Regulation of regulators: role of the complement factor H-related proteins

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Abbreviations:
aHUS, atypical hemolytic uremic syndrome; AMD, age-related macular degeneration; AP, alternative pathway; C3G, C3 glomerulopathy; C4BP, C4b binding protein; CCP, complement control protein; CP, classical pathway; CR1, complement receptor type 1; CRP, C-reactive protein; DAF, decay accelerating factor; ECM, extracellular matrix; FH, factor H; FHL-1, factor H-like protein 1; FHR, factor H-related protein; GAG, glycosaminoglycan; IgAN, IgA nephropathy; LP, lectin pathway; MBL, mannose binding lectin; MCP, membrane cofactor protein; MDA, malondialdehyde; PTX3, pentraxin 3; RCA, regulators of complement activation; SLE, systemic lupus erythematosus

Abstract
The complement system, while being an essential and very efficient effector component of innate immunity, may cause damage to the host and result in various inflammatory, autoimmune and infectious diseases or cancer, when it is improperly activated or regulated. Factor H is a serum glycoprotein and the main regulator of the activity of the alternative complement pathway. Factor H, together with its splice variant factor H-like protein 1 (FHL-1), inhibits complement activation at the level of the central complement component C3 and beyond. In humans, there are also five factor H-related (FHR) proteins, whose function is poorly characterized. While data indicate complement inhibiting activity for some of the FHRs, there is increasing evidence that FHRs have an opposite role compared with factor H and FHL-1, namely, they enhance complement activation directly and also by competing with the regulators FH and FHL-1. This review summarizes the current stand and recent data on the roles of factor H family proteins in health and disease, with focus on the function of FHR proteins.

Keywords: alternative pathway; complement; deregulation; factor H; factor H-related protein; inflammation

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1. Introduction

The immune system is an important defense system of our body. Its main function is to recognize host-, altered host and foreign structures, and protect against infections and tumors. It responds with tolerance to materials recognized as harmless self, while eliminating structures that are recognized as dangerous. The immune system performs recognition, transmitting and executing functions. Two major branches of the immune system were formed during evolution, the ancient innate immune system and the phylogenetically more recent adaptive immune system, which are intricately interconnected and act in cooperation with each other. The innate immune system primarily recognizes certain conserved molecular patterns associated with pathogens, whereas the elements of the adaptive immune system recognize with high specificity the different protein and non-protein type antigenic epitopes. The complement system is an important humoral component of innate immunity, one of our first defense lines. The inadequate functioning of the complement system, e.g. its deficiencies, misguided or exaggerated activation, plays a role in the development and course of various diseases [1, 2].

Because complement is an ancient component of multicellular organisms, molecules of this system are integrally involved in multiple host systems and organ functions, thus the complement system is richly interconnected with diverse other systems in our body, exhibiting canonical and non-canonical ("non-complement") functions [3]. Here, we focus on discussing especially the regulation of the alternative pathway of complement activation by factor H family proteins in health and disease.

2. The complement system – its activation and regulation

The complement system is composed of over 40 proteins, including soluble components, soluble and cell-bound regulatory molecules, and cell surface receptors. As an efficient effector arm of the innate immune system, complement plays a role in the removal of pathogens and other dangerous particles, such as immune complexes, cellular debris and dead cells; in inflammatory processes and activation of various cells, and bridges innate and adaptive immunity [1, 2, 4]. Depending on the activation trigger, the complement cascade follows one of three pathways: the classical (CP), the lectin (LP) or the alternative pathway (AP) (**Fig. 1**). The complement system in general is inactive until it is activated by various danger signals; however, as a monitoring and safe-guarding system, the AP is constantly active at a low level to detect the presence of pathogens and altered self. As a result of infection, activation of complement leads to opsonization, phagocytosis, and destruction of the pathogen, initiation of inflammation, and finally activation of the adaptive immune response [2].

Complement activation is primarily initiated by the recognition of certain structures via pattern recognition molecules. Recognition molecules that initiate complement activation are C1q in the CP, and mannose binding lectin (MBL), ficolins and collectins in the LP. There are no traditional recognition molecules for the AP that would trigger complement activation; although such a function was described for properdin, this was recently challenged [5, 6]. The complement system recognizes different microorganisms and pathogen-associated molecular patterns by soluble pattern recognition molecules. In the CP, C1q primarily recognizes the immune complexes of IgG and IgM, and binds to the Fc portion of the antibody molecules in the complex, but is also able to activate the CP in an antibody independent manner by binding to the pentraxins C-reactive protein (CRP) and pentraxin 3 (PTX3), polyanionic structures such as RNA and DNA, certain extracellular matrix proteins, altered - potentially dangerous - self structures such as beta-amyloid, prion protein, apoptotic cells and necrotic cells, as well as microbial ligands like LPS [4, 7]. MBL, collectins and ficolins of the LP bind to various carbohydrate structures.

Activation of the proteases associated with the recognition molecules of the CP and LP lead to the cleavage of C4 and C2, and the formation of the C4b2a convertase that cleaves C3

into the anaphylatoxin C3a peptide and the opsonic molecule C3b. The AP is constantly activated at a low rate by the spontaneous hydrolysis of the thioester bond in C3 and the formation of the initial C3(H_2O)Bb convertase, which also cleaves C3 into C3a and C3b. Through the active thioester group in C3b and C4b, these opsonic complement fragments can covalently attach to various surfaces and molecules via ester or amide bonds and generate the surface bound C3bBb AP C3 convertase and the C4b2a CP/LP C3 convertase enzymes, respectively. Subsequently, these convertases, by cleaving additional C3 molecules, generate further C3b and C3bBb. Thus, the AP auto-amplifies, as the generated C3b forms the core of a new AP C3 convertase, and activation of the CP or LP automatically turns the AP on. C3b when bound to these convertases generates the C5 convertase enzymes of the CP/LP and the AP, i.e. C4bC2aC3b and C3bBbC3b, respectively. Cleavage of C5 into the anaphylatoxin C5a and the terminal pathway initiator fragment C5b can lead to inflammation and the formation of the lytic membrane attack complex (**Fig. 1**).

To focus complement activation on proper targets and prevent damage to the host, the system is delicately regulated by fluid-phase and surface bound molecules, which control activation in body fluids and on various cellular and non-cellular (such as basement membranes) surfaces [1, 3, 7-9]. Several of the regulatory molecules are coded in chromosome 1q32, forming the human "regulators of complement activation (RCA) gene cluster". One RCA region harbours genes encoding C4b binding protein (C4BP), decay accelerating factor (DAF), complement receptor type 1 (CR1) and membrane cofactor protein (MCP), the other region includes the genes encoding members of the factor H (FH) protein family.

