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

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9 **Marcell Cserhalmi,^{1,2} Alexandra Papp,¹ Bianca Brandus,¹ Barbara Uzonyi,¹ Mihály**
10 **Józsi^{1,2}**

11
12 ¹ **Department of Immunology, ELTE Eötvös Loránd University, Budapest, Hungary**

13 ² **MTA-ELTE Complement Research Group, Department of Immunology, ELTE Eötvös**
14 **Loránd University, Budapest, Hungary**

15 16 **Corresponding author:**

17 Dr. Mihály Józsi, Department of Immunology, ELTE Eötvös Loránd University, Pázmány
18 Péter sétány 1/C, H-1117 Budapest, Hungary. Telephone: +36-1-381-2175. E-mail:
19 mihaly.jozsi@ttk.elte.hu
20

21 **Running title:** Factor H and factor H-related proteins
22

23 **Abbreviations:**

24 aHUS, atypical hemolytic uremic syndrome; AMD, age-related macular degeneration; AP,
25 alternative pathway; C3G, C3 glomerulopathy; C4BP, C4b binding protein; CCP,
26 complement control protein; CP, classical pathway; CR1, complement receptor type 1; CRP,
27 C-reactive protein; DAF, decay accelerating factor; ECM, extracellular matrix; FH, factor H;
28 FHL-1, factor H-like protein 1; FHR, factor H-related protein; GAG, glycosaminoglycan;
29 IgAN, IgA nephropathy; LP, lectin pathway; MBL, mannose binding lectin; MCP, membrane
30 cofactor protein; MDA, malondialdehyde; PTX3, pentraxin 3; RCA, regulators of
31 complement activation; SLE, systemic lupus erythematosus
32
33

34 **Abstract**

35 The complement system, while being an essential and very efficient effector component of
36 innate immunity, may cause damage to the host and result in various inflammatory,
37 autoimmune and infectious diseases or cancer, when it is improperly activated or regulated.
38 Factor H is a serum glycoprotein and the main regulator of the activity of the alternative
39 complement pathway. Factor H, together with its splice variant factor H-like protein 1 (FHL-
40 1), inhibits complement activation at the level of the central complement component C3 and
41 beyond. In humans, there are also five factor H-related (FHR) proteins, whose function is
42 poorly characterized. While data indicate complement inhibiting activity for some of the FHRs,
43 there is increasing evidence that FHRs have an opposite role compared with factor H and FHL-
44 1, namely, they enhance complement activation directly and also by competing with the
45 regulators FH and FHL-1. This review summarizes the current stand and recent data on the
46 roles of factor H family proteins in health and disease, with focus on the function of FHR
47 proteins.
48

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

52 **1. Introduction**

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

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

72

73 **2. The complement system – its activation and regulation**

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

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

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

102 into the anaphylatoxin C3a peptide and the opsonic molecule C3b. The AP is constantly
103 activated at a low rate by the spontaneous hydrolysis of the thioester bond in C3 and the
104 formation of the initial C3(H₂O)Bb convertase, which also cleaves C3 into C3a and C3b.
105 Through the active thioester group in C3b and C4b, these opsonic complement fragments can
106 covalently attach to various surfaces and molecules via ester or amide bonds and generate the
107 surface bound C3bBb AP C3 convertase and the C4b2a CP/LP C3 convertase enzymes,
108 respectively. Subsequently, these convertases, by cleaving additional C3 molecules, generate
109 further C3b and C3bBb. Thus, the AP auto-amplifies, as the generated C3b forms the core of
110 a new AP C3 convertase, and activation of the CP or LP automatically turns the AP on. C3b
111 when bound to these convertases generates the C5 convertase enzymes of the CP/LP and the
112 AP, i.e. C4bC2aC3b and C3bBbC3b, respectively. Cleavage of C5 into the anaphylatoxin C5a
113 and the terminal pathway initiator fragment C5b can lead to inflammation and the formation
114 of the lytic membrane attack complex (**Fig. 1**).

115 To focus complement activation on proper targets and prevent damage to the host, the
116 system is delicately regulated by fluid-phase and surface bound molecules, which control
117 activation in body fluids and on various cellular and non-cellular (such as basement
118 membranes) surfaces [1, 3, 7-9]. Several of the regulatory molecules are coded in chromosome
119 1q32, forming the human “regulators of complement activation (RCA) gene cluster”. One RCA
120 region harbours genes encoding C4b binding protein (C4BP), decay accelerating factor (DAF),
121 complement receptor type 1 (CR1) and membrane cofactor protein (MCP), the other region
122 includes the genes encoding members of the factor H (FH) protein family.

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

134

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

136 Six genes in tandem arrangement in the RCA cluster encode the serum glycoproteins that
137 constitute the human FH protein family (**Fig. 2**). Among these proteins, FH and FH-like protein
138 1 (FHL-1) are encoded by the *CFH* gene, and the factor H-related proteins (FHR-1 to FHR-5)
139 are encoded by the *CFHR1*, *CFHR2*, *CFHR3*, *CFHR4* and *CFHR5* genes [10-12]. These genes
140 arose through partial gene duplications, rendering this genomic region prone to rearrangements
141 (see also **section 4**). The FH family proteins are all exclusively composed of individually
142 folding globular domains called complement control protein (CCP) domains (also termed Sushi
143 domains or short consensus repeats, SCRs). The domains of the FHR proteins show varying
144 degree of amino acid sequence identity to the homologous domains in FH and/or other FHR
145 proteins; however, in general FHRs lack domains homologous to FH CCPs 1-4, i.e. the FH
146 domains that mediate the complement activation inhibiting effects, but they are present in FHL-
147 1 (**Fig. 2**).

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

152 characterized and in part controversial [11]. While some forms of complement inhibiting
153 activity have been described for the FHRs, recent data strongly support a role opposite to that
154 of FH and FHL-1 for the FHRs in complement activation: direct facilitation of alternative
155 pathway activation by binding C3b and promoting formation of the C3 convertase C3bBb, and
156 indirect enhancement of alternative pathway activation by competing with the regulators FH
157 and FHL-1 [9, 11, 21-26]. In addition, FHRs may influence complement activation by
158 interacting with other host molecules, e.g. by recruiting pentraxins that can bind C1q and allow
159 for CP activation, or being recruited by CRP and thus enhance AP activation [23, 24, 27, 28].
160

161 **3.1. Factor H**

162 FH is the main soluble regulator protein of the alternative pathway [29-31]. It is composed of
163 20 CCP domains, of which the N-terminal four domains mediate binding to C3b and are
164 responsible for the complement activation inhibiting activity of FH. While CCPs 1-4 are
165 sufficient for the complement regulatory activity [32, 33], a recent report indicates contribution
166 of the other adjacent CCP domains (also present in FHL-1) to a more pronounced regulatory
167 activity of FH [34]. FH affects the C3bBb convertase in two ways: it competes with factor B
168 for binding to C3b, thus prevents formation of the C3bBb convertase, and also accelerates the
169 decay of this convertase once already formed (“decay accelerating activity”). In addition, FH
170 regulates the C3b-containing C5 convertases. FH also acts as a cofactor for factor I in the
171 inactivation of C3b (“cofactor activity”). FH interacts with many other ligands, both in body
172 fluids and on various surfaces, several of them also directing its regulatory activity to cell
173 surfaces or to extracellular matrices, e.g. basement membranes (reviewed in more detail
174 elsewhere: [9, 35-37]). The major ligand and surface recognition domains reside in CCPs 6-7
175 and 19-20 of FH; importantly, these domains are variably conserved in the FHR proteins (see
176 below in **sections 3.3-3.7**) (**Fig. 2.**) [11]. Thus, FH inhibits alternative pathway activation in
177 blood plasma and other body fluids, as well as on cellular and noncellular surfaces. CCPs 19-
178 20 harbour a sialic acid binding site that is critical in the differentiation between self and nonself
179 by FH [38-42].

180 FH has two major C3b binding sites, in CCPs 1-4 and 19-20 [43]. The latter site is
181 specialized to bind C3b or its degradation product C3d when covalently bound on a self surface,
182 and this binding is facilitated by interaction of FH with cell surface sialic acid moieties [40, 41,
183 44, 45]. Thus, FH can recognize host cells that are attacked by complement and, by binding to
184 this surface, down-regulate complement activation and protect the host. Cell surface
185 polyanionic molecules, as markers of self, represent important ligands for FH, including
186 heparin and other glycosaminoglycans (GAGs) and sialic acids [42]. The composition of the
187 glycomatrix varies at different anatomic sites and can determine which GAG site in FH mediate
188 the binding and thus also influencing the strength of the interaction of this complement
189 regulator with various surfaces. It was demonstrated that FH uses primarily the GAG site in
190 CCPs 6-7 for binding to the Bruch’s membrane in the eye, whereas the GAG site in CCPs 19-
191 20 is responsible for binding to the glomerular basement membrane [15, 46].

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

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

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

207 The plasma concentration of FH is relatively high in comparison with the FHR proteins.
208 Average FH levels of 233-400 $\mu\text{g/ml}$ (in some cases, even higher concentrations) were
209 reported, but recent assays using well-characterized antibodies and excluding co-measurement
210 of FHL-1 and the FHRs found consistently $\sim 230 \mu\text{g/ml}$ [62-66].

