 109, 26.

Iwaki D, Kanno K, Takahashi M, Endo Y, Lynch NJ, Schwaeble WJ, Matsushita M, Okabe M, Fujita T (2006). Small mannose-binding lectin-associated protein plays a regulatory role in the lectin complement pathway. *J Immunol*, 177, 12.

Iwaki D, Kanno K, Takahashi M, Endo Y, Matsushita M, Fujita T (2011). The role of mannose-binding lectin-associated serine protease-3 in activation of the alternative complement pathway. *J Immunol*, 187, 7.

Jensen ML, Honoré C, Hummelshøj T, Hansen BE, Madsen HO, Garred P (2007). Ficolin-2 recognizes DNA and participates in the clearance of dying host cells. *Mol Immunol*, 44, 5.

Jusko M, Potempa J, Karim AY, Ksiazek M, Riesbeck K, Garred P, Eick S, Blom AM (2012). A metalloproteinase karilysin present in the majority of Tannerella forsythia isolates inhibits all pathways of the complement system. *J Immunol*, 188, 5.

Kilpatrick DC, Chalmers JD (2012). Human L-ficolin (ficolin-2) and its clinical significance. *J Biomed Biotechnol*, 2012.

Kilpatrick DC, Chalmers JD, MacDonald SL, Murray M, Mohammed A, Hart SP, Matsushita M, Hill A (2009). Stable bronchiectasis is associated with low serum L-ficolin concentrations. *Clin Respir J*, 3, 1.

Kilpatrick DC, Fujita T, Matsushita M (1999). P35, an opsonic lectin of the ficolin family, in human blood from neonates, normal adults, and recurrent miscarriage patients. *Immunol Lett*, 67, 2.

Kilpatrick DC, Swierzko AS, Matsushita M, Domzalska-Popadiuk I, Borkowska-Klos M, Szczapa J, Cedzynski M (2013). The relationship between FCN2 genotypes and serum (ficolin-2) L-ficolin protein concentrations from a large cohort of neonates. *Hum Immunol*.

Krarup A, Mitchell DA, Sim RB (2008). Recognition of acetylated oligosaccharides by human L-ficolin. *Immunol Lett*, 118, 2.

Krarup A, Sørensen UB, Matsushita M, Jensenius JC, Thiel S (2005). Effect of capsulation of opportunistic pathogenic bacteria on binding of the pattern recognition molecules mannan-binding lectin, L-ficolin, and H-ficolin. *Infect Immun*, 73, 2.

Krarup A, Thiel S, Hansen A, Fujita T, Jensenius JC (2004). L-ficolin is a pattern recognition molecule specific for acetyl groups. *J Biol Chem*, 279, 46.

Krarup A, Wallis R, Presanis JS, Gál P, Sim RB (2007). Simultaneous activation of complement and coagulation by MBL-associated serine protease 2. *PLoS One*, 2, 7.

Kuraya M, Ming Z, Liu X, Matsushita M, Fujita T (2005). Specific binding of L-ficolin and H-ficolin to apoptotic cells leads to complement activation. *Immunobiology*, 209, 9.

Lacroix M, Dumestre-Pérard C, Schoehn G, Houen G, Cesbron JY, Arlaud GJ, Thielens NM (2009). Residue Lys57 in the collagen-like region of human L-ficolin and its counterpart Lys47 in H-ficolin play a key role in the interaction with the mannan-binding lectin-associated serine proteases and the collectin receptor calreticulin. *J Immunol*, 182, 1.

Le Y, Lee SH, Kon OL, Lu J (1998). Human L-ficolin: plasma levels, sugar specificity, and assignment of its lectin activity to the fibrinogen-like (FBG) domain. *FEBS Lett*, 425, 2.

Liu J, Ali MA, Shi Y, Zhao Y, Luo F, Yu J, Xiang T, Tang J, Li D, Hu Q, Ho W, Zhang X (2009). Specifically binding of L-ficolin to N-glycans of HCV envelope glycoproteins E1 and E2 leads to complement activation. *Cell Mol Immunol*, 6, 4.