Regulation occurs at all main levels of the complement cascade. C1-inhibitor inactivates the proteases that associate with the recognition molecules of the CP and LP. The CP and LP are also inhibited at the level of C4b by the fluid-phase regulator C4BP, and at the level of C3b by C4BP, and the membrane regulators CR1, MCP and DAF. C4BP, CR1 and MCP are cofactors for the serine protease factor I in the proteolytic inactivation of C4b and C3b. CR1 and DAF can also accelerate the decay of the C3 and C5 convertases. The AP in the fluid-phase is inhibited by FH, which is also a convertase decay accelerator molecule and a cofactor for factor I in the cleavage of C3b. Properdin is a positive regulator and stabilizes the C3bBb convertase. The formation of the terminal complex of the complement system is regulated by the soluble vitronectin and clusterin, and the cell membrane-anchored CD59 molecule [1, 4].

3. The human factor H protein family – structure, ligands, and function

Six genes in tandem arrangement in the RCA cluster encode the serum glycoproteins that constitute the human FH protein family (**Fig. 2**). Among these proteins, FH and FH-like protein 1 (FHL-1) are encoded by the *CFH* gene, and the factor H-related proteins (FHR-1 to FHR-5) are encoded by the *CFHR1*, *CFHR2*, *CFHR3*, *CFHR4* and *CFHR5* genes [10-12]. These genes arose through partial gene duplications, rendering this genomic region prone to rearrangements (see also **section 4**). The FH family proteins are all exclusively composed of individually folding globular domains called complement control protein (CCP) domains (also termed Sushi domains or short consensus repeats, SCRs). The domains of the FHR proteins show varying degree of amino acid sequence identity to the homologous domains in FH and/or other FHR proteins; however, in general FHRs lack domains homologous to FH CCPs 1-4, i.e. the FH domains that mediate the complement activation inhibiting effects, but they are present in FHL-1 (**Fig. 2**).

The main source of these proteins is the liver, but several cell types were reported to produce locally FH and/or FHL-1, such as monocytes, dendritic cells, endothelial cells, fibroblasts, retinal pigment epithelial cells and keratinocytes [13-20]. FH and FHL-1 are inhibitors of the alternative complement pathway. The function of the FHR proteins is less

characterized and in part controversial [11]. While some forms of complement inhibiting activity have been described for the FHRs, recent data strongly support a role opposite to that of FH and FHL-1 for the FHRs in complement activation: direct facilitation of alternative pathway activation by binding C3b and promoting formation of the C3 convertase C3bBb, and indirect enhancement of alternative pathway activation by competing with the regulators FH and FHL-1 [9, 11, 21-26]. In addition, FHRs may influence complement activation by interacting with other host molecules, e.g. by recruiting pentraxins that can bind C1q and allow for CP activation, or being recruited by CRP and thus enhance AP activation [23, 24, 27, 28].

3.1. Factor H

FH is the main soluble regulator protein of the alternative pathway [29-31]. It is composed of 20 CCP domains, of which the N-terminal four domains mediate binding to C3b and are responsible for the complement activation inhibiting activity of FH. While CCPs 1-4 are sufficient for the complement regulatory activity [32, 33], a recent report indicates contribution of the other adjacent CCP domains (also present in FHL-1) to a more pronounced regulatory activity of FH [34]. FH affects the C3bBb convertase in two ways: it competes with factor B for binding to C3b, thus prevents formation of the C3bBb convertase, and also accelerates the decay of this convertase once already formed ("decay accelerating activity"). In addition, FH regulates the C3b-containing C5 convertases. FH also acts as a cofactor for factor I in the inactivation of C3b ("cofactor activity"). FH interacts with many other ligands, both in body fluids and on various surfaces, several of them also directing its regulatory activity to cell surfaces or to extracellular matrices, e.g. basement membranes (reviewed in more detail elsewhere: [9, 35-37]). The major ligand and surface recognition domains reside in CCPs 6-7 and 19-20 of FH; importantly, these domains are variably conserved in the FHR proteins (see below in **sections 3.3-3.7**) (**Fig. 2.**) [11]. Thus, FH inhibits alternative pathway activation in blood plasma and other body fluids, as well as on cellular and noncellular surfaces. CCPs 19-20 harbour a sialic acid binding site that is critical in the differentiation between self and nonself by FH [38-42].

FH has two major C3b binding sites, in CCPs 1-4 and 19-20 [43]. The latter site is specialized to bind C3b or its degradation product C3d when covalently bound on a self surface, and this binding is facilitated by interaction of FH with cell surface sialic acid moieties [40, 41, 44, 45]. Thus, FH can recognize host cells that are attacked by complement and, by binding to this surface, down-regulate complement activation and protect the host. Cell surface polyanionic molecules, as markers of self, represent important ligands for FH, including heparin and other glycosaminoglycans (GAGs) and sialic acids [42]. The composition of the glycomatrix varies at different anatomic sites and can determine which GAG site in FH mediate the binding and thus also influencing the strength of the interaction of this complement regulator with various surfaces. It was demonstrated that FH uses primarily the GAG site in CCPs 6-7 for binding to the Bruch's membrane in the eye, whereas the GAG site in CCPs 19-20 is responsible for binding to the glomerular basement membrane [15, 46].

FH can be recruited to other host surfaces, e.g. to extracellular matrices and apoptotic or necrotic cells, and protect these surfaces from overwhelming complement activation. FH binds to certain extracellular matrix proteins, such as fibromodulin, osteoadherin and chondroadherin, while it does not bind to biglycan, decorin and lumican [47-49]. On dead cells, identifed FH ligands include DNA, Annexin II and histones [50, 51]. In addition, FH may bind through soluble pattern recognition molecules, such as the pentraxins CRP and PTX3, which target the complement inhibiting activity of FH to these surfaces [52-56]. Malondialdehyde (MDA) epitopes generated upon oxidative stress are also recognized by FH, thus FH can inhibit local complement activation and inflammation on cellular debris and accumulated waste material [57, 58]. These ligands are all bound via binding sites in CCPs 6-7 and 19-20, although

the avidity and specificity of these interactions are apparently different and need to be further investigated.

CCPs 6-7 and 19-20 also mediate self-association of FH, which might be facilitated by zinc or polyanionic molecules such as heparin [59-61]. To clarify the physiological or pathological relevance of this self-association property, further studies are needed.

The plasma concentration of FH is relatively high in comparison with the FHR proteins. Average FH levels of 233-400 µg/ml (in some cases, even higher concentrations) were reported, but recent assays using well-characterized antibodies and excluding co-measurement of FHL-1 and the FHRs found consistently ~230 µg/ml [62-66].