211

212 **3.2. FHL-1**

213 FHL-1 is derived from the *CFH* gene by alternative splicing. It contains the N-terminal seven
214 CCP domains of FH, and four additional amino acids encoded by exon 10 that is only
215 transcribed in FHL-1 (Ser-Phe-Thr-Leu [SFTL]) [67, 68]. FHL-1 lacks the FH CCP 8-20
216 domains and thus the C-terminal sialic acid binding site, and has different cell surface
217 specificity and different role than FH in complement control on surfaces [34, 46]. Due to the
218 shared domains with FH, FHL-1 also binds C3b and has cofactor and convertase decay
219 accelerating activities [33]; it also binds to several other FH ligands with CCPs 6-7. It has been
220 reported that the C-terminal unique four amino acids influence the interaction of FHL-1 with
221 CRP and PTX3 [69]. Clark *et al.* reported that the retinal pigment epithelial cells in the eye are
222 able to express FHL-1, and FHL-1 can passively diffuse into the Bruch's membrane (the
223 innermost layer of the choroid), while due to its size FH is not able to go through this membrane
224 [15]. Thus, FHL-1 is probably the main complement inhibitory molecule that provides greater
225 protection at the key site of age-related macular degeneration (AMD) at the Bruch's membrane
226 than does FH [15]. It was shown that FHL-1 and the FH CCPs 6-8 fragment could not bind to
227 sialylated oligosaccharides [70], explaining the dominant role in host surface recognition of
228 CCPs 6-7 at the Bruch's membrane in the eye and CCPs 19-20 at the glomerular basement
229 membrane in the kidney.

230 Due to the lack of available FHL-1 specific antibodies, no reliable data on serum FHL-
231 1 concentration exist. One study reported an average FHL-1 serum concentration of 47 $\mu\text{g/ml}$,
232 determined from two samples [17]. Several recent studies that reported FH concentrations used
233 antibodies that do not detect the FHR proteins; however, these reported FH concentrations
234 often include the concentration of FHL-1, too.

235

236 **3.3. FHR-1**

237 FHR-1 consists of five CCP domains (**Fig. 2**), and has a molecular weight of 37 kDa (FHR-
238 1α) or 43 kDa (FHR- 1β), depending on the number of N-linked carbohydrate chains [71, 72].
239 Two allelic variants have been described, FHR-1*A (acidic isoform) and FHR-1*B (basic
240 isoform). The CCP3 domain of FHR-1*B is identical to CCP18 of FH, whereas CCP3 of FHR-
241 1*A differs from it in three amino acids [73]. As a consequence of the high sequence identity
242 between CCPs 4-5 of FHR-1 and CCPs 19-20 of FH (with FHR-1 CCP4 being identical to FH
243 CCP19, and the most C-terminal domains differing only in two amino acids), FHR-1 is also
244 able to bind several ligands of FH. For example, FHR-1 can bind to C3b, heparin, pentraxins
245 (PTX3, CRP) and certain microbial surface molecules [24, 74-80]. The role of FHR-1 in
246 complement regulation is controversial and discussed in **sections 3.8-3.10** in more detail.

247 The two N-terminal domains (CCPs 1-2) of FHR-1 are remarkably similar to CCPs 1-
248 2 of FHR-2 and FHR-5, and have been shown to mediate "head to tail" dimerization [81].
249 Circulating FHR-1 homodimers and FHR-1/FHR-2 heterodimers have been detected *ex vivo*
250 [82].

251 FHR-1 is certainly the most abundant glycoprotein among the FHRs, yet its plasma
252 concentration is still controversial. A number of studies established a concentration of ~40–
253 100 µg/ml [72, 77, 83, 84], although ~10-fold lower levels have more recently been reported
254 [82, 85]. The reason behind the notable deviation might be explained in part by the use of
255 different antibodies and ELISA set-ups and by the variation in frequency of a common deletion
256 polymorphism of the *CFHR1* and *CFHR3* genes (*delCFHR3-CFHR1*) among different
257 populations [86]. The *delCFHR3-CFHR1* allele is most frequent in African regions, whereas
258 the lowest frequency is seen within East Asia and South America [86]. This double gene
259 deletion is associated with lower FHR-1 levels in heterozygotes and complete FHR-1
260 deficiency in homozygotes, and is variably associated with diseases (see **section 4**). Beside the
261 population-dependency of the *delCFHR3-CFHR1* polymorphism, other factors may also
262 influence the accurate measurement of FHR-1 levels, e.g. the existence of FHR-1/FHR-2
263 heterodimers [82] and the ability of FHR-1 to interact with high-density lipoprotein particles
264 [87] or cells [78].
265

266 **3.4. FHR-2**

267 FHR-2 consists of four CCP domains. It exists in serum in a non-glycosylated (24 kDa) and a
268 glycosylated (29 kDa) form. The N-terminal CCPs 1-2 are distantly related to FH CCPs 6-7
269 (41% and 34% amino acid sequence identity), and its C-terminal CCPs are less similar to FH
270 CCPs 19-20 compared with FHR-1 (89% and 61% sequence identity, respectively) (**Fig. 2**)
271 [88]. The FHR-2 CCP1 and CCP2 domains exhibit a high degree of similarity to the CCPs 1-
272 2 domains of FHR-1 and FHR-5, and these domains mediate dimerization of the proteins [81].
273 *Ex vivo* FHR-2 homodimers and FHR-1/FHR-2 heterodimers have been described; the
274 existence of FHR-2/FHR-5 heterodimers is controversial [82, 89]. The serum concentration of
275 FHR-2 homodimers is approximately 3 µg/ml. Due to the very low concentration, FHR-2 is
276 the limiting factor in the formation of FHR-1/FHR-2 heterodimers; therefore, most FHR-2 are
277 present in heterodimer form in serum [82]. FHR-2 deficiency has not yet been described, but
278 hybrid proteins containing FHR-2 domains were identified (see later in **section 4**).
279

280 **3.5. FHR-3**

281 FHR-3 is composed of five CCP domains, each showing a remarkable sequence identity with
282 the CCP domains of FH or other FHR proteins, especially with FHR-4 [90]. CCPs 1 and 2 of
283 FHR-3 are homologous to CCPs 6 and 7 of FH (91 and 85% similarity, respectively), whereas
284 the C-terminal domains of FHR-3 (CCPs 3-5) demonstrate a high level of sequence identity
285 (>93%) with CCPs 2, 4, 6, 8 and 9 of FHR-4A and CCPs 2, 4 and 5 of FHR-4B (**Fig. 2**). Due
286 to the presence of homologous domains, FHR-3 shares some binding characteristics with FH;
287 thus, it is able to bind C3b and heparin [91]. Multiple forms of FHR-3 are detected in plasma
288 with molecular weights ranging from 37 to 50 kDa, likely representing differentially
289 glycosylated proteins [12, 73].

290 Similar to FHR-1, the serum concentration of FHR-3 is strongly influenced by the
291 presence of the *delCFHR3-CFHR1* allele. The mean concentration is estimated to be 0.81
292 µg/ml (22 nM) in healthy individuals carrying two *CFHR3* genes and about 2-fold lower in
293 individuals with only one *CFHR3* gene copy [92]. Interestingly, serum levels are also
294 determined by *CFHR3* gene variants [93]. Two genetic variants, *CFHR3**A and *CFHR3**B
295 have been reported [94]. A common polymorphism (c.721C>T) in exon 5 results in a proline
296 to serine change in CCP4 of FHR-3 and was observed to associate with higher levels of FHR-
297 3, thus allele *CFHR3**B (coding for serine in position 241) is considered a high-expression
298 allele and is associated with increased risk of the kidney disease atypical hemolytic uremic
299 syndrome (aHUS) [94]. The *delCFHR3-CFHR1* allele was shown to have protective effect in
300 AMD [95].

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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].

351 In addition, inhibition at the C5 level and/or the terminal pathway (lysis) was reported
352 for FHR-1 [77, 104], FHR-2 [105] and FHR-3 [104]. FHR-1 was studied by several other
353 groups and they found no terminal pathway inhibiting activity [24, 81, 106, 107]. On the other
354 hand, human FHR-1 expressed in the brain in a mouse model of neuromyelitis optica spectrum
355 disorders by applying engineered neural stem cells protected astrocytes from complement
356 activation and terminal complement complex formation [108]. Recently, FHR-5 was found to
357 inhibit both the alternative and the classical pathway C5 convertases in a bead based *in vitro*
358 model [109]. In these latter assays, the effective FHR-5 concentrations were close to serum
359 levels measured in samples from healthy donors or patients with glomerulonephritis [82, 83,
360 101, 110].

