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Complement factor H

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Complement factor H (fH) is a single chain plasma glycoprotein (approximately 150 kDa in size), with 20 domains termed complement control protein (CCP) domains or short consensus repeats (SCR). The complement factor H gene (CFH) is located on chromosome 1q32 in the regulators of complement activation (RCA) gene cluster, adjacent to the genes that code for the Complement factor H-Related Proteins (CFHRs). The RCA cluster includes additional regulators containing SCR domains, such as C4 Binding Protein (C4BP), Complement receptor type 1 (CR1), Complement decay-accelerating factor (DAF), Membrane cofactor protein (MCP). fH and C4BP are fluid-phase (soluble) complement regulators, while the remaining are membrane-bound and all these regulators share similarities in their structure and function. fH prevents the formation of the alternative pathway C3 (C3bBb) and C5 (C3bBb3b) convertases. This inhibitory effect is either by competition with Complement factor B (fB) for C3b binding, by convertase decay acceleration activity or by acting as a cofactor for the Complement factor I (fI)-mediated degradation of C3b. Important targets for fH binding, in the neighborhood of C3b on host cells, are glycosaminoglycans and sialic acid (polyanionic molecules), which increase the affinity of fH for C3b. In addition to C3b and polyanionic molecules, fH also interacts with various endogenous molecules, such as pentraxins, extracellular matrix (ECM) proteins, prion protein, adrenomedullin, DNA, annexin-II and histones, to inhibit complement activation on certain host surfaces such as glomerular basement membrane, the extracellular matrix, and late apoptotic cells. CFH gene mutations and polymorphisms, and auto-antibodies against fH adversely affect regulatory and target recognition functions of fH. Some of the diseases associated with fH dysfunction are atypical hemolytic uremic syndrome (aHUS), dense deposit disease (DDD; also termed membranoproliferative glomerulonephritis (MPGN) type II) and age-related macular degeneration (AMD). Interestingly, microbes and multicellular pathogens can recruit host fH to their surface in order to protect themselves from complement attack.

KEYWORDS
Adrenomedullin binding protein; Age-related maculopathy susceptibility 1; AHUS1; AMBP1; ARMD4; ARMS1; Beta-1-H-globulin; Beta-1H; CFH; CFHL3; Complement factor H; Factor H; Factor H-like 1; FH; FHL1; H factor 1; H factor 1 (complement); H factor 2 (complement); HF; HF1; HF2; HUS

IDENTIFIERS
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PROTEIN FUNCTION

Complement factor H (fH, beta 1H globulin or β1H) is a major regulator of the alternative complement pathway (AP). fH regulates complement activity by inhibiting the assembly of the AP C3 convertase, by facilitating the disassembly of already formed C3 (C3bBb) and C5 (C3bBb3b) convertases (called decay acceleration activity) (Whaley and Ruddy 1976; Weiler *et al*. 1976) or by acting as a cofactor for the complement factor I (fI)-mediated degradation of C3b (Pangburn *et al*. 1977). fH is a single chain plasma glycoprotein with 20 short consensus repeat (SCR) domains, also termed complement control protein (CCP) modules (Sim and DiScipio 1982; Ripoche *et al*. 1988). fH regulatory (cofactor and decay acceleration) activities are mediated by the four amino-terminal SCRs (SCR1-4) (Gordon *et al*. 1995; Kuhn *et al*. 1995; Kuhn and Zipfel 1996). The carboxy-terminal SCRs (SCR19-20) allow the surface recognition and attachment of fH to host cells, which facilitate inhibition of complement activation on surfaces (Pangburn 2002; Oppermann *et al*. 2006; Jokiranta *et al*. 2005; Ferreira *et al*. 2006).

The complement system which is a key component in the innate immune system is activated *via* three well-established pathways, the alternative (AP), classical (CP) and lectin pathway (LP). The molecules generated (peptide fragments and/or molecular complexes) by these activation processes have various roles in innate and acquired immunity. The classical and lectin pathways are activated by pathogens, pentraxins or immune complexes. The alternative pathway is spontaneously activated because the internal thioester bond in complement C3 is continuously hydrolyzed (C3(H20)) (at a low-rate activation called tick-over) in host plasma (Pangburn *et al*. 1981). C3(H20) then binds to complement factor B (fB), which is then cleaved by complement factor D (fD) to form a C3 convertase (C3(H20)Bb) (Fishelson *et al*. 1984; Lesavre *et al*. 1978; Hourcade *et al*. 2011). This C3 convertase cleaves C3 into C3a and C3b in fluid phase. The released C3a (an anaphylatoxin) has chemotactic functions (Hugli 1975; Hugli *et al*. 1975) while C3b can covalently attach to surfaces (this occurs immediately, otherwise C3b is degraded and inactivated) (Pangburn and Müller-Eberhard 1980).

