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H-Ficolin

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H-ficolin is a serum lectin synthesized (as a ~34 kDa polypeptide) predominantly by the liver and lung tissues and is one of the soluble pattern recognition receptors of the innate immune system. It is structurally similar to L- and M- ficolins, but is different in its tissue expression and binding affinities to pathogenic ligands. Ficolins have 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 H-ficolin molecules in circulation. The polypeptides in the structural subunit are cross-linked by disulphide bonds in the N-terminal region and the fibrinogen-like domain forms a globular structure. Thus, the overall structure of H-ficolin also resembles mannose/mannan- binding lectin (MBL). The primary role of H-ficolin is that of a pattern recognition receptor, recognizing acetylated sugar residues on the cell surface of different bacteria, viruses and other pathogens. There are two pathways by which H-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.

KEYWORDS
Collagen/fibrinogen domain-containing lectin 3 p35; Collagen/fibrinogen domain-containing protein 3; FCN3; FCNH; Ficolin (collagen/fibrinogen domain containing) 3 (Hakata antigen); Ficolin 3; Ficolin-3; H-ficolin; H-Ficolin; HAKA1; Hakata antigen; Thermolabile beta-2 macroglobulin

IDENTIFIERS
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PROTEIN FUNCTION
H-ficolin, one of the phylogenetically ancient ficolins (Garred *et al*. 2010), was first isolated as an auto-antigen in a systemic lupus erthematosus patient (Yae *et al*. 1991). Similar to other ficolins, H-ficolin has an N-terminal cysteine rich region, a collagenous domain, and a fibrinogen-like domain at the C-terminus (Sugimoto *et al*. 1998). Three polypeptide chains oligomerize through the collagenous region to form the basic structural subunit, a triple helix. H-ficolin circulates in serum mainly as a tetramer, hexamer or octamer of this structural subunit, thus having 12, 18 or 24 identical polypeptide chains (Hummelshoj *et al*. 2008). The fibrinogen-like domains of the polypeptides form a globular head, which binds to acetylated residues such as acetlyated BSA (an artificial ligand) or GlcNAc (N-acetyl glucosamine) on pathogenic surfaces (Hein *et al*. 2010, Sugimoto *et al*. 1998).

Complement activation: H-ficolin, in co-operation with MBL (mannose/mannan-binding lectin)-associated serine proteases (MASP-1 and MASP-2) can activate complement via the lectin pathway (Matsushita *et al*. 2002). Comparative studies (involving ficolins and MBL) revealed H-ficolin to be most effective in C4 deposition (Hummelshoj *et al*. 2008). It was demonstrated to inhibit the growth of *Aerococcus viridans* (Tsujimura *et al*. 2002), kill *Trypanosma cruzi* (Cestari *et al*. 2009), *Giardia intestinalis* (Evans-Osses *et al*. 2010) and inhibit replication of influenza A virus (IAV) (Verma *et al*. 2012). Sialic acid residues of H-ficolin are important for its activity against IAV (Verma *et al*. 2012).

H-ficolin may contribute to the clearance of apoptotic cells. This property depends on complement activation, binding to calreticulin (C1qR) and subsequent phagocytosis (Kuraya *et al*. 2005, Honoré *et al*. 2007). It was suggested that other than C1qR receptor complexes might be involved in mediating the opsonic effect of this lectin. H-ficolin was moreover reported to interact with necrotic cells. In contrast to MBL or L-ficolin, no binding to DNA was observed. H-ficolin was moreover reported to interact with necrotic cells (Honoré *et al*. 2007).

REGULATION OF ACTIVITY
Karilysin, a matrix metalloproteinase-like enzyme produced by periodontal pathogen *Tannerella forsythia*, cleaves H-ficolin along with other complement proteins, thereby inhibiting complement activation (Jusko *et al*. 2012). Unlike L-ficolin and M-ficolin, H-ficolin is resistant to bacterial collagenase treatment (Hummelshoj *et al*. 2008).