361 Recent studies re-evaluated the serum levels of the FHR proteins, and found that they
362 are in general much lower than previously estimated [82, 92, 98]; this issue is reviewed in more
363 detail in [9]. Thus, the above activities of the FHRs need to be further studied, either confirmed
364 or disproved. Even if some of the reported regulatory functions prove real when high
365 concentrations of the FHRs are applied, questions remain regarding their physiological
366 relevance when such concentrations and conditions do not occur *in vivo*. Some discrepancies
367 may be related to the different assay conditions, e.g. fluid-phase *versus* surface assays.
368

369 **3.9. FHR proteins as positive regulators of complement activation**

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

377 Competition between FHRs and FH for binding to several ligands was described. FHR-
378 1, FHR-3, FHR-4 and FHR-5 were shown to variably compete with FH for binding to C3b;
379 some of these differential effects may be related to the different avidities also determined by
380 homo- or heterodimerization of FHR-1 and FHR-5 [77, 81, 104, 111]. In addition, FHR-5 can
381 strongly inhibit FH binding to the pentraxins CRP and PTX3, as well as to extracellular matrix
382 and malondialdehyde-acetaldehyde epitopes, and enhance alternative pathway activation [23,
383 103]. In similar assays, FHR-1 was less effective in inhibiting FH binding to CRP and
384 enhancing complement activation, despite the conserved pentraxin binding site in the C
385 terminus of FHR-1 [24]. This is likely explained by the lower avidity of FHR-1 for the
386 relatively low density CRP and deposited C3b under the assay conditions. However,
387 recruitment of mCRP by FHR-1 can result in classical pathway activation by allowing
388 interaction of C1q with FHR-1 bound mCRP [24].

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

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

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

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

405

406 **3.10. Microbial ligands of factor H family proteins and role in infectious diseases**

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

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

422 Numerous microbial FH-binding proteins have been identified. The most well-studied
423 among these include the FH-binding protein (fHbp) of *Neisseria meningitidis* [121], the M
424 protein family of *Streptococcus pyogenes* [118], the elongation factor Tuf of *Pseudomonas*
425 *aeruginosa* [122], the pneumococcal surface protein C (PspC) from *Streptococcus pneumoniae*
426 [123], the staphylococcal binder of immunoglobulin (Sbi) of *Staphylococcus aureus* [124] and
427 several surface proteins of *Borrelia* [125-127] and *Leptospira* [74, 114] species. In addition to
428 pathogenic bacteria, the ability to bind FH was also demonstrated for eukaryotic organisms,
429 like *Candida albicans* [128], *Aspergillus fumigatus* [129] and even for the malaria unicellular
430 parasite *Plasmodium falciparum* [130] and the filarial parasite *Onchocerca volvulus* [131].

431 Strikingly, the main microbial ligand binding domains of FH, especially the CCPs 19-
432 20, are conserved among the FHR proteins, which led to the assumption that microbes can also
433 bind FHRs. However, because of the absence of FH-homologue regulatory domains it is
434 supposed that the FHRs cannot mediate the escape of pathogens from complement attack. In
435 fact, they might evolved as decoy proteins that counteract the FH sequestering strategy of
436 microbes [11, 115].

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

441 Several FHR-binding proteins have been identified in *Borrelia* spirochetes, collectively
442 termed Complement Regulator-Acquiring Surface Proteins (CRASPs) [76, 125, 137, 138]. ErpA
443 (CRASP-5, OspE) and ErpP (CRASP-3) were shown to interact with FHR-1, FHR-2 and FHR-
444 5, whereas ErpC (CRASP-4) bound to FHR-1 and FHR-2. Interestingly, binding of FH and
445 FHL-1 is mediated by two distinct proteins: CspA (CRASP-1) and CspZ (CRASP-2) [137,
446 138]. Protection of the bacteria against serum complement was shown to be solely mediated
447 by FH, and not by any of the FHRs, indicating no relevant complement inhibiting activity for
448 FHR-1, FHR-2 and FHR-5 under these conditions [135].

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

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

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

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

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

480

481 **4. Role in complement-mediated diseases**

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

487 Rare and common gene variants of FH and/or the FHRs have been linked to AMD,
488 aHUS, C3G, IgAN and systemic lupus erythematosus (SLE), strongly underlining the role of
489 these proteins in the regulation or modulation of complement activation [9, 11, 149-153]. While
490 many *CFH* gene variants have been described, not all of them have been functionally validated;
491 thus, the role of some of these variants in disease is uncertain. There are some genotype-
492 phenotype correlations, e.g. quantitative FH deficiency generally associates with C3G,
493 mutations in the FH complement regulatory N-terminal domains associate with C3G and C-
494 terminal mutations with defective surface recognition functions and aHUS [154-168]. In any
495 case, functional validation of variants is important to confirm disease association and gain
496 insight into disease pathomechanism [44, 55, 64, 151, 157, 159, 164, 167-180]. The FH Y402H
497 polymorphism affecting FH CCP7 is strongly associated with AMD [181-184]; however, in
498 light of recent data it is likely that the main protein functionally affected by this amino acid
499 exchange is FHL-1 and not FH in the context of AMD (see also **sections 3.1 and 3.2**) [15, 49,
500 58, 65, 69, 185-188].

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

510 The genomic region encoding the FH protein family is prone to rearrangements leading
511 to gene deletions or giving rise to genes coding for hybrid proteins. The most common change
512 is the joint deletion of the *CFHR3* and *CFHR1* genes. It occurs in the normal population with
513 allelic frequencies of 0-0.55, depending on the ethnic background [86]. The *CFHR3*-*CFHR1*
514 deletion may associate with certain *CFH* haplotypes [196, 197], thus as part of certain extended
515 haplotypes it was found to be protective in AMD and IgAN, whereas it is a risk factor in aHUS
516 and SLE [95, 198-201]. The double gene deletion of *CFHR1*-*CFHR4* is more rare and was
517 associated with aHUS [73, 202]. The protective effects of these *CFHR* gene deletions can be
518 explained by the removal of a competitor molecule (FHR-1 and/or FHR-3) of FH. The lack of
519 FHR-1 as a risk factor in the case of aHUS is explained by the observed association of FHR-1
520 deficiency with the presence of anti-FH autoantibodies in aHUS [203, 204]. Most of such FH-
521 specific autoantibodies bind to an epitope on the hypervariable loop in FH CCP20 [73, 202,
522 205-208], which may take an alternate conformation upon binding to certain ligands, e.g.
523 microbial proteins. Structural comparison of the C-terminal domains of FH and FHR-1
524 indicated that this changed conformation in FH CCP20 is similar to the homologous
525 conformation in FHR-1 CCP5; however, there is no tolerance induction against it when FHR-
526 1 is lacking in an individual. Thus, it was hypothesized that under certain conditions, especially
527 following infections, the lack of FHR-1 protein may directly lead to autoantibody generation
528 due to an induced neoepitope on FH CCP20 [205].

529 Hybrid proteins composed of FH and FHRs (indicated by double colons between the
530 proteins), namely FH::FHR-1, FHR-1::FH and FH::FHR-3 are associated with aHUS, because
531 these changes either replace FH CCP20, which harbors the surface/sialic acid recognition site
532 in FH (FH::FHR-1 and FH::FHR-3), or remove the regulatory CCPs 1-4 domains (FHR1::FH)
533 [25, 209-215]. Hybrid FHRs containing domains from two proteins (FHR-3::FHR-1, FHR-
534 1::FHR-5, FHR-2::FHR-5, FHR-5::FHR-2) and FHR-1 and FHR-5 with duplicated
535 dimerization domains (CCPs 1-2) due to intragenic duplications are associated with C3G; the
536 hybrids between FHR-1 and FHR-5 or FHR-2 and FHR-5 also have duplicated dimerization
537 domains [22, 89, 216-221]. These abnormal FHR proteins are thought to lead to enhanced
538 complement de-regulation at surfaces, especially in the kidney, likely because of their
539 enhanced oligomer formation and thus enhanced avidity towards disease-relevant ligands,
540 leading to increased glomerular C3 deposition and the manifestation of C3G [21, 22, 89]. The
541 composition of the various hybrid proteins and their characterization is described in detail
542 elsewhere [9, 153].

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

551 correlate with disease progression [83], increased glomerular FHR-5 deposition was associated
552 with progressive disease [223]. These latter data strongly support a role for both FHR-1 and
553 FHR-5 in promoting complement activation in IgAN.
554

555 **5. Concluding remarks**

556 The identified links between the individual members of the FH protein family and various
557 diseases gave impetus to further characterize these proteins. Evidence accumulated over the
558 past decade underline the versatile roles of FH, FHL-1 and the FHR proteins in infectious,
559 inflammatory and autoimmune diseases and cancer. While some controversies regarding the
560 functions and activities of the FHRs need to be resolved, currently available data attest to the
561 role of FHRs in relation to FH (and possibly FHL-1) in fine-tuning complement activity and
562 modulating physiological and pathological complement activation (**Fig. 3**). Thus, this protein
563 family includes the complement inhibitors FH and FHL-1, and the deregulator and complement
564 activator FHR proteins. It appears that under normal conditions there is little or no competition
565 between FHRs and FH, due to the lower FHR serum levels and their lower affinity to
566 physiological FH ligands. Increased FHR/FH ratio can shift the balance of complement
567 regulation towards activation and enhanced opsonization, as it was observed in infectious and
568 kidney diseases. The diversity among the FHRs in terms of structure, ligand binding and
569 function is likely related to the diverse ligands (e.g., altered host structures and/or microbial
570 structures) and circumstances where competition is favored. Further functional studies and
571 determination of FH/FHL-1/FHR levels or the presence of FHRs in various biological samples
572 will certainly provide further insight into the pathomechanism of diseases, potentially
573 identifying some of them as biomarkers of disease and providing novel possibilities of
574 therapeutic intervention.
575