Regulator of Alternative Complement Pathway: On altered-self or pathogen, fB can bind to the deposited C3b and a C3 convertase (C3bBb) is formed with the action of fD on C3bfB (this is stabilized by Properdin (fP) as C3bfBfP to prevent decay) (Medicus *et al*. 1976). On host cells, complement activation needs to be regulated to prevent harm to the host tissues, as demonstrated by several diseases associated with unregulated activation or deficiency of complement regulatory components. Complement activation is regulated by soluble (fH, complement factor H like 1 (CFHL-1), C1inh, C4BP, CFHRs, properdin, vitronectin, clusterin, fI and carboxypeptidase N) and/or membrane bound factors (complement receptor type 1 (CR1), DAF, MCP (CD46), CD59). fH is a plasma (soluble, fluid-phase) protein that

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regulates the alternative pathway (Trouw *et al*. 2007). fH can discriminate between self and non-self by recognizing the self (host) cells partially by polyanionic molecules, such as sialic acids and glycosaminoglycans (Fearon 1978; Kazatchkine *et al*. 1979; Kajander *et al*. 2011) near surface bound C3b leading to down-regulation of alternative pathway (Józsi *et al*. 2007). When host tissue misses the above said regulators, complement activation takes place on self-surface.

Role in chemotaxis and inflammation: fH was identified as a monocyte chemotactic factor (Nabil *et al*. 1997). fH cleavage by thrombin (coagulation factor IIa) generates a fragment, which has chemotactic activity for monocytes, implying that a receptor for this chemotactic fragment may exist (Nabil *et al*. 1997; Ohtsuka *et al*. 1993). fH plays a role in neutrophil adherence (to immobilized heparin or chondroitin A) and enhances the increase in generation of hydrogen peroxide/respiratory burst in C5a- or tumor necrosis factor (TNF)-α primed neutrophils (DiScipio *et al*. 1998; Schopf *et al*. 1982). fH when bound on *C. albicans* supports the migration and adherence of human neutrophils (Losse *et al*. 2010). fH can also protect host cells from oxidative stress by binding to malondialdehyde (MDA) epitopes, a lipid peroxidation product that accumulates in many pathophysiological processes like AMD (Weismann *et al*. 2011). Recently, a study identified an interaction between fH and L-selectin, which is an important adhesion molecule of leukocytes during inflammatory process. Further, this interaction was shown to increase TNF-α release from leukocytes (Malhotra *et al*. 1999).

Other roles: fH was shown to inhibit human B-cell differentiation *in vitro* in immunoglobulin-secreting cells without blocking the proliferative ability of the cells (Tsokos *et al*. 1985). fH treated B-lymphocytes have been reported to release endogenously-synthesized fI (C3b inactivator) (Crossley 1981; Lambris *et al*. 1980). fH can support the adhesion of neutrophils *via* CR3 (DiScipio *et al*. 1998; Losse *et al*. 2010). fH, by binding to monocytes, down regulates C1q-enhanced uptake of apoptotic cells (Kang *et al*. 2012). Apart from regulating the alternative pathway, fH also regulates classical pathway by a different mechanism. fH has been shown to compete with C1q for binding to Lipid-A of *Escherichia coli*, thus down-regulating classical pathway activation (Tan *et al*. 2011).

REGULATION OF ACTIVITY

Plasminogen, secreted into the blood as a zymogen from liver, enhances the cofactor activity of fH (Barthel *et al*. 2012). High levels of bioavailable zinc occurring in sub-retinal pigment epithelial deposits, [resulting in age-related macular degeneration (AMD)] inhibits fH activity through strong fH aggregation. Excess zinc binds weakly to a central region of fH, explaining how zinc inhibits fH regulation of C3b (Perkins *et al*. 2012). fH activity is also regulated by interacting with several host and pathogenic factors (see 'Interactions with Ligands and Other Proteins' section). As the main role of fH is to control complement activation, several pathogenic microbes use different strategies to capture fH from host plasma on their surface inhibiting the function of the complement system on the microbial surface (microbial complement evasion) (Ricklin *et al*. 2010).

INTERACTIONS

fH is the major plasma regulator of the central complement protein C3b in the alternative pathway (AP) of complement activation. fH interacts with C3b *via* domains that are associated both with its regulatory activity (SCRs1-4) and surface recognition site (SCRs 19-20), as well as sites that are found within domains SCRs8-18 (Jokiranta *et al*. 1996; Jokiranta *et al*. 2000; Wu *et al*. 2009). Further, fH having dual binding sites for C3b and glycosoaminoglycans (GAGs) or sialic acids, which increase the affinity of fH for C3b (Meri and Pangburn 1990; Pangburn 2000) on host cells, explains its role in discrimination between host and non-host cells (Kajander *et al*. 2011). A recent study also showed the low molar affinity of the fH-C3b complex, which indicates that the complex is not fully formed in plasma (Perkins *et al*. 2012). fH interacts with heparin (Khan *et al*. 2012), which is often used as an analogue of the polyanionic host cell surface molecules (GAGs or sialic acid) *via* SCR7 (Blackmore *et a*l. 1996) and SCR20 (Blackmore *et al*. 1998). Thioredoxin-1 (TRX-1) interacts with fH, so that TRX-1 acts additively to the function of fH in the inhibition of AP C3 convertase (Inomata *et al*. 2008).