3.2. FHL-1

FHL-1 is derived from the *CFH* gene by alternative splicing. It contains the N-terminal seven CCP domains of FH, and four additional amino acids encoded by exon 10 that is only transcribed in FHL-1 (Ser-Phe-Thr-Leu [SFTL]) [67, 68]. FHL-1 lacks the FH CCP 8-20 domains and thus the C-terminal sialic acid binding site, and has different cell surface specificity and different role than FH in complement control on surfaces [34, 46]. Due to the shared domains with FH, FHL-1 also binds C3b and has cofactor and convertase decay accelerating activities [33]; it also binds to several other FH ligands with CCPs 6-7. It has been reported that the C-terminal unique four amino acids influence the interaction of FHL-1 with CRP and PTX3 [69]. Clark *et al.* reported that the retinal pigment epithelial cells in the eye are able to express FHL-1, and FHL-1 can passively diffuse into the Bruch's membrane (the innermost layer of the choroid), while due to its size FH is not able to go through this membrane [15]. Thus, FHL-1 is probably the main complement inhibitory molecule that provides greater protection at the key site of age-related macular degeneration (AMD) at the Bruch's membrane than does FH [15]. It was shown that FHL-1 and the FH CCPs 6-8 fragment could not bind to sialylated oligosaccharides [70], explaining the dominant role in host surface recognition of CCPs 6-7 at the Bruch's membrane in the eye and CCPs 19-20 at the glomerular basement membrane in the kidney.

Due to the lack of available FHL-1 specific antibodies, no reliable data on serum FHL-1 concentration exist. One study reported an average FHL-1 serum concentration of 47 µg/ml, determined from two samples [17]. Several recent studies that reported FH concentrations used antibodies that do not detect the FHR proteins; however, these reported FH concentrations often include the concentration of FHL-1, too.

3.3. FHR-1

FHR-1 consists of five CCP domains (**Fig. 2**), and has a molecular weight of 37 kDa (FHR-1α) or 43 kDa (FHR-1β), depending on the number of N-linked carbohydrate chains [71, 72]. Two allelic variants have been described, FHR-1*A (acidic isoform) and FHR-1*B (basic isoform). The CCP3 domain of FHR-1*B is identical to CCP18 of FH, whereas CCP3 of FHR-1*A differs from it in three amino acids [73]. As a consequence of the high sequence identity between CCPs 4-5 of FHR-1 and CCPs 19-20 of FH (with FHR-1 CCP4 being identical to FH CCP19, and the most C-terminal domains differing only in two amino acids), FHR-1 is also able to bind several ligands of FH. For example, FHR-1 can bind to C3b, heparin, pentraxins (PTX3, CRP) and certain microbial surface molecules [24, 74-80]. The role of FHR-1 in complement regulation is controversial and discussed in **sections 3.8**-**3.10** in more detail.

The two N-terminal domains (CCPs 1-2) of FHR-1 are remarkably similar to CCPs 1-2 of FHR-2 and FHR-5, and have been shown to mediate "head to tail" dimerization [81]. Circulating FHR-1 homodimers and FHR-1/FHR-2 heterodimers have been detected *ex vivo* [82].

FHR-1 is certainly the most abundant glycoprotein among the FHRs, yet its plasma concentration is still controversial. A number of studies established a concentration of ~40–100 µg/ml [72, 77, 83, 84], although ~10-fold lower levels have more recently been reported [82, 85]. The reason behind the notable deviation might be explained in part by the use of different antibodies and ELISA set-ups and by the variation in frequency of a common deletion polymorphism of the *CFHR1* and *CFHR3* genes (del*CFHR3-CFHR1*) among different populations [86]. The del*CFHR3-CFHR1* allele is most frequent in African regions, whereas the lowest frequency is seen within East Asia and South America [86]. This double gene deletion is associated with lower FHR-1 levels in heterozygotes and complete FHR-1 deficiency in homozygotes, and is variably associated with diseases (see **section 4**). Beside the population-dependency of the del*CFHR3-CFHR1* polymorphism, other factors may also influence the accurate measurement of FHR-1 levels, e.g. the existence of FHR-1/FHR-2 heterodimers [82] and the ability of FHR-1 to interact with high-density lipoprotein particles [87] or cells [78].

3.4. FHR-2

FHR-2 consists of four CCP domains. It exists in serum in a non-glycosylated (24 kDa) and a glycosylated (29 kDa) form. The N-terminal CCPs 1-2 are distantly related to FH CCPs 6-7 (41% and 34% amino acid sequence identity), and its C-terminal CCPs are less similar to FH CCPs 19-20 compared with FHR-1 (89% and 61% sequence identity, respectively) (**Fig. 2**) [88]. The FHR-2 CCP1 and CCP2 domains exhibit a high degree of similarity to the CCPs 1-2 domains of FHR-1 and FHR-5, and these domains mediate dimerization of the proteins [81]. *Ex vivo* FHR-2 homodimers and FHR-1/FHR-2 heterodimers have been described; the existence of FHR-2/FHR-5 heterodimers is controversial [82, 89]. The serum concentration of FHR-2 homodimers is approximately 3 µg/ml. Due to the very low concentration, FHR-2 is the limiting factor in the formation of FHR-1/FHR-2 heterodimers; therefore, most FHR-2 are present in heterodimer form in serum [82]. FHR-2 deficiency has not yet been described, but hybrid proteins containing FHR-2 domains were identified (see later in **section 4**).

3.5. FHR-3

FHR-3 is composed of five CCP domains, each showing a remarkable sequence identity with the CCP domains of FH or other FHR proteins, especially with FHR-4 [90]. CCPs 1 and 2 of FHR-3 are homologous to CCPs 6 and 7 of FH (91 and 85% similarity, respectively), whereas the C-terminal domains of FHR-3 (CCPs 3-5) demonstrate a high level of sequence identity (>93%) with CCPs 2, 4, 6, 8 and 9 of FHR-4A and CCPs 2, 4 and 5 of FHR-4B (**Fig. 2**). Due to the presence of homologous domains, FHR-3 shares some binding characteristics with FH; thus, it is able to bind C3b and heparin [91]. Multiple forms of FHR-3 are detected in plasma with molecular weights ranging from 37 to 50 kDa, likely representing differentially glycosylated proteins [12, 73].