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587 **References**

- 588 [1] N.S. Merle, S.E. Church, V. Fremeaux-Bacchi, L.T. Roumenina, Complement System
589 Part I - Molecular Mechanisms of Activation and Regulation, *Front Immunol* 6 (2015) 262.
590 [2] N.S. Merle, R. Noe, L. Halbwachs-Mecarelli, V. Fremeaux-Bacchi, L.T. Roumenina,
591 Complement System Part II: Role in Immunity, *Front Immunol* 6 (2015) 257.
592 [3] D. Ricklin, D.C. Mastellos, E.S. Reis, J.D. Lambris, The renaissance of complement
593 therapeutics, *Nat Rev Nephrol* 14(1) (2017) 26-47.
594 [4] D. Ricklin, G. Hajishengallis, K. Yang, J.D. Lambris, Complement: a key system for
595 immune surveillance and homeostasis, *Nat Immunol* 11(9) (2010) 785-97.
596 [5] M. Harboe, C. Johnson, S. Nymo, K. Ekholt, C. Schjalm, J.K. Lindstad, A. Pharo, B.C.
597 Hellerud, K. Nilsson Ekdahl, T.E. Mollnes, P.H. Nilsson, Properdin binding to complement
598 activating surfaces depends on initial C3b deposition, *Proc Natl Acad Sci U S A* 114(4)
599 (2017) E534-E539.

600 [6] D. Spitzer, L.M. Mitchell, J.P. Atkinson, D.E. Hourcade, Properdin can initiate
601 complement activation by binding specific target surfaces and providing a platform for de
602 novo convertase assembly, *J Immunol* 179(4) (2007) 2600-8.

603 [7] A.P. Sjoberg, L.A. Trouw, A.M. Blom, Complement activation and inhibition: a delicate
604 balance, *Trends Immunol* 30(2) (2009) 83-90.

605 [8] S. Meri, Self-nonsel discrimination by the complement system, *FEBS Lett* 590(15)
606 (2016) 2418-34.

607 [9] P. Sanchez-Corral, R.B. Pouw, M. Lopez-Trascasa, M. Jozsi, Self-Damage Caused by
608 Dysregulation of the Complement Alternative Pathway: Relevance of the Factor H Protein
609 Family, *Front Immunol* 9 (2018) 1607.

610 [10] M. Jozsi, S. Meri, Factor H-related proteins, *Methods Mol Biol* 1100 (2014) 225-36.

611 [11] M. Jozsi, A. Tortajada, B. Uzonyi, E. Goicoechea de Jorge, S. Rodriguez de Cordoba,
612 Factor H-related proteins determine complement-activating surfaces, *Trends Immunol* 36(6)
613 (2015) 374-84.

614 [12] C. Skerka, Q. Chen, V. Fremeaux-Bacchi, L.T. Roumenina, Complement factor H
615 related proteins (CFHRs), *Mol Immunol* 56(3) (2013) 170-80.

616 [13] R.A. Brooimans, A.A. van der Ark, W.A. Buurman, L.A. van Es, M.R. Daha,
617 Differential regulation of complement factor H and C3 production in human umbilical vein
618 endothelial cells by IFN-gamma and IL-1, *J Immunol* 144(10) (1990) 3835-40.

619 [14] M. Chen, J.V. Forrester, H. Xu, Synthesis of complement factor H by retinal pigment
620 epithelial cells is down-regulated by oxidized photoreceptor outer segments, *Exp Eye Res*
621 84(4) (2007) 635-45.

622 [15] S.J. Clark, C.Q. Schmidt, A.M. White, S. Hakobyan, B.P. Morgan, P.N. Bishop,
623 Identification of factor H-like protein 1 as the predominant complement regulator in Bruch's
624 membrane: implications for age-related macular degeneration, *J Immunol* 193(10) (2014)
625 4962-70.

626 [16] K.O. Dixon, J. O'Flynn, N. Klar-Mohamad, M.R. Daha, C. van Kooten, Properdin and
627 factor H production by human dendritic cells modulates their T-cell stimulatory capacity and
628 is regulated by IFN-gamma, *Eur J Immunol* 47(3) (2017) 470-480.

629 [17] M.A. Friese, J. Hellwage, T.S. Jokiranta, S. Meri, H.J. Muller-Quernheim, H.H. Peter,
630 H. Eibel, P.F. Zipfel, Different regulation of factor H and FHL-1/reconectin by inflammatory
631 mediators and expression of the two proteins in rheumatoid arthritis (RA), *Clin Exp Immunol*
632 121(2) (2000) 406-15.

633 [18] Y. Katz, R.C. Strunk, Synthesis and regulation of complement protein factor H in human
634 skin fibroblasts, *J Immunol* 141(2) (1988) 559-63.

635 [19] K.K. Timar, M.C. Pasch, N.H. van den Bosch, H. Jarva, S. Junnikkala, S. Meri, J.D.
636 Bos, S.S. Asghar, Human keratinocytes produce the complement inhibitor factor H: synthesis
637 is regulated by interferon-gamma, *Mol Immunol* 43(4) (2006) 317-25.

638 [20] K. Whaley, Biosynthesis of the complement components and the regulatory proteins of
639 the alternative complement pathway by human peripheral blood monocytes, *J Exp Med*
640 151(3) (1980) 501-16.

641 [21] Q. Chen, M. Manzke, A. Hartmann, M. Buttner, K. Amann, D. Pauly, M. Wiesener, C.
642 Skerka, P.F. Zipfel, Complement Factor H-Related 5-Hybrid Proteins Anchor Properdin and
643 Activate Complement at Self-Surfaces, *J Am Soc Nephrol* 27(5) (2016) 1413-25.

644 [22] Q. Chen, M. Wiesener, H.U. Eberhardt, A. Hartmann, B. Uzonyi, M. Kirschfink, K.
645 Amann, M. Buettner, T. Goodship, C. Hugo, C. Skerka, P.F. Zipfel, Complement factor H-
646 related hybrid protein deregulates complement in dense deposit disease, *J Clin Invest* 124(1)
647 (2014) 145-55.

648 [23] A.I. Csincsi, A. Kopp, M. Zoldi, Z. Banlaki, B. Uzonyi, M. Hebecker, J.J. Caesar, M.C.
649 Pickering, K. Daigo, T. Hamakubo, S.M. Lea, E. Goicoechea de Jorge, M. Jozsi, Factor H-

650 related protein 5 interacts with pentraxin 3 and the extracellular matrix and modulates
651 complement activation, *J Immunol* 194(10) (2015) 4963-73.

652 [24] A.I. Csincsi, Z. Szabo, Z. Banlaki, B. Uzonyi, M. Cserhalmi, E. Karpati, A. Tortajada,
653 J.J.E. Caesar, Z. Prohaszka, T.S. Jokiranta, S.M. Lea, S. Rodriguez de Cordoba, M. Jozsi,
654 FHR-1 Binds to C-Reactive Protein and Enhances Rather than Inhibits Complement
655 Activation, *J Immunol* 199(1) (2017) 292-303.

656 [25] E. Goicoechea de Jorge, A. Tortajada, S.P. Garcia, S. Gastoldi, H.M. Merinero, J.
657 Garcia-Fernandez, E. Arjona, M. Cao, G. Remuzzi, M. Noris, S. Rodriguez de Cordoba,
658 Factor H Competitor Generated by Gene Conversion Events Associates with Atypical
659 Hemolytic Uremic Syndrome, *J Am Soc Nephrol* 29(1) (2018) 240-249.

660 [26] M. Hebecker, M. Jozsi, Factor H-related protein 4 activates complement by serving as a
661 platform for the assembly of alternative pathway C3 convertase via its interaction with C3b
662 protein, *J Biol Chem* 287(23) (2012) 19528-36.

663 [27] M. Hebecker, A.I. Okemefuna, S.J. Perkins, M. Mihlan, M. Huber-Lang, M. Jozsi,
664 Molecular basis of C-reactive protein binding and modulation of complement activation by
665 factor H-related protein 4, *Mol Immunol* 47(6) (2010) 1347-55.

666 [28] M. Mihlan, M. Hebecker, H.M. Dahse, S. Halbich, M. Huber-Lang, R. Dahse, P.F.
667 Zipfel, M. Jozsi, Human complement factor H-related protein 4 binds and recruits native
668 pentameric C-reactive protein to necrotic cells, *Mol Immunol* 46(3) (2009) 335-44.

669 [29] M.K. Pangburn, R.D. Schreiber, H.J. Muller-Eberhard, Human complement C3b
670 inactivator: isolation, characterization, and demonstration of an absolute requirement for the
671 serum protein beta1H for cleavage of C3b and C4b in solution, *J Exp Med* 146(1) (1977)
672 257-70.

673 [30] J.M. Weiler, M.R. Daha, K.F. Austen, D.T. Fearon, Control of the amplification
674 convertase of complement by the plasma protein beta1H, *Proc Natl Acad Sci U S A* 73(9)
675 (1976) 3268-72.

676 [31] K. Whaley, S. Ruddy, Modulation of the alternative complement pathways by beta 1 H
677 globulin, *J Exp Med* 144(5) (1976) 1147-63.