Apart from binding to C3b, fH interacts with several other molecules and cell surface receptors. Several endogenous ligands, such as, extracellular matrix proteins (ECM) proteins (fibromodulin, osteoadherin and chondroadherin) (Sjöberg *et al*. 2005; Sjöberg *et al*. 2007; Sjöberg *et al*. 2009a), the pentraxins C-reactive protein (CRP) (Perkins *et al*. 2012) and pentraxin-3 (PTX3) (Deban *et al*. 2008; Okemefuna *et al*. 2010), amyloid deposits, prions (Sjöberg *et al*. 2008), adiponectin (Peake and Shen 2010), adrenomedullin and DNA, bind the complement inhibitors C4BP and/or fH. Several of these host ligands also interact with the complement activator C1q, pointing to a balance between complement activation and inhibition (Sjöberg *et al*. 2009b). The binding sites for such ligands are generally located outside the domains responsible for the complement regulatory activity of fH, and thus enable bound fH to down-regulate complement activation.

Apoptotic cells expose several molecules that can bind fH, including DNA, annexin-II and histones (Leffler *et al*. 2008; recent review by Kopp *et al*. 2012). It is thought that the binding of both complement inhibitors and activators simultaneously on these cells could result in safe opsonization and uptake of the apoptotic or necrotic cells, without causing inflammatory and lytic effects (Sjöberg *et al*. 2009b; Mihlan *et al*. 2009). The monomeric form of CRP (mCRP) can bind to apoptotic or necrotic cells and recruits fH, which facilitates a non-inflammatory way of uptake of such cells (Mihlan *et al*. 2009).

fH directly binds to leukocytes and platelets through integrin receptors such as $\alpha_M\beta_2$ (CR3) and $\alpha_{IIb}\beta_3$, respectively. Monocytes (Kang *et al*. 2012) and neutrophils (Avery and Gordon 1993; Ross 2002; DiScipio *et al*. 1998) use the β2 integrin receptor $\alpha_M\beta_2$ (CR3, CD11b/CD18, $\alpha_M\beta_2$ integrin or Mac-1) (Avery and Gordon 1993; Ross 2002; DiScipio *et al*. 1998). fH was also reported to bind to L-selectin, and immobilized fH (but not fluid-phase fH) induced the release of TNF-α from leukocytes (Malhotra *et al*. 1999). fH binding to human tonsil B lymphocytes and Raji B-lymphoblastoid cells (Erdei and Sim 1987) was observed and fH binding to human B lymphocytes stimulated a calcium-dependent fI release (Lambris *et al*. 1980). The fH receptor on B cells remains unidentified. Resting platelets use the β3 integrin receptor $\alpha_{IIb}\beta_3$ and this binding is increased when platelets become activated (Vaziri-Sani *et al*. 2005; Mnjoyan *et al*. 2008). This fH binding to platelets through $\alpha_{IIb}\beta_3$ and *via* thrombospondin (Vaziri-Sani

et al. 2005; Mnjoyan *et al*. 2008) occurs in the absence of complement. fH isoforms phi(Φ)1 and Φ2 (based on post-translational modifications, the nature of which remains unclear), have an identical polypeptide backbone with similar ability to bind to cell-bound C3b (Ripoche *et al*. 1984; Malhotra *et al*. 1999) . However, binding to lymphoid cell surfaces is associated with the fH Φ2 subpopulation, as demonstrated by direct binding experiments of these two forms of fH to Raji cells (Ripoche *et al*. 1988). The Φ2 subpopulation was also shown to interact with monocytes, which induced secretion of interleukin (IL)-1β by the latter (Iferroudjene *et al*. 1991). In Alzheimer's disease, fH was shown to bind to heparan sulfate proteoglycans (HSPGs) and to co-localize with $\alpha_M\beta_2$, in the amyloid-β (Aβ) plaques in the brain (Strohmeyer *et al*. 2002).

Interaction with microbial ligands and proteins: The absence of host-like (polyanionic) markers allows AP activation on pathogens, but many common pathogens mimic host markers, express proteins that bind host complement regulators, or inactivate/inhibit certain complement components, allowing them to escape detection by this innate defense system. Several organisms (including viruses, bacteria, fungi and parasites) using one or more of these evasive strategies can bind fH, and thereby protect themselves from complement attack (Lambris *et al*. 2008) or even use fH for host tissue invasion.