Similar to FHR-1, the serum concentration of FHR-3 is strongly influenced by the presence of the del*CFHR3-CFHR1* allele. The mean concentration is estimated to be 0.81 µg/ml (22 nM) in healthy individuals carrying two *CFHR3* genes and about 2-fold lower in individuals with only one *CFHR3* gene copy [92]. Interestingly, serum levels are also determined by *CFHR3* gene variants [93]. Two genetic variants, *CFHR3*A* and *CFHR3*B* have been reported [94]. A common polymorphism (c.721C>T) in exon 5 results in a proline to serine change in CCP4 of FHR-3 and was observed to associate with higher levels of FHR-3, thus allele *CFHR3*B* (coding for serine in position 241) is considered a high-expression allele and is associated with increased risk of the kidney disease atypical hemolytic uremic syndrome (aHUS) [94]. The del*CFHR3-CFHR1* allele was shown to have protective effect in AMD [95].

3.6. FHR-4

CFHR4 is the only *CFHR* gene from which two splice variants are expressed, FHR-4A and FHR-4B [96, 97], although the existence of the latter has recently been questioned [98]. FHR-4A consists of 9 CCP domains (86 kDa), from which CCPs 1-4 show high similarity to CCPs 5-8, probably as a result of a partial, internal gene duplication (**Fig. 2**) [96]. FHR-4B consists of 5 CCP domains (43 kDa); all these are also present in FHR-4A. The sequence of FHR-4B CCP1 is 98% identical to FHR-4A CCP1, and FHR-4B CCPs 2-5 have 100% sequence identity to FHR-4A CCPs 6-9. Like FHR-3, both variants lack the N-terminal dimerization motif characteristic of FHR-1, FHR-2 and FHR-5.

The total amount of FHR-4A and FHR-4B in serum was previously determined as 25.4 μg/ml [26]. Recently, novel well-characterized FHR-4A specific monoclonal antibodies have been applied to determine FHR-4 serum levels; this novel ELISA measured 10 times lower FHR-4A concentration (2.55 ± 1.46 μg/ml) in serum. It is very challenging to generate an FHR-4B specific antibody because FHR-4B domains are practically identical with those of FHR-4A. FHR-4B was not detectable in plasma with different monoclonal antibodies, which in turn recognized the recombinant FHR-4B [98]. This may mean that the FHR-4B serum concentration is so low that it is not detectable, or it is absent from serum. FHR-4 is also capable of binding to the central molecule of the complement system, C3b [26, 91, 99]. It has been reported that FHR-4 is able to activate complement, and bind to pentameric CRP and participate in the opsonization of necrotic cells by pCRP binding [26-28].

3.7. FHR-5

FHR-5 (65 kDa) which was identified in human glomerular complement deposits [100] is special among the FHRs because it contains CCPs homologous to the middle part of FH (**Fig. 2**). FHR-5 consists of nine domains that are related to CCPs 6-7, CCPs 10-14 and CCPs 19-20 of FH, but the two N-terminal domains of FHR-5, which are responsible for dimer formation, are more similar to CCPs 1-2 of FHR-1 and FHR-2 (>85%) [82, 100]. However, *in vivo* it seems that FHR-5 mostly exists as homodimers, raising difficulties in determining serum concentrations [82]. Serum concentration of FHR-5 in the range of 3-6 μg/ml was initially reported [101], which was essentially confirmed by recent studies reporting 2.46 μg/ml [83] and 1.66 μg/ml [82] concentrations. However, it was also demonstrated that locally, under specific conditions such as inflammation or infection, FHR-5 serum level can be increased [83, 102].

Due to the sequence similarity, FHR-5 binds to some FH ligands, such as C3b, heparin, pentraxins (mCRP, PTX3) and ECM but, contrary to FH, FHR-5 rather enhances complement activation on surfaces and allows alternative pathway C3 convertase assembly [23, 101, 103]. Moreover, FHR-5 competes with FH for binding to different ligands and surface molecules and inhibits FH regulatory activity, a process which is termed FH deregulation [23, 81].

3.8. Data supporting complement regulatory roles for the FHR proteins

Early studies on the FHRs investigated their potential complement inhibiting capacity, based on their interaction with C3b and assuming functional analogy with FH. Indeed, recombinant FHR-3 and FHR-4 were able to act as cofactors for factor I in C3b cleavage when applied at very high concentrations (400 μg/ml). In addition, both FHRs enhanced the cofactor activity of FH [91]. Later, a strong cofactor activity, although at supraphysiological concentrations, was also reported for FHR-3 [104]. Similarly, for FHR-5 weak cofactor activity and fluid phase C3 convertase inhibiting activity were reported [101]. FHR-2 was shown to have neither cofactor nor decay accelerating activity but to be capable of binding to C3b and C3d; FHR-2 was also shown to inhibit the activity of the C3bBb convertase [105].

In addition, inhibition at the C5 level and/or the terminal pathway (lysis) was reported for FHR-1 [77, 104], FHR-2 [105] and FHR-3 [104]. FHR-1 was studied by several other groups and they found no terminal pathway inhibiting activity [24, 81, 106, 107]. On the other hand, human FHR-1 expressed in the brain in a mouse model of neuromyelitis optica spectrum disorders by applying engineered neural stem cells protected astrocytes from complement activation and terminal complement complex formation [108]. Recently, FHR-5 was found to inhibit both the alternative and the classical pathway C5 convertases in a bead based *in vitro* model [109]. In these latter assays, the effective FHR-5 concentrations were close to serum levels measured in samples from healthy donors or patients with glomerulonephritis [82, 83, 101, 110].

Recent studies re-evaluated the serum levels of the FHR proteins, and found that they are in general much lower than previously estimated [82, 92, 98]; this issue is reviewed in more detail in [9]. Thus, the above activities of the FHRs need to be further studied, either confirmed or disproved. Even if some of the reported regulatory functions prove real when high concentrations of the FHRs are applied, questions remain regarding their physiological relevance when such concentrations and conditions do not occur *in vivo*. Some discrepancies may be related to the different assay conditions, e.g. fluid-phase *versus* surface assays.

3.9. FHR proteins as positive regulators of complement activation

In recent years, accumulating data on the FHR proteins strongly indicate a role for them in complement activation that stands in sharp contrast to that of FH and FHL-1. While initially – due to their structural similarity with FH – only complement inhibiting activities were investigated, later studies revealed that FHRs can enhance complement activation both directly and indirectly (i.e., via competing with FH). Thus, they emerge as "regulators of the regulators", namely competitive inhibitors of FH (and possibly FHL-1), resulting in de-regulation of complement activation (**Fig. 3**) [11, 81].