678 [32] D.L. Gordon, R.M. Kaufman, T.K. Blackmore, J. Kwong, D.M. Lublin, Identification of
679 complement regulatory domains in human factor H, *J Immunol* 155(1) (1995) 348-56.

680 [33] S. Kuhn, C. Skerka, P.F. Zipfel, Mapping of the complement regulatory domains in the
681 human factor H-like protein 1 and in factor H1, *J Immunol* 155(12) (1995) 5663-70.

682 [34] A. Dopler, L. Guntau, M.J. Harder, A. Palmer, B. Hochsmann, H. Schrezenmeier, T.
683 Simmet, M. Huber-Lang, C.Q. Schmidt, Self versus Nonself Discrimination by the Soluble
684 Complement Regulators Factor H and FHL-1, *J Immunol* 202(7) (2019) 2082-2094.

685 [35] A. Kopp, M. Hebecker, E. Svobodova, M. Jozsi, Factor h: a complement regulator in
686 health and disease, and a mediator of cellular interactions, *Biomolecules* 2(1) (2012) 46-75.

687 [36] E. Makou, A.P. Herbert, P.N. Barlow, Functional anatomy of complement factor H,
688 *Biochemistry* 52(23) (2013) 3949-62.

689 [37] C.Q. Schmidt, A.P. Herbert, H.G. Hocking, D. Uhrin, P.N. Barlow, Translational mini-
690 review series on complement factor H: structural and functional correlations for factor H,
691 *Clin Exp Immunol* 151(1) (2008) 14-24.

692 [38] B.S. Blaum, J.P. Hannan, A.P. Herbert, D. Kavanagh, D. Uhrin, T. Stehle, Structural
693 basis for sialic acid-mediated self-recognition by complement factor H, *Nat Chem Biol* 11(1)
694 (2015) 77-82.

695 [39] V.P. Ferreira, A.P. Herbert, H.G. Hocking, P.N. Barlow, M.K. Pangburn, Critical role of
696 the C-terminal domains of factor H in regulating complement activation at cell surfaces, *J*
697 *Immunol* 177(9) (2006) 6308-16.

698 [40] T.S. Jokiranta, Z.Z. Cheng, H. Seeberger, M. Jozsi, S. Heinen, M. Noris, G. Remuzzi, R.
699 Ormsby, D.L. Gordon, S. Meri, J. Hellwage, P.F. Zipfel, Binding of complement factor H to

endothelial cells is mediated by the carboxy-terminal glycosaminoglycan binding site, *Am J Pathol* 167(4) (2005) 1173-81.

[41] M. Jozsi, M. Oppermann, J.D. Lambris, P.F. Zipfel, The C-terminus of complement factor H is essential for host cell protection, *Mol Immunol* 44(10) (2007) 2697-706.

[42] S. Meri, M.K. Pangburn, Discrimination between activators and nonactivators of the alternative pathway of complement: regulation via a sialic acid/polyanion binding site on factor H, *Proc Natl Acad Sci U S A* 87(10) (1990) 3982-6.

[43] C.Q. Schmidt, A.P. Herbert, D. Kavanagh, C. Gandy, C.J. Fenton, B.S. Blaum, M. Lyon, D. Uhrin, P.N. Barlow, A new map of glycosaminoglycan and C3b binding sites on factor H, *J Immunol* 181(4) (2008) 2610-9.

[44] T. Kajander, M.J. Lehtinen, S. Hyvarinen, A. Bhattacharjee, E. Leung, D.E. Isenman, S. Meri, A. Goldman, T.S. Jokiranta, Dual interaction of factor H with C3d and glycosaminoglycans in host-nonhost discrimination by complement, *Proc Natl Acad Sci U S A* 108(7) (2011) 2897-902.

[45] H.P. Morgan, C.Q. Schmidt, M. Guariento, B.S. Blaum, D. Gillespie, A.P. Herbert, D. Kavanagh, H.D. Mertens, D.I. Svergun, C.M. Johansson, D. Uhrin, P.N. Barlow, J.P. Hannan, Structural basis for engagement by complement factor H of C3b on a self surface, *Nat Struct Mol Biol* 18(4) (2011) 463-70.

[46] S.J. Clark, L.A. Ridge, A.P. Herbert, S. Hakobyan, B. Mulloy, R. Lennon, R. Wurzner, B.P. Morgan, D. Uhrin, P.N. Bishop, A.J. Day, Tissue-specific host recognition by complement factor H is mediated by differential activities of its glycosaminoglycan-binding regions, *J Immunol* 190(5) (2013) 2049-57.

[47] A. Sjoberg, P. Onnerfjord, M. Morgelin, D. Heinegard, A.M. Blom, The extracellular matrix and inflammation: fibromodulin activates the classical pathway of complement by directly binding C1q, *J Biol Chem* 280(37) (2005) 32301-8.

[48] A.P. Sjoberg, G.A. Manderson, M. Morgelin, A.J. Day, D. Heinegard, A.M. Blom, Short leucine-rich glycoproteins of the extracellular matrix display diverse patterns of complement interaction and activation, *Mol Immunol* 46(5) (2009) 830-9.

[49] A.P. Sjoberg, L.A. Trouw, S.J. Clark, J. Sjolander, D. Heinegard, R.B. Sim, A.J. Day, A.M. Blom, The factor H variant associated with age-related macular degeneration (His-384) and the non-disease-associated form bind differentially to C-reactive protein, fibromodulin, DNA, and necrotic cells, *J Biol Chem* 282(15) (2007) 10894-900.

[50] J. Leffler, A.P. Herbert, E. Norstrom, C.Q. Schmidt, P.N. Barlow, A.M. Blom, M. Martin, Annexin-II, DNA, and histones serve as factor H ligands on the surface of apoptotic cells, *J Biol Chem* 285(6) (2010) 3766-76.

[51] L.A. Trouw, A.A. Bengtsson, K.A. Gelderman, B. Dahlback, G. Sturfelt, A.M. Blom, C4b-binding protein and factor H compensate for the loss of membrane-bound complement inhibitors to protect apoptotic cells against excessive complement attack, *J Biol Chem* 282(39) (2007) 28540-8.

[52] L. Deban, H. Jarva, M.J. Lehtinen, B. Bottazzi, A. Bastone, A. Doni, T.S. Jokiranta, A. Mantovani, S. Meri, Binding of the long pentraxin PTX3 to factor H: interacting domains and function in the regulation of complement activation, *J Immunol* 181(12) (2008) 8433-40.

[53] D. Gershov, S. Kim, N. Brot, K.B. Elkon, C-Reactive protein binds to apoptotic cells, protects the cells from assembly of the terminal complement components, and sustains an antiinflammatory innate immune response: implications for systemic autoimmunity, *J Exp Med* 192(9) (2000) 1353-64.

[54] H. Jarva, T.S. Jokiranta, J. Hellwage, P.F. Zipfel, S. Meri, Regulation of complement activation by C-reactive protein: targeting the complement inhibitory activity of factor H by an interaction with short consensus repeat domains 7 and 8-11, *J Immunol* 163(7) (1999) 3957-62.

750 [55] A. Kopp, S. Strobel, A. Tortajada, S. Rodriguez de Cordoba, P. Sanchez-Corral, Z.
751 Prohaszka, M. Lopez-Trascasa, M. Jozsi, Atypical hemolytic uremic syndrome-associated
752 variants and autoantibodies impair binding of factor h and factor h-related protein 1 to
753 pentraxin 3, *J Immunol* 189(4) (2012) 1858-67.

754 [56] M. Mihlan, S. Stippa, M. Jozsi, P.F. Zipfel, Monomeric CRP contributes to complement
755 control in fluid phase and on cellular surfaces and increases phagocytosis by recruiting factor
756 H, *Cell Death Differ* 16(12) (2009) 1630-40.

757 [57] S. Hyvarinen, K. Uchida, M. Varjosalo, R. Jokela, T.S. Jokiranta, Recognition of
758 malondialdehyde-modified proteins by the C terminus of complement factor H is mediated
759 via the polyanion binding site and impaired by mutations found in atypical hemolytic uremic
760 syndrome, *J Biol Chem* 289(7) (2014) 4295-306.

761 [58] D. Weismann, K. Hartvigsen, N. Lauer, K.L. Bennett, H.P. Scholl, P. Charbel Issa, M.
762 Cano, H. Brandstatter, S. Tsimikas, C. Skerka, G. Superti-Furga, J.T. Handa, P.F. Zipfel, J.L.
763 Witztum, C.J. Binder, Complement factor H binds malondialdehyde epitopes and protects
764 from oxidative stress, *Nature* 478(7367) (2011) 76-81.

765 [59] R. Nan, J. Gor, S.J. Perkins, Implications of the progressive self-association of wild-type
766 human factor H for complement regulation and disease, *J Mol Biol* 375(4) (2008) 891-900.

767 [60] R. Nan, S. Tetchner, E. Rodriguez, P.J. Pao, J. Gor, I. Lengyel, S.J. Perkins, Zinc-
768 induced self-association of complement C3b and Factor H: implications for inflammation and
769 age-related macular degeneration, *J Biol Chem* 288(26) (2013) 19197-210.