Fungi: fH and CFHL-1 from human serum bind to *Aspergillus fumigatus* conidia (conidia is one of the developmental stages) (Behnsen *et al*. 2008). Surface expressed *Candida albicans* phosphoglycerate mutase (CaGpm1p) and pH-regulated antigen 1 (Pra1) are virulence factors that utilize the host fH and CFHL-1 for immune evasion (Poltermann *et al*. 2007; Luo *et al*. 2009). In contrast, fH and CFHR1, when bound on the surface of *C. albicans*, can facilitate interaction with host cells and enhance the antimicrobial activity of human neutrophils (Losse *et al*. 2010). *Saccharomyces cerevisiae* phosphoglycerate mutase (ScGpm1p) also binds fH and CFHL-1 (Poltermann *et al*. 2007).

Gram positive bacteria: *Streptococcus pneumoniae* was shown to bind fH, which was correlated with reduced complement activation and opsonophagocytosis (Neeleman *et al*. 1999). fH binds to PspC, a surface protein of *S. pneumoniae* (Dave *et al*. 2004), and mediates entry of the pathogen into epithelial cells and neutrophils expressing CR3 ($\alpha_M\beta_2$), a receptor protein, due to fH-CR3 interaction (Agarwal *et al*. 2010; Hammerschmidt *et al*. 2007). *Streptococcus pyogenes* produces M-protein (the major virulence factor of group A streptococci), Fba and Scl (streptococcal collagen-like) proteins, all of which bind to fH which thereby contributes to evasion of opsonization and complement attack (Johnsson *et al*. 1998; Kotarsky *et al*. 1998; Horstmann *et al*. 1992; Pandiripally *et al*. 2002; Reuter *et al*. 2010). The fH variant Y402H binds less efficiently to M6 protein of *S. pyogenes* (Yu *et al*. 2007; Ormsby *et al*. 2008), resulting in increased C3b deposition and phagocytosis (Haapasalo *et al*. 2008; Haapasalo *et al*. 2012). These functional data are supported by a genetic association study, which showed that the 402H variant is protective against streptococcal tonsillitis (Haapasalo *et al*. 2012). *Streptococcus suis* serotype 2 which causes sepsis in humans, produces Fhb (fH-binding protein). Fhb interacts with fH and counters complement activation (Pian *et al*. 2012). Likewise, proline-rich streptococcal β protein of *S. agalactiae* counters complement attack (Areschoug *et al*. 2002). Sbi (*Staphylococcus aureus* binder of IgG) protein of *S. aureus*, which forms a tripartite complex with fH and C3b, acts as a potent inhibitor of the AP (Haupt *et al*. 2008). SdrE is another surface protein by *S. aureus*, which binds fH to evade complement attack (Sharp *et al*. 2012).

Gram negative bacteria: *Neisseria gonorrhoeae* porin proteins, Por1A and its sialylated counterpart Por1B, bind to fH (Ngampasutadol *et al*. 2008; Ram *et al*. 1998a). fH mediates binding of *N. gonorrhoeae* to CR3-transfected cells (Agarwal *et al*. 2010). fH binding protein (fHbp), a surface lipoprotein, is present on the surface of all strains of *Neisseria meningitides* and binds to SCR6 of fH (Ram *et al*. 1999; Schneider *et al*. 2009) . Neisserial surface protein A (NspA), another *N. meningitidis* protein, interacts with fH to regulate complement activation (Lewis *et al*. 2012). Moreover, fH interacts with neisserial sialic acids *via* domains 16-20 (Ram *et al*. 1998b). fH binds to Tuf , the elongation factor in *Pseudomonas aeruginosa*, at the bacterial surface, which may facilitate tissue invasion (Kunert *et al*. 2007). *Borrelia burgdorferi* evades complement-mediated killing by interacting with complement regulators such as fH (and CFHRs) through distinct surface proteins such as, CRASPs (complement regulator-acquiring surface proteins) (Hammerschmidt *et al*. 2012; Alitalo *et al*. 2001; Kraiczy *et al*. 2001) and OspE (outer surface lipoprotein) (Hellwage *et al*. 2001). *Borrelia hermsii* binds to fH *via* FhbA (fH-binding protein A) (Hovis *et al*. 2006). *Escherichia coli* interacts with fH *via* Lipid A (Tan *et al*. 2011). Acquisition of fH or CFHL-1 on the Leptospira surface is crucial for bacterial survival in the serum and binding of these complement regulators is mediated by leptospiral immunoglobulin-like (Lig) proteins (Castiblanco-Valencia *et al*. 2012). *Leptospira interrogans* membrane protein LfhA binds fH, therefore contributing to the resistance of pathogenic leptospires to complement-mediated killing during leptospiremic phases of the disease (Verma *et al*. 2006). *Salmonella enterica* binds to fH *via* the outer membrane protein Rck (Ho *et al*. 2010). *Yersinia enterocolitica* can also recruit fH, which binds to the outer membrane proteins Ail and YadA (Biedzka-Sarek *et al*. 2008). *Rickettsia conorii* interacts with fH *via* membrane bound rOmpB and is resistant to complement attack (Riley *et al*. 2012).