Competition between FHRs and FH for binding to several ligands was described. FHR-1, FHR-3, FHR-4 and FHR-5 were shown to variably compete with FH for binding to C3b; some of these differential effects may be related to the different avidities also determined by homo- or heterodimerization of FHR-1 and FHR-5 [77, 81, 104, 111]. In addition, FHR-5 can strongly inhibit FH binding to the pentraxins CRP and PTX3, as wells as to extracellular matrix and malondialdehyde-acetaldehyde epitopes, and enhance alternative pathway activation [23, 103]. In similar assays, FHR-1 was less effective in inhibiting FH binding to CRP and enhancing complement activation, despite the conserved pentraxin binding site in the C terminus of FHR-1 [24]. This is likely explained by the lower avidity of FHR-1 for the relatively low density CRP and deposited C3b under the assay conditions. However, recruitment of mCRP by FHR-1 can result in classical pathway activation by allowing interaction of C1q with FHR-1 bound mCRP [24].

For FHR-1, FHR-4 and FHR-5 it was shown that, by binding C3b, they can serve as a platform for the assembly of a functionally active C3bBbP convertase, and enhance activation of the alternative pathway [23, 24, 26]. FHR-5 was also reported to recruit properdin via the CCPs 1-2 and thus activate the alternative pathway [21]. Both FHR-1 and FHR-4 were shown to activate the classical pathway (C4 deposition) by binding CRP, the monomeric CRP form (FHR-1) or the native, pentameric CRP (FHR-4) [24, 27, 28].

While non-human FHRs have not yet been characterized in detail, recent functional studies on murine FHR proteins also support a role for them in the enhancement of complement activation by competing with FH and by C3b binding and convertase assembly [112, 113].

These functions also need to be studied further, especially for their physiological relevance. However, the association of enhanced complement activation with elevated FHR levels or pathological, avidity gain-of-function dimerization mutants of FHR-1, FHR-2 and

FHR-5 in diseases such as IgA nephropathy (IgAN) and C3 glomerulopathy (C3G), as well as protection against AMD in the absence of FHR-1 and FHR-3, are strongly suggestive of a major role of FHRs in balancing FH (and FHL-1) mediated inhibition and thus regulating the prime regulators of the AP (see **section 4**).

3.10. Microbial ligands of factor H family proteins and role in infectious diseases

A major function of host complement is to provide immediate protection from infectious agents by opsonization and supporting opsonophagocytosis, initiation of inflammatory processes and complement-mediated cell lysis [2]. However, during co-evolution with their hosts, several pathogenic microbes acquired means to evade recognition and elimination assisted by the complement system. One of the commonly used microbial strategies is to bind host complement regulators, such as FH, FHL-1, C4BP, and vitronectin, to inhibit the AP, CP, LP, and the terminal complement pathway [114-116].

Binding of FH provides microbial protection by inhibiting the assembly of the alternative pathway C3 convertase and by accelerating the decay of already formed convertases, thus preventing further activation and amplification of the complement cascade. Two major microbial interaction sites have been described in FH: one within CCPs 6 and 7, the other within the carboxyl-terminal domains CCPs 19 and 20 [115, 117]. The majority of microbes utilize both sites for an efficient protection; however, pathogens like *Streptococcus pyogenes* and *Treponema denticola* bind only via CCPs 6-7 [118, 119]. Some microbes bind at additional sites in FH, like *Streptococcus pneumoniae* in CCPs 8-14 [120].

Numerous microbial FH-binding proteins have been identified. The most well-studied among these include the FH-binding protein (fHbp) of *Neisseria meningitidis* [121], the M protein family of *Streptococcus pyogenes* [118], the elongation factor Tuf of *Pseudomonas aeruginosa* [122], the pneumococcal surface protein C (PspC) from *Streptococcus pneumoniae* [123], the staphylococcal binder of immunoglobulin (Sbi) of *Staphylococcus aureus* [124] and several surface proteins of *Borrelia* [125-127] and *Leptospira* [74, 114] species. In addition to pathogenic bacteria, the ability to bind FH was also demonstrated for eukaryotic organisms, like *Candida albicans* [128], *Aspergillus fumigatus* [129] and even for the malaria unicellular parasite *Plasmodium falciparum* [130] and the filarial parasite *Onchocerca volvulus* [131].

Strikingly, the main microbial ligand binding domains of FH, especially the CCPs 19-20, are conserved among the FHR proteins, which led to the assumption that microbes can also bind FHRs. However, because of the absence of FH-homologue regulatory domains it is supposed that the FHRs cannot mediate the escape of pathogens from complement attack. In fact, they might evolved as decoy proteins that counteract the FH sequestering strategy of microbes [11, 115].

Indeed, binding of FHR-1 to numerous microorganisms was described but the relevance of FHR-1 binding to the microbes was rarely investigated [74, 76, 78, 79, 122, 124, 132-135]. FHR-4 binding was demonstrated for *Candida albicans* and *Fusobacterium necrophorum*, but the functional significance of these interactions is not yet determined [78, 136].

Several FHR-binding proteins have been identified in *Borrelia* spirochetes, collectively termed Complement Regulator-Aquiring Surface Proteins (CRASPs) [76, 125, 137, 138]. ErpA (CRASP-5, OspE) and ErpP (CRASP-3) were shown to interact with FHR-1, FHR-2 and FHR-5, whereas ErpC (CRASP-4) bound to FHR-1 and FHR-2. Interestingly, binding of FH and FHL-1 is mediated by two distinct proteins: CspA (CRASP-1) and CspZ (CRASP-2) [137, 138]. Protection of the bacteria against serum complement was shown to be solely mediated by FH, and not by any of the FHRs, indicating no relevant complement inhibiting activity for FHR-1, FHR-2 and FHR-5 under these conditions [135].

Pathogenic *Leptospira* species were also demonstrated to bind FHL-1 and FHR-1 via different surface molecules [139]. The best characterized surface proteins are the leptospiral

complement regulator-acquiring protein A (LcpA), the leptospiral immunoglobulin-like proteins A and B (LigA, LigB), and the leptospiral endostatin-like proteins A and B (LenA, LenB). LcpA was shown to bind FH by the C-terminal CCP20 domain [114]. Both LigA and LigB, which have identical N-terminal parts and differ in their C-terminal amino acid sequence, bind FHL-1 and FHR-1 [74]. LenA and LenB can also interact with FH, and LenA binds both FH and FHR-1, but not FHL-1 [140, 141]. The functional consequence of FHR-1 binding to *Leptospira* has not yet been investigated.