770 [61] M.K. Pangburn, N. Rawal, C. Cortes, M.N. Alam, V.P. Ferreira, M.A. Atkinson,
771 Polyanion-induced self-association of complement factor H, *J Immunol* 182(2) (2009) 1061-
772 8.

773 [62] M. Ansari, P.M. McKeigue, C. Skerka, C. Hayward, I. Rudan, V. Vitart, O. Polasek,
774 A.M. Armbrrecht, J.R. Yates, Z. Vatauvuk, G. Bencic, I. Kolcic, B.A. Oostra, C.M. Van Duijn,
775 S. Campbell, C.M. Stanton, J. Huffman, X. Shu, J.C. Khan, H. Shahid, S.P. Harding, P.N.
776 Bishop, I.J. Deary, A.T. Moore, B. Dhillon, P. Rudan, P.F. Zipfel, R.B. Sim, N.D. Hastie, H.
777 Campbell, A.F. Wright, Genetic influences on plasma CFH and CFHR1 concentrations and
778 their role in susceptibility to age-related macular degeneration, *Hum Mol Genet* 22(23)
779 (2013) 4857-69.

780 [63] P.F. de Paula, J.E. Barbosa, P.R. Junior, V.P. Ferriani, M.R. Latorre, V. Nudelman, L.
781 Isaac, Ontogeny of complement regulatory proteins - concentrations of factor h, factor I, c4b-
782 binding protein, properdin and vitronectin in healthy children of different ages and in adults,
783 *Scand J Immunol* 58(5) (2003) 572-7.

784 [64] J. Esparza-Gordillo, J.M. Soria, A. Buil, L. Almasy, J. Blangero, J. Fontcuberta, S.
785 Rodriguez de Cordoba, Genetic and environmental factors influencing the human factor H
786 plasma levels, *Immunogenetics* 56(2) (2004) 77-82.

787 [65] S. Hakobyan, C.L. Harris, A. Tortajada, E. Goicochea de Jorge, A. Garcia-Layana, P.
788 Fernandez-Robredo, S. Rodriguez de Cordoba, B.P. Morgan, Measurement of factor H
789 variants in plasma using variant-specific monoclonal antibodies: application to assessing risk
790 of age-related macular degeneration, *Invest Ophthalmol Vis Sci* 49(5) (2008) 1983-90.

791 [66] R. Sofat, P.P. Mangione, J.R. Gallimore, S. Hakobyan, T.R. Hughes, T. Shah, T.
792 Goodship, F. D'Aiuto, C. Langenberg, N. Wareham, B.P. Morgan, M.B. Pepys, A.D.
793 Hingorani, Distribution and determinants of circulating complement factor H concentration
794 determined by a high-throughput immunonephelometric assay, *J Immunol Methods* 390(1-2)
795 (2013) 63-73.

796 [67] R. Misasi, H.P. Huemer, W. Schwaeble, E. Solder, C. Larcher, M.P. Dierich, Human
797 complement factor H: an additional gene product of 43 kDa isolated from human plasma
798 shows cofactor activity for the cleavage of the third component of complement, *Eur J*
799 *Immunol* 19(9) (1989) 1765-8.

800 [68] W. Schwaeble, J. Zwirner, T.F. Schulz, R.P. Linke, M.P. Dierich, E.H. Weiss, Human
801 complement factor H: expression of an additional truncated gene product of 43 kDa in human
802 liver, *Eur J Immunol* 17(10) (1987) 1485-9.

803 [69] M. Swinkels, J.H. Zhang, V. Tilakaratna, G. Black, R. Perveen, S. McHarg, A.
804 Inforzato, A.J. Day, S.J. Clark, C-reactive protein and pentraxin-3 binding of factor H-like
805 protein 1 differs from complement factor H: implications for retinal inflammation, *Sci Rep*
806 8(1) (2018) 1643.

807 [70] C.Q. Schmidt, A.L. Hipgrave Ederveen, M.J. Harder, M. Wuhrer, T. Stehle, B.S. Blaum,
808 Biophysical analysis of sialic acid recognition by the complement regulator Factor H,
809 *Glycobiology* 28(10) (2018) 765-773.

810 [71] C. Skerka, R.D. Horstmann, P.F. Zipfel, Molecular cloning of a human serum protein
811 structurally related to complement factor H, *J Biol Chem* 266(18) (1991) 12015-20.

812 [72] C. Timmann, M. Leippe, R.D. Horstmann, Two major serum components antigenically
813 related to complement factor H are different glycosylation forms of a single protein with no
814 factor H-like complement regulatory functions, *J Immunol* 146(4) (1991) 1265-70.

815 [73] C. Abarrategui-Garrido, R. Martinez-Barricarte, M. Lopez-Trascasa, S.R. de Cordoba, P.
816 Sanchez-Corral, Characterization of complement factor H-related (CFHR) proteins in plasma
817 reveals novel genetic variations of CFHR1 associated with atypical hemolytic uremic
818 syndrome, *Blood* 114(19) (2009) 4261-71.

819 [74] M.M. Castiblanco-Valencia, T.R. Fraga, L.B. Silva, D. Monaris, P.A. Abreu, S. Strobel,
820 M. Jozsi, L. Isaac, A.S. Barbosa, Leptospiral immunoglobulin-like proteins interact with
821 human complement regulators factor H, FHL-1, FHR-1, and C4BP, *J Infect Dis* 205(6)
822 (2012) 995-1004.

823 [75] J.P. Hannan, J. Laskowski, J.M. Thurman, G.S. Hageman, V.M. Holers, Mapping the
824 Complement Factor H-Related Protein 1 (CFHR1):C3b/C3d Interactions, *PLoS One* 11(11)
825 (2016) e0166200.

826 [76] K. Haupt, P. Kraiczky, R. Wallich, V. Brade, C. Skerka, P.F. Zipfel, Binding of human
827 factor H-related protein 1 to serum-resistant *Borrelia burgdorferi* is mediated by borreliac
828 complement regulator-acquiring surface proteins, *J Infect Dis* 196(1) (2007) 124-33.

829 [77] S. Heinen, A. Hartmann, N. Lauer, U. Wiehl, H.M. Dahse, S. Schirmer, K. Gropp, T.
830 Enghardt, R. Wallich, S. Halbich, M. Mihlan, U. Schlotzer-Schrehardt, P.F. Zipfel, C.
831 Skerka, Factor H-related protein 1 (CFHR-1) inhibits complement C5 convertase activity and
832 terminal complex formation, *Blood* 114(12) (2009) 2439-47.

833 [78] J. Losse, P.F. Zipfel, M. Jozsi, Factor H and factor H-related protein 1 bind to human
834 neutrophils via complement receptor 3, mediate attachment to *Candida albicans*, and enhance
835 neutrophil antimicrobial activity, *J Immunol* 184(2) (2010) 912-21.

836 [79] T. Reiss, T.F.A. Rosa, K. Blaesius, R.P. Bobbert, P.F. Zipfel, C. Skerka, G. Pradel,
837 Cutting Edge: FHR-1 Binding Impairs Factor H-Mediated Complement Evasion by the
838 Malaria Parasite *Plasmodium falciparum*, *J Immunol* 201(12) (2018) 3497-3502.

839 [80] M. Reuter, C.C. Caswell, S. Lukomski, P.F. Zipfel, Binding of the human complement
840 regulators CFHR1 and factor H by streptococcal collagen-like protein 1 (Sc11) via their
841 conserved C termini allows control of the complement cascade at multiple levels, *J Biol*
842 *Chem* 285(49) (2010) 38473-85.

843 [81] E. Goicoechea de Jorge, J.J. Caesar, T.H. Malik, M. Patel, M. Colledge, S. Johnson, S.
844 Hakobyan, B.P. Morgan, C.L. Harris, M.C. Pickering, S.M. Lea, Dimerization of
845 complement factor H-related proteins modulates complement activation in vivo, *Proc Natl*
846 *Acad Sci U S A* 110(12) (2013) 4685-90.

847 [82] A.E. van Beek, R.B. Pouw, M.C. Brouwer, G. van Mierlo, J. Geissler, P. Ooijevaar-de
848 Heer, M. de Boer, K. van Leeuwen, T. Rispens, D. Wouters, T.W. Kuijpers, Factor H-Related

849 (FHR)-1 and FHR-2 Form Homo- and Heterodimers, while FHR-5 Circulates Only As
850 Homodimer in Human Plasma, *Front Immunol* 8 (2017) 1328.

851 [83] N.R. Medjeral-Thomas, H.J. Lomax-Browne, H. Beckwith, M. Willicombe, A.G.
852 McLean, P. Brookes, C.D. Pusey, M. Falchi, H.T. Cook, M.C. Pickering, Circulating
853 complement factor H-related proteins 1 and 5 correlate with disease activity in IgA
854 nephropathy, *Kidney Int* 92(4) (2017) 942-952.

855 [84] A. Tortajada, E. Gutierrez, E. Goicoechea de Jorge, J. Anter, A. Segarra, M. Espinosa,
856 M. Blasco, E. Roman, H. Marco, L.F. Quintana, J. Gutierrez, S. Pinto, M. Lopez-Trascasa,
857 M. Praga, S. Rodriguez de Cordoba, Elevated factor H-related protein 1 and factor H
858 pathogenic variants decrease complement regulation in IgA nephropathy, *Kidney Int* 92(4)
859 (2017) 953-963.