Parasites: *Onchocerca volvulus* and *Echinococcus granulosus* bind fH and thereby protect themselves from complement (Lambris *et al*. 2008; Diaz *et al*. 1997).

Viruses: Interaction between fH and *Human immunodeficiency virus* (HIV) gp120 and gp41 proteins, suggests a possible and efficient mechanism of downregulation of the complement cascade at the surface of the virus (Pintér *et al*. 1995a; Pintér *et al*. 1995b; Sadlon *et al*. 1994; Stoiber *et al*. 1997).

PHENOTYPES

fH, a major regulator of alternative complement activation, prevents complement-mediated damage to host tissues and cells. Dysfunction of fH protein (through gene mutations, polymorphisms and auto-antibodies) results in several diseases (Rodríguez *et al*. 2004). The phenotypic outcome of CFH gene variants (mutations or polymorphisms) depends on their differential impact on fH function in plasma or on cell/tissue surfaces (Boon *et al*. 2009; de Córdoba and de Jorge 2008). The phenotypic spectrum includes: a. renal diseases, such as dense deposit disease (DDD) (also called membranoproliferative glomerulonephritis (MPGN) type II) (Licht *et al*. 2006; de Córdoba and de Jorge 2008; Boon *et al*. 2009; Józsi and Zipfel 2008) and atypical hemolytic uremic syndrome (aHUS)

(Warwicker *et al*. 1998; Richards *et al*. 2001) and b. ocular phenotypes, such as basal laminar drusen and age-related macular degeneration (AMD) (Troutbeck *et al*. 2012; Anderson *et al*. 2010). aHUS and DDD are associated with deficiencies and polymorphisms in other components of the alternative complement pathway as well, including C3, fB, fI and MCP(CD46). DDD is characterized by proliferation of mesangial and endothelial cells and by thickening of the peripheral capillary walls. The definitive diagnosis is made upon the presence of electron dense deposits in the glomerular basement membrane. Increased deposition of C3 protein in the glomeruli is observed (Appel *et al*. 2005; Smith *et al*. 2011), which occurs due to unregulated alternative pathway (AP). As fH is a key player in regulation of AP, dysfunction of fH due to mutations or auto-antibodies can result in DDD (Sugimoto *et al*. 2012; Appel *et al*. 2005; Dragon-Durey *et al*. 2004; de Córdoba and de Jorge 2008; Licht *et al*. 2009). Some of the fH mutations documented to cause DDD are homozygous cysteine-to-serine change in SCR7 of fH (Dragon-Durey *et al*. 2004) and homozygous deletion of Lys224 (Licht *et al*. 2006). Allelic variants associated with high risk of DDD are p.Tyr402His and p.Val62Ile (Abrera-Abeleda *et al*. 2011). The few known and characterized auto-antibodies against fH bind to the C3b binding region (i.e., SCRs1-4) of fH and cause disruption of AP regulation (Jokiranta *et al*. 1999; Goodship *et al*. 2012; Nozal *et al*. 2012).

aHUS is associated with AP dysregulation, caused by polymorphisms, mutations and deletions in complement genes (inherited), or by auto-antibodies (acquired) (Gnappi *et al*. 2012; Loirat *et al*. 2011; Geerdink *et al*. 2012). The SCR domains 18-20 alone are associated with around 30 missense mutations (Morgan *et al*. 2012; http://www.fh-hus.org/). Functional analyses of mutant fH proteins demonstrated that in several cases the interaction with C3b, heparin and/or endothelial cells is affected (Manuelian *et al*. 2003; Sánchez-Corral *et al*. 2002; Józsi *et al*.2006). The binding of fH to endothelial cells through cell surface polyanionic molecules (such as glycosaminoglycans, GAGs) and C3b is impaired in aHUS and is associated with endothelial damage (Kopp 2012; Józsi *et al*. 2004; Kajander *et al*. 2011; Morgan *et al*. 2011).The CFH gene can be affected by gene conversion and partial gene deletions, which result in hybrid fH proteins such as CFH/CFHR1 and CFH/CFHR3, causing impairment of the complement regulatory activity of fH at the cell surface (Heinen *et al*. 2006; Venables *et al*. 2006; Francis *et al*. 2012). Anti-fH auto-antibodies are detected in approximately 10% of aHUS patients (Goodship *et al*. 2012; Dragon-Durey *et al*. 2005; Józsi *et al*. 2008) and interfere with fH recognition functions (Józsi *et al*. 2007; Strobel *et al*. 2011; Strobel *et al*. 2010; Blanc *et al*. 2012). The development of fH auto-antibodies is associated with the deletion of the CFHR1 gene (Józsi *et al*. 2008; Dragon-Durey *et al*. 2009; Abarrategui-Garrido *et al*. 2009; Moore *et al*. 2010). aHUS-associated mutations in fH SCR20 and auto-antibodies can also inhibit the binding of fH to pentraxin (PTX3) and this may result in impaired complement regulation locally (Kopp *et al*. 2012).