FHR-1 has recently been reported to bind to *Plasmodium falciparum*, the causative agent of malaria, compete with FH for binding to the parasite, and impair FH regulatory activity and C3b inactivation on the parasite surface [79, 134]. Also, the Sbi protein of *Staphylococcus aureus* was shown to bind to C3b and, in addition, to FH and FHR-1, and thus form tripartite complexes [124]; FHR-1 binding resulted in competitive inhibition of FH binding and enhanced complement activation in serum [142].

Binding of FH increases the survival of *Neisseria meningitidis* in human serum by downregulating complement activation on its surface [121, 143, 144]. FHR-3 was shown to bind to the fHbp surface lipoprotein with similar affinity as FH; however, fHbp variants and SNPs within the *CFH* and *CFHR3* genes also influence the binding affinities [111, 145]. Furthermore, a competition between FH and FHR-3 was demonstrated, which had a significant effect on the survival of *N. meningitidis* in serum bactericidal assays [111]. Thus, FHR-3 binding favours microbial clearance and the relative serum levels and affinities of these FH family proteins determine serum susceptibility of *N. meningitidis*.

These evidence emphasize a host protective role of the FHRs against infections by promoting complement activation on microbes. Further studies should investigate such mechanisms in the case of additional microbes, including *in vivo* studies, and experiments addressing the role of the other FHRs in host-pathogen interactions. In addition to their role in modulating complement activation, FHRs may influence the activation of immune cells and thus innate and adaptive immune responses by binding to cellular receptors [78] or receptor ligands [146]; such non-canonical functions of FH and the FHRs are discussed in more detail elsewhere [147].

4. Role in complement-mediated diseases

The role of FH, FHL-1 and the FHRs in infectious diseases was described above. Of note, exploitation of FH and FHL-1 similar to that seen in the case of microbes, may occur by tumor cells by expressing and binding these complement regulators, and is discussed in more detail elsewhere [35, 148]. This section summarizes the current knowledge on the role of the factor H family proteins in complement-associated inflammatory and autoimmune diseases.

Rare and common gene variants of FH and/or the FHRs have been linked to AMD, aHUS, C3G, IgAN and systemic lupus erythematosus (SLE), strongly underlining the role of these proteins in the regulation or modulation of complement activation [9, 11, 149-153]. While many *CFH* gene variants have been described, not all of them have been functionally validated; thus, the role of some of these variants in disease is uncertain. There are some genotype-phenotype correlations, e.g. quantitative FH deficiency generally associates with C3G, mutations in the FH complement regulatory N-terminal domains associate with C3G and C-terminal mutations with defective surface recognition functions and aHUS [154-168]. In any case, functional validation of variants is important to confirm disease association and gain insight into disease pathomechanism [44, 55, 64, 151, 157, 159, 164, 167-180]. The FH Y402H polymorphism affecting FH CCP7 is strongly associated with AMD [181-184]; however, in light of recent data it is likely that the main protein functionally affected by this amino acid exchange is FHL-1 and not FH in the context of AMD (see also **sections 3.1 and 3.2**) [15, 49, 58, 65, 69, 185-188].

Disease-associated variants of FHRs include *CFHR1*A* linked to AMD [189] and both *CFHR1*B* and *CFHR3*B* predisposing to aHUS, the latter two being linked together with *CFH(H3)* in an extended aHUS-risk haplotype [73, 94]. Several *CFHR5* variants were described in patients with aHUS, dense deposit disease (formerly termed membranoproliferative glomerulonephritis type II), AMD and IgAN [154, 190-193]. Few of these mutant FHR proteins were functionally analyzed, FHR-1*A and FHR-1*B for pentraxin binding [24, 55] and some FHR-5 mutants for C3b binding [193], but no clear pathological effects have yet been demonstrated. Variations in the *CFHR2* and *CFHR4* genes were also observed and analyzed only at the genetic level in connection with diseases [194, 195].

The genomic region encoding the FH protein family is prone to rearrangements leading to gene deletions or giving rise to genes coding for hybrid proteins. The most common change is the joint deletion of the *CFHR3* and *CFHR1* genes. It occurs in the normal population with allelic frequencies of 0-0.55, depending on the ethnic background [86]. The *CFHR3-CFHR1* deletion may associate with certain *CFH* haplotypes [196, 197], thus as part of certain extended haplotypes it was found to be protective in AMD and IgAN, whereas it is a risk factor in aHUS and SLE [95, 198-201]. The double gene deletion of *CFHR1-CFHR4* is more rare and was associated with aHUS [73, 202]. The protective effects of these *CFHR* gene deletions can be explained by the removal of a competitor molecule (FHR-1 and/or FHR-3) of FH. The lack of FHR-1 as a risk factor in the case of aHUS is explained by the observed association of FHR-1 deficiency with the presence of anti-FH autoantibodies in aHUS [203, 204]. Most of such FH-specific autoantibodies bind to an epitope on the hypervariable loop in FH CCP20 [73, 202, 205-208], which may take an alternate conformation upon binding to certain ligands, e.g. microbial proteins. Structural comparison of the C-terminal domains of FH and FHR-1 indicated that this changed conformation in FH CCP20 is similar to the homologous conformation in FHR-1 CCP5; however, there is no tolerance induction against it when FHR-1 is lacking in an individual. Thus, it was hypothesized that under certain conditions, especially following infections, the lack of FHR-1 protein may directly lead to autoantibody generation due to an induced neoepitope on FH CCP20 [205].

Hybrid proteins composed of FH and FHRs (indicated by double colons between the proteins), namely FH::FHR-1, FHR-1::FH and FH::FHR-3 are associated with aHUS, because these changes either replace FH CCP20, which harbors the surface/sialic acid recognition site in FH (FH::FHR-1 and FH::FHR-3), or remove the regulatory CCPs 1-4 domains (FHR1::FH) [25, 209-215]. Hybrid FHRs containing domains from two proteins (FHR-3::FHR-1, FHR-1::FHR-5, FHR-2::FHR-5, FHR-5::FHR-2) and FHR-1 and FHR-5 with duplicated dimerization domains (CCPs 1-2) due to intragenic duplications are associated with C3G; the hybrids between FHR-1 and FHR-5 or FHR-2 and FHR-5 also have duplicated dimerization domains [22, 89, 216-221]. These abnormal FHR proteins are thought to lead to enhanced complement de-regulation at surfaces, especially in the kidney, likely because of their enhanced oligomer formation and thus enhanced avidity towards disease-relevant ligands, leading to increased glomerular C3 deposition and the manifestation of C3G [21, 22, 89]. The composition of the various hybrid proteins and their characterization is described in detail elsewhere [9, 153].