860 [85] P. Zhang, M. Zhu, M. Geng-Spyropoulos, M. Shardell, M. Gonzalez-Freire, V.
861 Gudnason, G. Eiriksdottir, D. Schaumberg, J.E. Van Eyk, L. Ferrucci, R.D. Semba, A novel,
862 multiplexed targeted mass spectrometry assay for quantification of complement factor H
863 (CFH) variants and CFH-related proteins 1-5 in human plasma, *Proteomics* 17(6) (2017).

864 [86] L.V. Holmes, L. Strain, S.J. Staniforth, I. Moore, K. Marchbank, D. Kavanagh, J.A.
865 Goodship, H.J. Cordell, T.H. Goodship, Determining the population frequency of the
866 CFHR3/CFHR1 deletion at 1q32, *PLoS One* 8(4) (2013) e60352.

867 [87] W.M. Prodinger, J. Hellwage, M. Spruth, M.P. Dierich, P.F. Zipfel, The C-terminus of
868 factor H: monoclonal antibodies inhibit heparin binding and identify epitopes common to
869 factor H and factor H-related proteins, *Biochem J* 331 (Pt 1) (1998) 41-7.

870 [88] C. Skerka, C. Timmann, R.D. Horstmann, P.F. Zipfel, Two additional human serum
871 proteins structurally related to complement factor H. Evidence for a family of factor H-
872 related genes, *J Immunol* 148(10) (1992) 3313-8.

873 [89] A. Tortajada, H. Yebenes, C. Abarrategui-Garrido, J. Anter, J.M. Garcia-Fernandez, R.
874 Martinez-Barricarte, M. Alba-Dominguez, T.H. Malik, R. Bedoya, R. Cabrera Perez, M.
875 Lopez Trascasa, M.C. Pickering, C.L. Harris, P. Sanchez-Corral, O. Llorca, S. Rodriguez de
876 Cordoba, C3 glomerulopathy-associated CFHR1 mutation alters FHR oligomerization and
877 complement regulation, *J Clin Invest* 123(6) (2013) 2434-46.

878 [90] C. Skerka, S. Kuhn, K. Gunther, K. Lingelbach, P.F. Zipfel, A novel short consensus
879 repeat-containing molecule is related to human complement factor H, *J Biol Chem* 268(4)
880 (1993) 2904-8.

881 [91] J. Hellwage, T.S. Jokiranta, V. Koistinen, O. Vaarala, S. Meri, P.F. Zipfel, Functional
882 properties of complement factor H-related proteins FHR-3 and FHR-4: binding to the C3d
883 region of C3b and differential regulation by heparin, *FEBS Lett* 462(3) (1999) 345-52.

884 [92] R.B. Pouw, M.C. Brouwer, J. Geissler, L.V. van Herpen, S.S. Zeerleder, W.A.
885 Willemin, D. Wouters, T.W. Kuijpers, Complement Factor H-Related Protein 3 Serum
886 Levels Are Low Compared to Factor H and Mainly Determined by Gene Copy Number
887 Variation in CFHR3, *PLoS One* 11(3) (2016) e0152164.

888 [93] R.B. Pouw, I. Gomez Delgado, A. Lopez Lera, S. Rodriguez de Cordoba, D. Wouters,
889 T.W. Kuijpers, P. Sanchez-Corral, High Complement Factor H-Related (FHR)-3 Levels Are
890 Associated With the Atypical Hemolytic-Uremic Syndrome-Risk Allele CFHR3*B, *Front*
891 *Immunol* 9 (2018) 848.

892 [94] M.E. Bernabeu-Herrero, M. Jimenez-Alcazar, J. Anter, S. Pinto, D. Sanchez Chinchilla,
893 S. Garrido, M. Lopez-Trascasa, S. Rodriguez de Cordoba, P. Sanchez-Corral, Complement
894 factor H, FHR-3 and FHR-1 variants associate in an extended haplotype conferring increased
895 risk of atypical hemolytic uremic syndrome, *Mol Immunol* 67(2 Pt B) (2015) 276-86.

896 [95] A.E. Hughes, N. Orr, H. Esfandiary, M. Diaz-Torres, T. Goodship, U. Chakravarthy, A
897 common CFH haplotype, with deletion of CFHR1 and CFHR3, is associated with lower risk
898 of age-related macular degeneration, *Nat Genet* 38(10) (2006) 1173-7.

899 [96] M. Jozsi, H. Richter, I. Loschmann, C. Skerka, F. Buck, U. Beisiegel, A. Erdei, P.F.
900 Zipfel, FHR-4A: a new factor H-related protein is encoded by the human FHR-4 gene, *Eur J*
901 *Hum Genet* 13(3) (2005) 321-9.

902 [97] C. Skerka, J. Hellwege, W. Weber, A. Tilkorn, F. Buck, T. Marti, E. Kampen, U.
903 Beisiegel, P.F. Zipfel, The human factor H-related protein 4 (FHR-4). A novel short
904 consensus repeat-containing protein is associated with human triglyceride-rich lipoproteins, *J*
905 *Biol Chem* 272(9) (1997) 5627-34.

906 [98] R.B. Pouw, M.C. Brouwer, A.E. van Beek, M. Jozsi, D. Wouters, T.W. Kuijpers,
907 Complement Factor H-Related Protein 4A Is the Dominant Circulating Splice Variant of
908 CFHR4, *Front Immunol* 9 (2018) 729.

909 [99] J. Hellwege, C. Skerka, P.F. Zipfel, Biochemical and functional characterization of the
910 factor-H-related protein 4 (FHR-4), *Immunopharmacology* 38(1-2) (1997) 149-57.

911 [100] J.L. McRae, P.J. Cowan, D.A. Power, K.I. Mitchelhill, B.E. Kemp, B.P. Morgan, B.F.
912 Murphy, Human factor H-related protein 5 (FHR-5). A new complement-associated protein, *J*
913 *Biol Chem* 276(9) (2001) 6747-54.

914 [101] J.L. McRae, T.G. Duthy, K.M. Griggs, R.J. Ormsby, P.J. Cowan, B.A. Cromer, W.J.
915 McKinstry, M.W. Parker, B.F. Murphy, D.L. Gordon, Human factor H-related protein 5 has
916 cofactor activity, inhibits C3 convertase activity, binds heparin and C-reactive protein, and
917 associates with lipoprotein, *J Immunol* 174(10) (2005) 6250-6.

918 [102] M. Narkio-Makela, J. Hellwege, O. Tahkokallio, S. Meri, Complement-regulator factor
919 H and related proteins in otitis media with effusion, *Clin Immunol* 100(1) (2001) 118-26.

920 [103] R.B. Rudnick, Q. Chen, E.D. Stea, A. Hartmann, N. Papac-Milicevic, F. Person, M.
921 Wiesener, C.J. Binder, T. Wiech, C. Skerka, P.F. Zipfel, FHR5 Binds to Laminins, Uses
922 Separate C3b and Surface-Binding Sites, and Activates Complement on Malondialdehyde-
923 Acetaldehyde Surfaces, *J Immunol* 200(7) (2018) 2280-2290.

924 [104] L.G. Fritsche, N. Lauer, A. Hartmann, S. Stippa, C.N. Keilhauer, M. Oppermann, M.K.
925 Pandey, J. Kohl, P.F. Zipfel, B.H. Weber, C. Skerka, An imbalance of human complement
926 regulatory proteins CFHR1, CFHR3 and factor H influences risk for age-related macular
927 degeneration (AMD), *Hum Mol Genet* 19(23) (2010) 4694-704.

928 [105] H.U. Eberhardt, D. Buhlmann, P. Hortschansky, Q. Chen, S. Bohm, M.J. Kemper, R.
929 Wallich, A. Hartmann, T. Hallstrom, P.F. Zipfel, C. Skerka, Human factor H-related protein
930 2 (CFHR2) regulates complement activation, *PLoS One* 8(11) (2013) e78617.

931 [106] T. Meszaros, A.I. Csincsi, B. Uzonyi, M. Hebecker, T.G. Fulop, A. Erdei, J. Szebeni,
932 M. Jozsi, Factor H inhibits complement activation induced by liposomal and micellar drugs
933 and the therapeutic antibody rituximab in vitro, *Nanomedicine* (2016).

934 [107] S. Strobel, C. Abarrategui-Garrido, E. Fariza-Requejo, H. Seeberger, P. Sanchez-
935 Corral, M. Jozsi, Factor H-related protein 1 neutralizes anti-factor H autoantibodies in
936 autoimmune hemolytic uremic syndrome, *Kidney Int* 80(4) (2011) 397-404.

937 [108] K. Shi, Z. Wang, Y. Liu, Y. Gong, Y. Fu, S. Li, K. Wood, J. Hao, G.X. Zhang, F.D.
938 Shi, Y. Yan, CFHR1-Modified Neural Stem Cells Ameliorated Brain Injury in a Mouse
939 Model of Neuromyelitis Optica Spectrum Disorders, *J Immunol* 197(9) (2016) 3471-3480.