The common polymorphism Y402H, located in SCR7 of fH, has been shown to be associated with AMD, which is the most common cause of visual loss in elderly people of developed countries (Edwards *et al*. 2005; Hageman *et al*. 2005). This polymorphism has been extensively studied *via* genetic and molecular methods (Haines *et al*. 2005; Edwards *et al*. 2005; Hageman *et al*. 2005; Klein *et al*. 2005; Lin *et al*. 2008; Montes *et al*. 2008; Lauer *et al*. 2011). Most of the functions of fH in complement regulation are accomplished through interacting with other molecules and cell. The 402H variant shows reduced binding to monomeric CRP (mCRP) (Sjöberg *et al*. 2007; Lauer *et al*. 2011; Skerka *et al*. 2007; Laine *et al*. 2007; Yu *et al*. 2007; Herbert *et al*. 2007; Ormsby *et al*. 2008), the ECM protein fibromodulin (Sjöberg *et al*. 2007), heparin (Clark *et al*. 2006; Blackmore *et al*. 1996) , malondialdehyde (Weismann *et al*. 2007), streptococcal M protein (Blackmore *et al*. 1996) and the Bruch's membrane (Clark *et al*. 2010). This polymorphism does not affect fH binding to retinal pigment epithelial cells (Ormsby *et al*. 2008). On the other hand, the fH 402H variant binds stronger to DNA and to necrotic cells than the 402Y variant (Sjöberg *et al*. 2007). In addition to the common risk haplotype carrying Y402H, other common protective and neutral haplotypes (Hageman *et al*. 2006; Hughes *et al*. 2006; Spencer *et al*. 2007) are also observed. A deletion of CFHR1 and/or CFHR3 genes in RCA gene cluster segregates with one of the protective CFH haplotypes (Hageman *et al*. 2006; Hughes *et al*. 2006). Additionally, CFH polymorphisms that reduce the risk of AMD have been identified (recent review by Kopp *et al*. 2012).

MAJOR SITES OF EXPRESSION

Liver (hepatocytes) is the main source of plasma fH. Other cells/tissues, which have been shown to produce fH include monocytes (Whaley 1980), fibroblasts (Katz and Strunk 1988), endothelial cells (Brooimans *et al*. 1990), keratinocytes (Timár *et al*. 2006), platelets (Devine and Rosse 1987), retinal pigment epithelial cells (Chen *et al*. 2007) and adipocytes (Moreno-Navarrete *et al*. 2010).

SPLICE VARIANTS

The CFH gene has one splice variant, CFHL-1 (also known as reconectin). The CFHL-1 protein (~43 kDa in size) includes SCR domains 1-7 of fH and four additional amino acid residues at the C-terminal end (Ripoche *et al*. 1988; Kristensen *et al*. 1986). Similarly to fH, the presence of SCRs 1-7 enables CFHL-1 to act as a co-factor for C3b degradation and as a decay acceleration factor (Kühn and Zipfel 1996; Kühn *et al*. 1995). It has been demonstrated that the first four N-terminal SCRs (SCRs 1-4) of CFHL-1, like fH, are essential and sufficient for both these activities (Kühn and Zipfel 1996; Kühn *et al*. 1995). In addition, a heparin-binding site has been localized to SCR7 of fH and CFHL-1 (Gordon *et al*. 1995). The SCR4 of both proteins includes the sequence Arg-Gly-Asp (RGD), a motif that is responsible for the major adhesive activity of matrix proteins like fibronectin (Hellwage *et al*. 1997). CFHL-1 has been shown to bind to pathogens such as *Borrelia burgdorferi* via BbCRASP (Kraiczy *et al*. 2001; Hartmann *et al*. 2006), *Borrelia hermsii via* FhbA (Hovis *et al*. 2006), *Candida albicans via* Gpm1p (Poltermann *et al*. 2007) and Pra1 (Luo *et al*. 2009), *Neisseria gonorrhoeae via* Por1A (Ram *et al*. 1998) and Por1B (Ngampasutadol *et al*. 2008), and *Streptococcus pyogenes via* Fba (Pandiripally *et al*. 2002) and M protein (Horstmann *et al*. 1988). However, the absence of SCR domains 8-20 prevents CFHL-1 from having a full-fledged surface binding activity. Also, this protein generally has a lower physiological concentration in plasma as compared to fH (Zipfel and Skerka 1999).