Recent studies measuring FHR serum levels in various patient cohorts and healthy controls indicate the importance of the balance between the complement regulator FH and the de-regulator FHR proteins. Elevated FHR-3 serum levels were measured in aHUS patients (in association with the *CFHR3*B* allele), as well as in patients with SLE, rheumatoid arthritis, and polymyalgia rheumatica, and in septic patients [92, 93, 222]. Elevated FHR-1 and FHR-5 serum levels, or lower FH levels (thus increased FHR-1/FH ratios), have been found in IgAN patients and the increased concentration of FHR-1 relative to FH correlated with disease progression [83, 84]. While in the case of FHR-5 its slightly increased serum level did not

correlate with disease progression [83], increased glomerular FHR-5 deposition was associated with progressive disease [223]. These latter data strongly support a role for both FHR-1 and FHR-5 in promoting complement activation in IgAN.

5. Concluding remarks

The identified links between the individual members of the FH protein family and various diseases gave impetus to further characterize these proteins. Evidence accumulated over the past decade underline the versatile roles of FH, FHL-1 and the FHR proteins in infectious, inflammatory and autoimmune diseases and cancer. While some controversies regarding the functions and activities of the FHRs need to be resolved, currently available data attest to the role of FHRs in relation to FH (and possibly FHL-1) in fine-tuning complement activity and modulating physiological and pathological complement activation (**Fig. 3**). Thus, this protein family includes the complement inhibitors FH and FHL-1, and the deregulator and complement activator FHR proteins. It appears that under normal conditions there is little or no competition between FHRs and FH, due to the lower FHR serum levels and their lower affinity to physiological FH ligands. Increased FHR/FH ratio can shift the balance of complement regulation towards activation and enhanced opsonization, as it was observed in infectious and kidney diseases. The diversity among the FHRs in terms of structure, ligand binding and function is likely related to the diverse ligands (e.g., altered host structures and/or microbial structures) and circumstances where competition is favored. Further functional studies and determination of FH/FHL-1/FHR levels or the presence of FHRs in various biological samples will certainly provide further insight into the pathomechanism of diseases, potentially identifying some of them as biomarkers of disease and providing novel possibilities of therapeutic intervention.

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Figure legends

Figure 1. Overview of complement activation and its regulation by factor H.

Complement is activated through three main pathways, initiated by the binding of recognition molecules, such as C1q in the classial pathway and mannose-binding lectin and ficolins in the lectin pathway, as well as by the spontaneous hydrolysis of C3b in the alternative pathway. The activation cascades generate C3 convertases that cleave C3 and produce active C3b molecules, which covalently bind to target surfaces and opsonize them for enhanced phagocytosis; further activation and the deposition of additional C3b molecules generate C5 convertases that trigger the terminal pathway, which may ultimately lead to target cell lysis. FH inhibits complement activation at the level of the central C3b molecule, thus also blocks the amplification loop and the terminal pahway.

Figure 2. The human factor H protein family.

Members of the FH protein family are exclusively built up from complement control protein (CCP) domains. FH is composed of 20 CCPs, of which the N-terminal CCPs 1-4 mediate the complement regulatory (cofactor and convertase decay acceleration) activities. Major ligand binding and surface recognition sites are located in CCPs 6-7 and 19-20. FHL-1 is derived by alternative splicing from the *CFH* gene and essentially contains the N-terminal seven CCPs, thus shares complement regulatory activity with FH, as well as the N-terminal ligand/surface recognition site (CCPs 6-7). By contrast, the FHR proteins lack homologs of the complement regulatory domains, but do include domains that display variable degree of sequence identity to the ligand- and surface recognition domains of FH. In addition, FHR-1, FHR-2 and FHR-5 contain unique N-terminal domains that mediate homo- and heterooligomerization of these proteins.

Each CCP is represented by a circle, the major binding and activity sites are indicated by color coding. The CCPs of the molecules are aligned vertically based on highest sequence similarity to each other. Numbers indicate the percentage of amino acid sequence identity to the corresponding FH domains or, in the case of the dimerization domains, to each other.

Figure 3. Roles of factor H family proteins under physiological and disease conditions.

The figure shows a schematic overview of the roles of FH versus FHR proteins in complement regulation and activation on various surfaces in light of the latest data [9, 11, 115]. The alternative pathway is continuously active and probes any surface by generating and depositing active C3b fragments at a low rate. The nature of the surfaces and the relative concentrations of functionally active FH and FHRs influence the degree of complement activation.

(A) Healthy host cells are recognized by FH via cell surface glycosaminoglycans or sialic acids (indicated by the brown dots), which engage the C-terminal C3b/C3d binding site to anchor FH to the surface when C3b is deposited in low density due to the continuous, low-level activation of the alternative pathway. Surface-bound FH promotes inactivation of C3b and the C3bBb convertase, and thus down-regulates local complement activation. There is no significant competition between FH and the FHRs under these conditions.

(B) Changes in their relative amounts or avidity influence binding of FH and FHRs to host cells and may associate with diseases. Mutations in FH or the generation of autoantibodies that affect the recognition of host glycans and/or surface-bound C3b/C3d, can cause insufficient complement control on surfaces. In addition, FHR proteins – particularly when their avidities increase due to nonphysiological oligomerization caused by e.g. duplication of their dimerization domains, or due to the appearance of new ligands (indicated by orange triangles) on altered cells – may compete with FH for ligand and surface binding and, similarly, result in enhanced complement activation. Moreover, some FHRs may propagate alternative pathway activation by binding C3b and thus recruiting C3 convertase to the surface (indicated by black

arrow). While enhancing C3 fragment deposition and thus opsonization, FHRs may inhibit the terminal pathway and membrane attack complex (MAC) formation, a potential activity that needs further clarification (indicated by dotted line).
(C) Pathogens, even though generally lacking host-like glycosaminoglycans/sialic acid, may sequester host FH by expressing FH binding surface proteins (schematically shown in black), thus disguising themselves as "self" and reducing complement activation on their surface.
(D) FHR proteins may bind to FH-binding microbial proteins and competitively inhibit the recruitment of this host complement inhibitor, as shown for FHR-3 and FHR-1. Consequently, complement activation is enhanced on the microbial surface.

Fig. 1.