Lu J, Le Y (1998). Ficolins and the fibrinogen-like domain. *Immunobiology*, 199, 2.

Luz PR, Boldt AB, Grisbach C, Kun JF, Velavan TP, Messias-Reason IJ (2013). Association of L-Ficolin Levels and FCN2 Genotypes with Chronic Chagas Disease. *PLoS One*, 8, 4.

Lynch NJ, Roscher S, Hartung T, Morath S, Matsushita M, Maennel DN, Kuraya M, Fujita T, Schwaeble WJ (2004). L-ficolin specifically binds to lipoteichoic acid, a cell wall constituent of Gram-positive bacteria, and activates the lectin pathway of complement. *J Immunol*, 172, 2.

Ma YG, Cho MY, Zhao M, Park JW, Matsushita M, Fujita T, Lee BL (2004). Human mannose-binding lectin and L-ficolin function as specific pattern recognition proteins in the lectin activation pathway of complement. *J Biol Chem*, 279, 24.

Ma YJ, Doni A, Hummelshøj T, Honoré C, Bastone A, Mantovani A, Thielens NM, Garred P (2009). Synergy between ficolin-2 and pentraxin 3 boosts innate immune recognition and complement deposition. *J Biol Chem*, 284, 41.

Matsushita M, Endo Y, Fujita T (2000). Cutting edge: complement-activating complex of ficolin and mannose-binding lectin-associated serine protease. *J Immunol*, 164, 5.

Matsushita M, Endo Y, Taira S, Sato Y, Fujita T, Ichikawa N, Nakata M, Mizuochi T (1996). A novel human serum lectin with collagen- and fibrinogen-like domains that functions as an opsonin. *J Biol Chem*, 271, 5.

Matsushita M, Fujita T (1992). Activation of the classical complement pathway by mannose-binding protein in association with a novel C1s-like serine protease. *J Exp Med*, 176, 6.

Megyeri M, Harmat V, Major B, Végh A, Balczer J, Héja D, Szilágyi K, Datz D, Pál G, Závodszky P, Gál P, Dobó J (2013). Quantitative Characterization of the Activation Steps of Mannan-binding Lectin (MBL)-associated Serine Proteases (MASPs) Points to the Central Role of MASP-1 in the Initiation of the Complement Lectin Pathway. *J Biol Chem*, 288, 13.

Meijvis SC, Herpers BL, Endeman H, de Jong B, van Hannen E, van Velzen-Blad H, Krediet RT, Struijk DG, Biesma DH, Bos WJ (2011). Mannose-binding lectin (MBL2) and ficolin-2 (FCN2) polymorphisms in patients on peritoneal dialysis with staphylococcal peritonitis. *Nephrol Dial Transplant*, 26, 3.

Messias-Reason IJ, Schafranski MD, Kremsner PG, Kun JF (2009). Ficolin 2 (FCN2) functional polymorphisms and the risk of rheumatic fever and rheumatic heart disease. *Clin Exp Immunol*, 157, 3.

Munthe-Fog L, Hummelshøj T, Hansen BE, Koch C, Madsen HO, Skjødt K, Garred P (2007). The impact of FCN2 polymorphisms and haplotypes on the Ficolin-2 serum levels. *Scand J Immunol*, 65, 4.

Ouf EA, Ojurongbe O, Akindele AA, Sina-Agbaje OR, Van Tong H, Adeyeba AO, Kremsner PG, Kun JF, Velavan T (2012). Ficolin-2 levels and FCN2 genetic polymorphisms as a susceptibility factor in schistosomiasis. *J Infect Dis*, 206, 4.

Pan Q, Chen H, Wang F, Jeza VT, Hou W, Zhao Y, Xiang T, Zhu Y, Endo Y, Fujita T, Zhang XL (2012). L-ficolin binds to the glycoproteins hemagglutinin and neuraminidase and inhibits influenza A virus infection both in vitro and in vivo. *J Innate Immun*, 4, 3.

