H-Ficolin

Anjana Chandrasekhar1, Ashok Reddy Dinasarapu1, Maciej Cedyżyński2, Shankar Subramaniam3

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 disulfide 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

PROTEIN FUNCTION
H-ficolin, one of the phyleogenetically ancient ficolins (Garred et al. 2010), was first isolated as an auto-antigen in a systemic lupus erythematosus 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 (Matsushima 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 Trypanosoma 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
Karylsin, 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:


1Department of Bioengineering, University of California, San Diego, CA 92093, US.
2Laboratory of Immunobiology of infections, Institute of Medical Biology of PAS, 93-232, PL.
3Department of Bioengineering, University of California at San Diego, CA 92093, US.
Correspondence should be addressed to Anjana Chandrasekhar: a4chandra@ucsd.edu
Published online: 30 Oct 2013 | doi:10.6072/H0.MP.A004267.01
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 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).

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 Biotechnology (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

<table>
<thead>
<tr>
<th>STATE DESCRIPTION</th>
<th>LOCATION</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-FCN (native)</td>
<td>extracellular</td>
<td>Sugimoto R et al. 1998; Yae Y et al. 1991</td>
</tr>
<tr>
<td>H-FCN triple helix</td>
<td>extracellular</td>
<td>Yae Y et al. 1991; Sugimoto R et al. 1998</td>
</tr>
<tr>
<td>H-FCN octadecamer</td>
<td>extracellular</td>
<td>Lacroix M et al. 2009</td>
</tr>
<tr>
<td>H-FCN/2(sMAP)</td>
<td>extracellular</td>
<td>Lacroix M et al. 2009; Zacho RM et al. 2012; Csuka D et al. 2013</td>
</tr>
<tr>
<td>H-FCN/CRT</td>
<td>extracellular</td>
<td>Lacroix M et al. 2009; Kuraya M et al.</td>
</tr>
<tr>
<td>H-FCN-acetyl groups</td>
<td>extracellular</td>
<td>Garlatti V et al. 2007; Sugimoto R et al. 1998</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENTS

The UCSD Signaling Gateway Molecule Pages (SGMP) is funded by NIH/NIGMS Grant 1 R01 GM078005-01. The work of MC was partially supported by European Fund Innovative Economy (grant POIG.01.02.10-107/09) and National Science Centre (Poland) (grant N N402 353438). The authors thank Dr. John D. Lambris, University of Pennsylvania, Philadelphia, UCSD-SGMP editorial board member, for extensive discussions.

SUPPLEMENTARY

Supplementary information is available online.

REFERENCES


detected by precipitating (auto) antibody in sera of patients with systemic lupus erythematosus. *Biochim Biophys Acta*, 1078, 3.


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.)