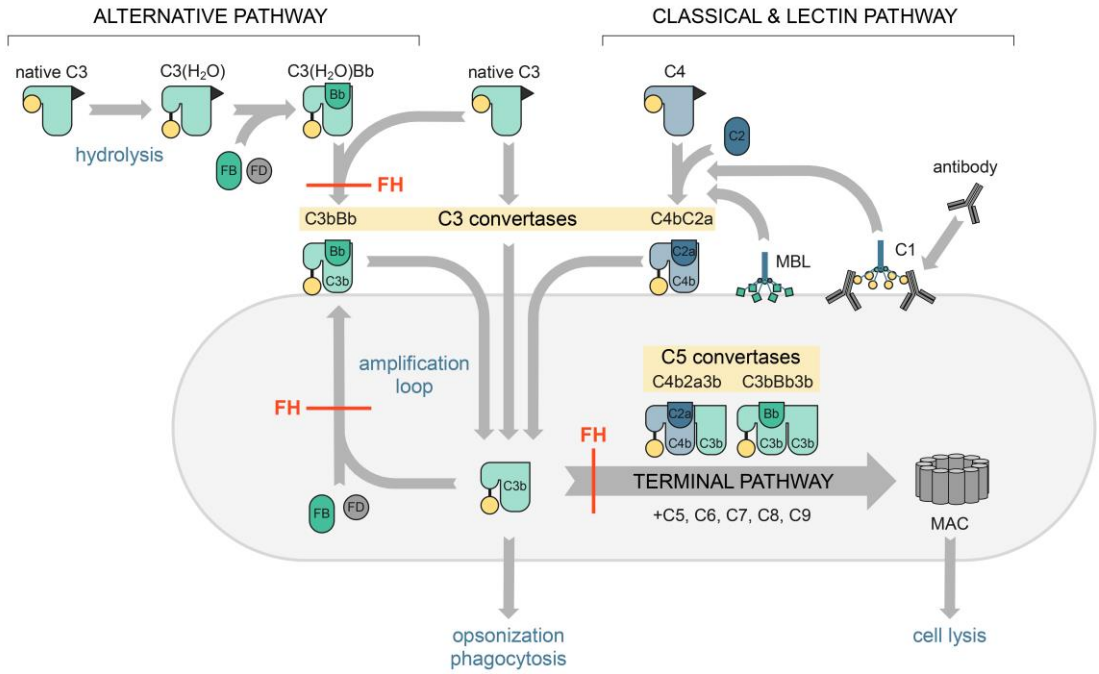
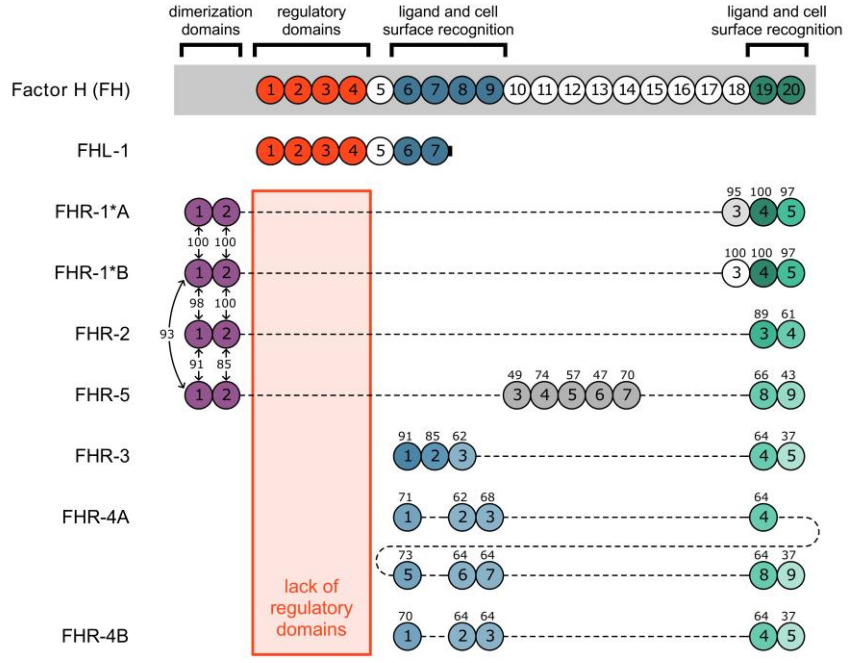
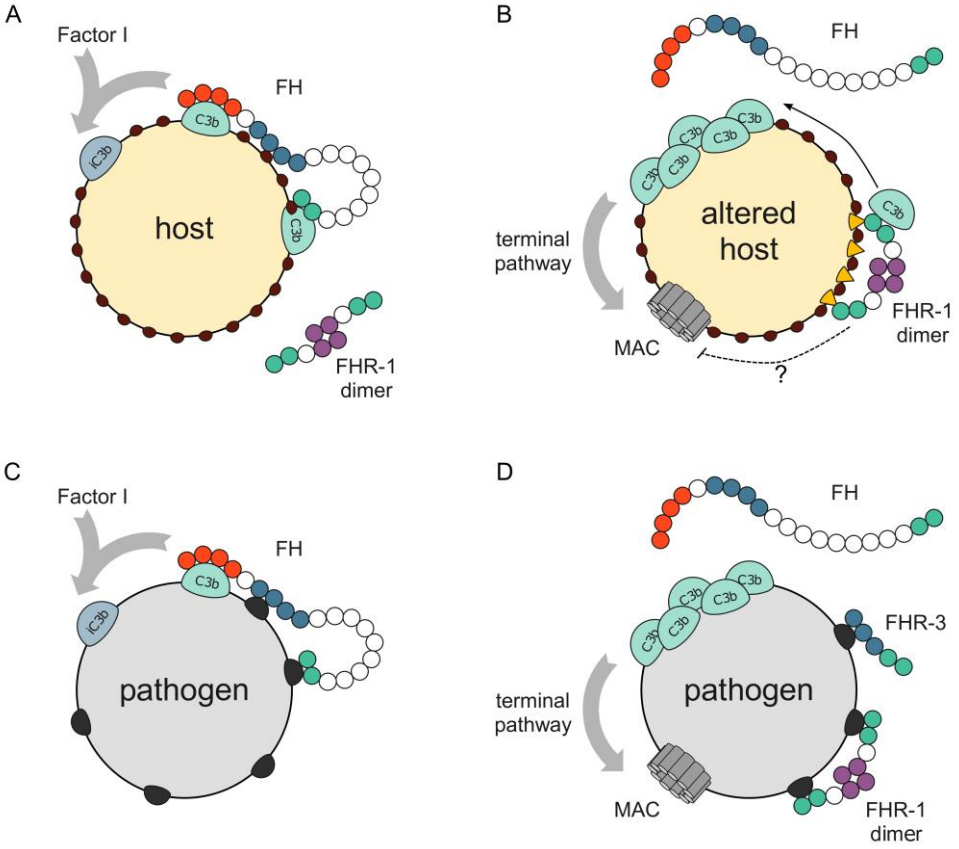


Fig. 2.



1440 Fig. 3.



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