Presanis JS, Hajela K, Ambrus G, Gál P, Sim RB (2004). Differential substrate and inhibitor profiles for human MASP-1 and MASP-2. *Mol Immunol*, 40, 13.

Roos A, Rastaldi MP, Calvaresi N, Oortwijn BD, Schlagwein N, van Gijlswijk-Janssen DJ, Stahl GL, Matsushita M, Fujita T, van Kooten C, Daha MR (2006). Glomerular activation of the lectin pathway of complement in IgA nephropathy is associated with more severe renal disease. *J Am Soc Nephrol*, 17, 6.

Sallenbach S, Thiel S, Aebi C, Otth M, Bigler S, Jensenius JC, Schlapbach LJ, Ammann RA (2011). Serum concentrations of lectin-pathway components in healthy neonates, children and adults: mannan-binding lectin (MBL), M-, L-, and H-ficolin, and MBL-associated serine protease-2 (MASP-2). *Pediatr Allergy Immunol*, 22, 4.

Skjoedt MO, Hummelshoj T, Palarasah Y, Hein E, Munthe-Fog L, Koch C, Skjodt K, Garred P (2011). Serum concentration and interaction properties of MBL/ficolin associated protein-1. *Immunobiology*, 216, 5.

Skjoedt MO, Hummelshoj T, Palarasah Y, Honore C, Koch C, Skjodt K, Garred P (2010). A novel mannose-binding lectin/ficolin-associated protein is highly expressed in heart and skeletal muscle tissues and inhibits complement activation. *J Biol Chem*, 285, 11.

Swierzko AS, Atkinson AP, Cedzynski M, Macdonald SL, Szala A, Domzalska-Popadiuk I, Borkowska-Klos M, Jopek A, Szczapa J, Matsushita M, Szemraj J, Turner ML, Kilpatrick DC (2009). Two factors of the lectin pathway of complement, l-ficolin and mannan-binding lectin, and their associations with prematurity, low birthweight and infections in a large cohort of Polish neonates. *Mol Immunol*, 46, 4.

Taira S, Kodama N, Matsushita M, Fujita T (2000). Opsonic function and concentration of human serum ficolin/P35. *Fukushima J Med Sci*, 46, 1-2.

Takahashi M, Endo Y, Fujita T, Matsushita M (1999). A truncated form of mannose-binding lectin-associated serine protease (MASP)-2 expressed by alternative polyadenylation is a component of the lectin complement pathway. *Int Immunol*, 11, 5.

Teillet F, Gaboriaud C, Lacroix M, Martin L, Arlaud GJ, Thielens NM (2008). Crystal structure of the CUB1-EGF-CUB2 domain of human MASP-1/3 and identification of its interaction sites with mannan-binding lectin and ficolins. *J Biol Chem*, 283, 37.

Thiel S, Vorup-Jensen T, Stover CM, Schwaeble W, Laursen SB, Poulsen K, Willis AC, Eggleton P, Hansen S, Holmskov U, Reid KB, Jensenius JC (1997). A second serine protease associated with mannan-binding lectin that activates complement. *Nature*, 386, 6624.

Yang K, Dinasarapu AR, Reis ES, Deangelis RA, Ricklin D, Subramaniam S, Lambris JD (2013). CMAP: Complement Map Database. *Bioinformatics*.

Zhang J, Koh J, Lu J, Thiel S, Leong BS, Sethi S, He CY, Ho B, Ding JL (2009). Local inflammation induces complement crosstalk which amplifies the antimicrobial response. *PLoS Pathog*, 5, 1.

de Messias-Reason I, Kremsner PG, Kun JF (2009). Functional haplotypes that produce normal ficolin-2 levels protect against clinical leprosy. *J Infect Dis*, 199, 6.

This molecule exists in 23 states , has 25 transitions between these states and has 2 enzyme functions.(Please zoom in the pdf file to view details.)