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

H-ficolin-MASP Complex: Similar to other ficolins, MBL and collection-11, the collagen region of the oligomeric form of H-ficolin interacts with different MASP proteins (Lacroix *et al*. 2009). Its Lys47 residue is crucial for this interaction (Lacroix *et al*. 2009). All the MASP proteins, MASP-1, MASP-2, MASP-3, MAp44 (MAP-1) and sMAP (MAp19); bind to ficolins in a homo-dimeric form and the binding is Ca^{2+} dependent (Gregory *et al*. 2004, Teillet *et al*. 2008, Skjoedt *et al*. 2012). 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). H-ficolin associated MASP-1 gets auto-activated (by proteolytic cleavage), upon binding of H-ficolin to sugar residues on pathogen surfaces (Matsushita *et al*. 2002, Teillet *et al*. 2008). Activated MASP-1 cleaves and activates MASP-2 (Degn *et al*. 2012, Héja *et al*. 2012a, Héja *et al*. 2012b). MASP-2

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sequentially activates complement proteins C4 and C2 through its serine protease activity (Wallis *et al*. 2007). The concentration of H-ficolin-MASP-2 complex is directly correlated with C4 deposition (Csuka *et al*. 2013). MASP-3 is a splice variant of *MASP1*, which has a serine protease domain with no known physiological relevant substrates (Matsushita *et al*. 2002, Skjoedt *et al*. 2010b, Teillet *et al*. 2008). Interestingly, high serum concentrations of MASP-3 were found in complex with H-ficolin (in comparison to MBL and other ficolins) (Skjoedt *et al*. 2010b). MAp44, expressed mainly in the heart, is yet another splice variant of *MASP1*. It however does not have a serine protease domain (Skjoedt *et al*. 2011, Skjoedt *et al*. 2010a, Degn *et al*. 2009). Similar to MASP-3, H-ficolin is the preferred partner for MAp44 (Skjoedt *et al*. 2011,Skjoedt *et al*. 2010a). sMAP, a splice variant of *MASP2*, also lacks a serine protease domain (Matsushita *et al*. 2002). However, the physiological role of this interaction is yet to be demonstrated.

Interactions with pathogens: H-ficolin can interact with certain Gram-negative bacteria or their lipopolysaccharides (LPS) (Garlatti *et al*. 2007) on a variety of pathogens such as *Escherichia coli* O111 (LPS), *Salmonella typhimurium* and *Salmonella minnesota* (Sugimoto *et al*. 1998), *Hafnia alvei* (Swierzko *et al*. 2012), Gram positive *Aerococcus viridans* (the ligand is a polysaccharide (Krarup *et al*. 2005, Matsushita *et al*. 2002), parasites *Trypanosoma cruzi* (Cestari *et al*. 2009, Cestari and Ramirez 2010), *Giardia intestinalis* (Evans-Osses *et al*. 2010) and influenza A virus (Verma *et al*. 2012).

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

PHENOTYPES

The only polymorphism of *FCN3* resulting in a phenotype is +1637delC, which is a frameshift mutation distorting the C-terminal end of H-ficolin (Munthe-Fog *et al*. 2008). While heterozygous mutation results in lower levels of the protein, homozygous mutation has been documented to result in congenital deficiency (Munthe-Fog *et al*. 2009, Michalski *et al*. 2012) and severe necrotising enterocolitis in pre-mature infants (Schlapbach *et al*. 2011). High serum levels of H-ficolin have been associated with decreased survival of kidney grafts (Bay *et al*. 2013), rheumatoid arthritis (Roy *et al*. 2013) and systemic lupus erythematosus (Andersen *et al*. 2009). Interestingly, while gene expression of *FCN3* is reduced in ovarian cancers, the serum concentration of H-ficolin is higher as compared to controls (Szala *et al*. 2013). Contradictory results have been obtained in association studies of serum levels with type 2 diabetes. While some show high levels to be associated with the disease (Li *et al*. 2008, Zheng *et al*. 2011), one study shows low levels to be predictive of diabetes (Chen *et al*. 2012).