REGULATION OF CONCENTRATION

As such, fH is a key player in complement homeostasis, inhibiting excessive activation of the complement cascade, with an emphasis on the alternative pathway. Recently, fH serum concentrations have been measured in different age groups

using monoclonal antibodies and improved assays (Hakobyan *et al*. 2008). The mean fH concentrations were 233µg/mL in young adults and 269µg/mL in elderly individuals (Hakobyan *et al*. 2008). In a different study, an fH serum concentration of 263µg/mL was reported (Hakobyan *et al*. 2010). This corresponds to ~1.7 µM. Interferon (IFN)-γ induces increase of CFH expression by transcriptional activation by STAT1, and its suppression by oxidative stress is mediated by acetylation of FOXO3. This modification of FOXO3 enhances binding of FOXO3 to the CFH promoter, thereby reducing binding of STAT1 to the promoter and the expression of CFH (Wu *et al*. 2007). There is sufficient evidence of miRNAs that bind and regulate the CFH gene. miRNA-125b, miRNA-146a and miRNA-155 have high affinity binding sites in the CFH mRNA 3'-UTR, supportive of their roles in regulation of CFH and the immune response (Lukiw *et al*. 2012). Interleukin (IL)-27 increases the expression of CFH in the retina (Amadi-Obi *et al*. 2012). Several tumor cells have been reported to express increased amounts of fH and also proteins that bind fH. The latter belong to the SIBLING (small integrin-binding ligand, N-linked glycoproteins) family, such as bone sialoprotein, osteopontin and dentin matrix protein-1 (Junnikkala *et al*. 2000; Junnikkala *et al*. 2002; Ajona *et al*. 2004; Wilczek *et al*. 2004; Fedarko *et al*. 2000). These SIBLING proteins bind first to a cell surface receptor and then to fH. Increased secretion of these proteins blocks the lytic activity of the alternative pathway of complement by recruiting fH and thereby enables survival and metastasis of tumor cells. In fact, fH has been described as a diagnostic marker for lung adenocarcinoma (Cui *et al*. 2011). In addition, anti-fH autoantibodies have been documented in early non–small cell lung cancer, perhaps to control tumor progression, but whether they have only diagnostic or also functional relevance, is yet unclear (Amornsiripanitch *et al*. 2010; recent review by Kopp *et al*. 2012).

ANTIBODIES

Monoclonal and polyclonal antibodies that recognize human fH are available from various commercial sources, such as LSBio, OriGene, Quidel, CompTech, Enzo Life Sciences, and Everest Biotech.

