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 (complement); H factor 2 (complement); HF; HFI; HF2; HUS

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PROTEIN FUNCTION
Complement factor H (fH, beta 1H globulin or beta1H) 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) (Whalley 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(H2O)) (at a low-rate activation called tick-over) in host plasma (Pangburn et al. 1981). C3(H2O) then binds to complement factor B (fB), which is then cleaved by complement factor D (fD) to form a C3 convertase (C3(H2O)Bb) (Fishehlo 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 C3bB (this is stabilized by Properdin (IP) as C3bBF 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; Schoepf 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 SCR8-18 (Jokiranta et al. 1996; Jokiranta et al. 2000; Wu et al. 2009). Further, fH having dual binding sites for C3b and glycosaminoglycans (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 al. 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 αMβ2 (CR3) and αMβ1, respectively. Monocytes (Kang et al. 2012) and neutrophils (Avery and Gordon 1993; Ross 2002; DiScipio et al. 1998) use the β2 integrin receptor αMβ2 (CR3, CD11b/CD18, αMβ2 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 fH release (Lambris et al. 1980). The fH receptor on B cells remains unidentified. Resting platelets use the β3 integrin receptor αIIbβ3 and this binding is increased when platelets become activated (Vaziri-Sani et al. 2005; Mnjoyan et al. 2008). This fH binding to platelets through αIIbβ3 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 αMβ2, 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 phosphoglycercate mutase (CaGmp1p) 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 CFHRI, 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 phosphoglycercate mutase (ScGmp1p) 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 (Neelam 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 (αMβ2), 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). SdE 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 meningitidis and bends 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; Kraicz 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 leptospirales to complement-mediated killing during leptospiremia 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 tOmpB 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. 1997; 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 (Rodriguez 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).
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 (Weissmann 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 (Brookmans 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; Kuhn 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; Kuhn 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 FlhA (Hovis et al. 2006), Candida albicans via Gpm1p (Pollermann et al. 2007) and Pral1 (Luo et al. 2009), Neisseria gonorrhoeae via PorA (Ram et al. 1998) and PorB (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.
| 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; Martinez A et al. 2003 |
| fH/IBSP           | extracellular region | Fedarko NS et al. 2000 |
| fH/IlbB3          | plasma membrane | Vaziri-Sani F et al. 2005; Mnjoyan Z et al. 2008 |
| fH/Mb2            | 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; Lambiris JD et al. 1988 |
| fH/C3b            | extracellular region | Farnies 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; Iwata H et al. 1999; Mihlan M et al. 2009; Okemefuna Al 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/Calp1p (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/LfaA (L. interrogans) | extracellular region | Verma A et al. 2006 |
| fH/Hbp (N. meningitidis) | extracellular region | Schneider MC et al. 2009 |
| fH/NspA (N. meningitidis) | extracellular region | Lewis LA et al. 2012 |
| fH/Orf1 (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/OmpB (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/ScI (S. pyogenes)     | extracellular region | Reuter M et al. 2010                                                 |
| fH/Fhb (S. suis)         | extracellular region | Pian Y et al. 2012                                                   |
| fH/AiI (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.)