Low serum levels of H-ficolin are associated with pre-eclampsia in pregnant women (Wang *et al*. 2007, Halmos *et al*. 2012), lower birth weight and pre-term deliveries (Michalski *et al*. 2012), increased risk of fever and neutropenia in children treated for pediatric cancers (Schlapbach *et al*. 2009), increased risk of chronic heart failure (Prohászka *et al*. 2013), adverse outcome in patients with acute ischemic stroke (Füst *et al*. 2011), increased severity of hereditary angioedema (due to C1-inhibitor (C1-INH) deficiency) (Csuka *et al*. 2013) and sarcoidosis pathalogy (Svendsen *et al*. 2008). Lower cord blood levels were associated with gram-positive sepsis in neonates (Schalpbach *et al*. 2010). No difference in serum levels was observed between patients with Crohn's disease and controls (Nielsen *et al*. 2007). However, Crohn's disease patients with of ASCA (anti-*Saccharomyces cerevisiae* mannan antibodies) showed lower H-ficolin concentrations (Schaffer *et al*. 2013).

MAJOR SITES OF EXPRESSION

H-ficolin, a product of *FCN3*, is primarily expressed in the lung followed by liver and is the most highly expressed gene (among other lectin pathway components) in these tissues (Hummelshoj *et al*. 2008) and has reduced expression in hepatocellular and squamous cell lung carcinomas (Luo *et al*. 2006, Shi *et al*. 2011). A recent study has shown FCN3 expression in the ovary (Szala *et al*. 2013).

SPLICE VARIANTS

FCN3 gene is located on chromosome 1p36.11 and expresses two different splice variants. One of them is the full length protein composed of eight exons, while the other has only seven exons and lacks amino acids 79-89 (Garred *et al*. 2009).

REGULATION OF CONCENTRATION

The serum concentration in healthy donors was found to be 7-23 µg/ml (Yae *et al*. 1991), 11.2-33.8 µg/ml (Krarup *et al*. 2005), 2.3-75 µg/ml (Sallenbach *et al*. 2011) and varies with age (newborns to adults) (Sallenbach *et al*. 2011, Szala *et al*. 2013). In a group of ~600 neonates, the concentration of H-ficolin in newborns was detected to be 14.6 µg/ml. However, newborns born preterm or with low birth weight had much lower concentrations of 13 µg/ml and 10.9 µg/ml respectively (Michalski *et al*. 2012, Cedzynski *et al*. 2012).

ANTIBODIES

The following companies sell polyclonal antibodies against human H-ficolin: Santa Cruz Biotechnolgy (Abs against epitopes 166-220 and N-terminal region), Abbio and R&D systems. Monoclonal antibodies are sold by Hycult Biotechnology and Enzo Life Sciences.

Table 1: Functional States

STATE DESCRIPTION	LOCATION	REFERENCES
H-FCN (native)	extracellular region	
H-FCN triple helix	extracellular region	Sugimoto R *et al.* 1998; Yae Y *et al.* 1991
H-FCN octadecamer	extracellular region	Yae Y *et al.* 1991; Sugimoto R *et al.* 1998
H-FCN/MASP-1	extracellular region	Lacroix M *et al.* 2009
H-FCN/MASP-2	extracellular region	Lacroix M *et al.* 2009
H-FCN/ 2(MASP-3)	extracellular region	Teillet F *et al.* 2008; Lacroix M *et al.* 2009
H-FCN/ 2(sMAP)	extracellular region	Lacroix M *et al.* 2009; Zacho RM *et al.* 2012; Csuka D *et al.* 2013
H-FCN/CRT	extracellular region	Lacroix M *et al.* 2009; Kuraya M *et al.*
H-FCN/ 2(MAp44)	extracellular region	Degn SE *et al.* 2013; Degn SE *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
H-FCN-acetyl groups	extracellular region	Garlatti V *et al.* 2007; Sugimoto R *et al.* 1998
H-FCN-LPS	extracellular region	Swierzko A *et al.* 2012
H-FCN/active 2(MASP-1)/2(MASP-2)	extracellular region	Héja D *et al.* 2012; Héja D *et al.* 2012; Møller-Kristensen M *et al.* 2007
H-FCN/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 14 states , has 14 transitions between these states and has 2 enzyme functions.(Please zoom in the pdf file to view details.)