Table 1: Functional States

STATE DESCRIPTION	LOCATION	REFERENCES
fH	extracellular region	Zipfel PF *et al.* 1999
proteo-fH (K)	Unknown	Saito A *et al.* 2008
proteo-fH (T)	extracellular region	Ohtsuka H *et al.* 1993
2(fH)	extracellular region	Nan R *et al.* 2011; Nan R *et al.* 2008; Perkins SJ *et al.* 2012
fH/ADM	extracellular space	Pio R *et al.* 2001; Martínez A *et al.* 2003
fH/IBSP	extracellular region	Fedarko NS *et al.* 2000
fH/αIIbβ3	plasma membrane	Vaziri-Sani F *et al.* 2005; Mnjoyan Z *et al.* 2008
fH/αMβ2	plasma membrane	Ross GD *et al.* ; DiScipio RG *et al.* 1998
fH/Osteopontin	extracellular region	Fedarko NS *et al.* 2000
fH/Thioredoxin	extracellular region	Inomata Y *et al.* 2008
fH/Fibrinogen	extracellular region	Horstmann RD *et al.* 1992
fH/Adiponectin	extracellular region	Kondo H *et al.* 2002; Peake P and Shen Y 2010
fH/Fibromodulin	extracellular region	Sjöberg A *et al.* 2005
C1q/fH/Fibromodulin	extracellular region	Sjöberg A *et al.* 2005
fH/Chondroadherin	extracellular region	Sjöberg AP *et al.* 2009
fH/fI	extracellular region	Blom AM *et al.* 2003; DiScipio RG *et al.* 1992; Ross GD *et al.* 1982; Soames CJ and Sim RB 1997
fH/C3d	extracellular region	Jokiranta TS *et al.* 2000; Lambris JD *et al.* 1988
fH/C3b	extracellular region	Farries TC *et al.* ; DiScipio RG *et al.* 1981; Jokiranta TS *et al.* 2000; Jokiranta TS *et al.* 2001; Soames CJ and Sim RB 1997
fH/PTX3	extracellular space	Bottazzi B *et al.* ; Braunschweig A and Józsi M ; Deban L *et al.* 2011; Deban L *et al.* 2008; Kopp A *et al.* 2012
fH/CRP	extracellular region	Hakobyan S *et al.* 2008; Jarva H *et al.* 1999; Mihlan M *et al.* 2009; Okemefuna AI *et al.* 2010; Pepys MB and Hirschfield GM 2003
fH/PrP	extracellular region	Sjöberg AP *et al.* 2008
fH/Thrombospondin	extracellular region	Vaziri-Sani F *et al.* 2005; Carron JA *et al.* 1996
fH/DMP1	extracellular region	Jain A *et al.* 2002
fH/SELL	plasma membrane	Malhotra R *et al.* 1999
fH-MDA	extracellular region	Weismann D *et al.* 2011
fH-GAGs	plasma membrane	Jokiranta TS *et al.* 2005; Prosser BE *et al.* 2007; Herbert AP *et al.* 2007
fH-Heparin	extracellular region	Blackmore TK *et al.* 1998; Blackmore TK *et al.* 1996; Pangburn MK *et al.* 1991; Sahu A and Pangburn MK 1993
fH-DNA	extracellular region	Leffler J *et al.* 2010; Sjöberg AP *et al.* 2007
fH-Zinc	extracellular region	Nan R *et al.* 2008
fH/Annexin2	extracellular region	Leffler J *et al.* 2010
fH/Histone2[a,b]/Histone1	extracellular region	Leffler J *et al.* 2010
fH/Histone[3,4]	extracellular region	Leffler J *et al.* 2010
fH/CRASP (B. burgdorferi)	extracellular region	Hammerschmidt C *et al.*
fH/OspE (B. burgdorferi)	extracellular region	Hellwage J *et al.* 2001
fH/FhbA (B. hermsii)	extracellular region	Hovis KM *et al.* 2006
fH/CaGpm1p (C. albicans)	extracellular region	Poltermann S *et al.* 2007
fH/Pra1 (C. albicans)	extracellular region	Luo S *et al.* 2009
fH-Lipid A (E. coli)	extracellular region	Tan LA *et al.* 2011
fH/HIV-gp41 (HIV)	extracellular region	Pintér C *et al.* 1995
fH/HIV-gp120 (HIV)	extracellular region	Pintér C *et al.* 1995; Sadlon TA *et al.* 1994
fH/Lig (L. interrogans)	extracellular region	Castiblanco-Valencia MM *et al.* 2012
fH/LfhA (L. interrogans)	extracellular region	Verma A *et al.* 2006
fH/fHbp (N. meningitidis)	extracellular region	Schneider MC *et al.* 2009
fH/NspA (N.meningitidis)	extracellular region	Lewis LA *et al.* 2012
fH/Por1 (N. gonorrhoea)	extracellular region	Ngampasutadol J *et al.* 2008; Ram S *et al.* 1998
fH/TufB (P. aeruginosa)	extracellular region	Kunert A *et al.* 2007
fH/rOmpB (R. conorii)	extracellular region	Riley SP *et al.* 2012
fH/beta protein (S. agalactiae)	extracellular region	Areschoug T *et al.* 2002
fH/Sbi (S. aureus)	extracellular region	Haupt K *et al.* 2008
fH/Sbi/C3d (S. aureus)	extracellular region	Haupt K *et al.* 2008
fH/SdrE (S. aureus)	extracellular region	Sharp JA *et al.*
fH/ScGpm1p (S. cerevisiae)	extracellular region	Poltermann S *et al.* 2007
fH/Rck (S. enterica)	extracellular region	Ho DK *et al.* 2010
fH/PspC (S. pneumoniae)	extracellular region	Dave S *et al.* 2004

fH/M-Protein (S.pyogenes)	extracellular region	Sharma AK and Pangburn MK 1997; Horstmann RD *et al.* 1992; Horstmann RD *et al.* 1988
fH/Fba (S. pyogenes)	extracellular region	Pandiripally V *et al.* 2002
fH/Scl (S. pyogenes)	extracellular region	Reuter M *et al.* 2010
fH/Fhb (S. suis)	extracellular region	Pian Y *et al.* 2012
fH/Ail (Y. enterocolitica)	extracellular region	Biedzka-Sarek M *et al.* 2008; Ho DK *et al.* 2012
fH/YadA (Y. enterocolitica)	extracellular region	Biedzka-Sarek M *et al.* 2008

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SUPPLEMENTARY

Supplementary information is available online.

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This molecule exists in 60 states , has 60 transitions between these states and has 1 enzyme functions.(Please zoom in the pdf file to view details.)