940 [109] S.A. Zwarthoff, E.T.M. Berends, S. Mol, M. Ruyken, P.C. Aerts, M. Jozsi, C.J.C. de
941 Haas, S.H.M. Rooijackers, R.D. Gorham, Jr., Functional Characterization of Alternative and
942 Classical Pathway C3/C5 Convertase Activity and Inhibition Using Purified Models, *Front*
943 *Immunol* 9 (2018) 1691.

944 [110] K.A. Vernon, E. Goicoechea de Jorge, A.E. Hall, V. Fremeaux-Bacchi, T.J. Aitman,
945 H.T. Cook, R. Hangartner, A. Koziell, M.C. Pickering, Acute presentation and persistent
946 glomerulonephritis following streptococcal infection in a patient with heterozygous
947 complement factor H-related protein 5 deficiency, *Am J Kidney Dis* 60(1) (2012) 121-5.

948 [111] J.J. Caesar, H. Lavender, P.N. Ward, R.M. Exley, J. Eaton, E. Chittock, T.H. Malik, E.
949 Goicoechea De Jorge, M.C. Pickering, C.M. Tang, S.M. Lea, Competition between
950 antagonistic complement factors for a single protein on *N. meningitidis* rules disease
951 susceptibility, *Elife* 3 (2014).

952 [112] A.H. Antonioli, J. White, F. Crawford, B. Renner, K.J. Marchbank, J.P. Hannan, J.M.
953 Thurman, P. Marrack, V.M. Holers, Modulation of the Alternative Pathway of Complement
954 by Murine Factor H-Related Proteins, *J Immunol* 200(1) (2018) 316-326.

955 [113] M. Cserhalmi, A.I. Csincsi, Z. Mezei, A. Kopp, M. Hebecker, B. Uzonyi, M. Jozsi, The
956 Murine Factor H-Related Protein FHR-B Promotes Complement Activation, *Front Immunol*
957 8 (2017) 1145.

958 [114] L.B. da Silva, S. Miragaia Ldos, L.C. Breda, C.M. Abe, M.C. Schmidt, A.M. Moro, D.
959 Monaris, J.N. Conde, M. Jozsi, L. Isaac, P.A. Abreu, A.S. Barbosa, Pathogenic *Leptospira*
960 species acquire factor H and vitronectin via the surface protein LcpA, *Infect Immun* 83(3)
961 (2015) 888-97.

962 [115] M. Jozsi, Factor H Family Proteins in Complement Evasion of Microorganisms, *Front*
963 *Immunol* 8 (2017) 571.

964 [116] J.D. Lambris, D. Ricklin, B.V. Geisbrecht, Complement evasion by human pathogens,
965 *Nat Rev Microbiol* 6(2) (2008) 132-42.

966 [117] T. Meri, H. Amdahl, M.J. Lehtinen, S. Hyvarinen, J.V. McDowell, A. Bhattacharjee, S.
967 Meri, R. Marconi, A. Goldman, T.S. Jokiranta, Microbes bind complement inhibitor factor H
968 via a common site, *PLoS Pathog* 9(4) (2013) e1003308.

969 [118] T.K. Blackmore, V.A. Fischetti, T.A. Sadlon, H.M. Ward, D.L. Gordon, M protein of
970 the group A *Streptococcus* binds to the seventh short consensus repeat of human complement
971 factor H, *Infect Immun* 66(4) (1998) 1427-31.

972 [119] J.V. McDowell, J. Lankford, L. Stamm, T. Sadlon, D.L. Gordon, R.T. Marconi,
973 Demonstration of factor H-like protein 1 binding to *Treponema denticola*, a pathogen
974 associated with periodontal disease in humans, *Infect Immun* 73(11) (2005) 7126-32.

975 [120] H. Jarva, R. Janulczyk, J. Hellwage, P.F. Zipfel, L. Bjorck, S. Meri, *Streptococcus*
976 *pneumoniae* evades complement attack and opsonophagocytosis by expressing the *pspC*
977 locus-encoded Hic protein that binds to short consensus repeats 8-11 of factor H, *J Immunol*
978 168(4) (2002) 1886-94.

979 [121] M. Pizza, J. Donnelly, R. Rappuoli, Factor H-binding protein, a unique meningococcal
980 vaccine antigen, *Vaccine* 26 Suppl 8 (2008) I46-8.

981 [122] A. Kunert, J. Losse, C. Gruszyn, M. Huhn, K. Kaendler, S. Mikkat, D. Volke, R.
982 Hoffmann, T.S. Jokiranta, H. Seeberger, U. Moellmann, J. Hellwage, P.F. Zipfel, Immune
983 evasion of the human pathogen *Pseudomonas aeruginosa*: elongation factor Tuf is a factor H
984 and plasminogen binding protein, *J Immunol* 179(5) (2007) 2979-88.

985 [123] R. Janulczyk, F. Iannelli, A.G. Sjöholm, G. Pozzi, L. Bjorck, Hic, a novel surface
986 protein of *Streptococcus pneumoniae* that interferes with complement function, *J Biol Chem*
987 275(47) (2000) 37257-63.

988 [124] K. Haupt, M. Reuter, J. van den Elsen, J. Burman, S. Halbich, J. Richter, C. Skerka,
989 P.F. Zipfel, The *Staphylococcus aureus* protein Sbi acts as a complement inhibitor and forms
990 a tripartite complex with host complement Factor H and C3b, *PLoS Pathog* 4(12) (2008)
991 e1000250.

992 [125] J. Hellwage, T. Meri, T. Heikkila, A. Alitalo, J. Panelius, P. Lahdenne, I.J. Seppala, S.
993 Meri, The complement regulator factor H binds to the surface protein OspE of *Borrelia*
994 *burgdorferi*, *J Biol Chem* 276(11) (2001) 8427-35.

995 [126] P. Kraiczy, C. Skerka, V. Brade, P.F. Zipfel, Further characterization of complement
996 regulator-acquiring surface proteins of *Borrelia burgdorferi*, *Infect Immun* 69(12) (2001)
997 7800-9.

998 [127] P. Kraiczy, C. Skerka, M. Kirschfink, V. Brade, P.F. Zipfel, Immune evasion of
999 *Borrelia burgdorferi* by acquisition of human complement regulators FHL-1/reconnectin and
1000 Factor H, *Eur J Immunol* 31(6) (2001) 1674-84.

1001 [128] T. Meri, A. Hartmann, D. Lenk, R. Eck, R. Wurzner, J. Hellwage, S. Meri, P.F. Zipfel,
1002 The yeast *Candida albicans* binds complement regulators factor H and FHL-1, *Infect Immun*
1003 70(9) (2002) 5185-92.

1004 [129] G. Vogl, I. Lesiak, D.B. Jensen, S. Perkhofer, R. Eck, C. Speth, C. Lass-Flörl, P.F.
1005 Zipfel, A.M. Blom, M.P. Dierich, R. Wurzner, Immune evasion by acquisition of
1006 complement inhibitors: the mould *Aspergillus* binds both factor H and C4b binding protein,
1007 *Mol Immunol* 45(5) (2008) 1485-93.

1008 [130] A.T. Kennedy, C.Q. Schmidt, J.K. Thompson, G.E. Weiss, T. Taechalertpaisarn, P.R.
1009 Gilson, P.N. Barlow, B.S. Crabb, A.F. Cowman, W.H. Tham, Recruitment of Factor H as a
1010 Novel Complement Evasion Strategy for Blood-Stage *Plasmodium falciparum* Infection, *J*
1011 *Immunol* 196(3) (2016) 1239-48.

1012 [131] T. Meri, T.S. Jokiranta, J. Hellwage, A. Bialonski, P.F. Zipfel, S. Meri, *Onchocerca*
1013 *volvulus microfilariae* avoid complement attack by direct binding of factor H, *J Infect Dis*
1014 185(12) (2002) 1786-93.

1015 [132] S. Agarwal, S. Ram, J. Ngampasutadol, S. Gulati, P.F. Zipfel, P.A. Rice, Factor H
1016 facilitates adherence of *Neisseria gonorrhoeae* to complement receptor 3 on eukaryotic cells,
1017 *J Immunol* 185(7) (2010) 4344-53.

1018 [133] J. Behnsen, A. Hartmann, J. Schmalzer, A. Gehrke, A.A. Brakhage, P.F. Zipfel, The
1019 opportunistic human pathogenic fungus *Aspergillus fumigatus* evades the host complement
1020 system, *Infect Immun* 76(2) (2008) 820-7.

1021 [134] T.F. Rosa, A. Flammersfeld, C.J. Ngwa, M. Kiesow, R. Fischer, P.F. Zipfel, C. Skerka,
1022 G. Pradel, The *Plasmodium falciparum* blood stages acquire factor H family proteins to evade
1023 destruction by human complement, *Cell Microbiol* 18(4) (2016) 573-90.

1024 [135] C. Siegel, T. Hallstrom, C. Skerka, H. Eberhardt, B. Uzonyi, T. Beckhaus, M. Karas, R.
1025 Wallich, B. Stevenson, P.F. Zipfel, P. Kraiczy, Complement factor H-related proteins CFHR2
1026 and CFHR5 represent novel ligands for the infection-associated CRASP proteins of *Borrelia*
1027 *burgdorferi*, *PLoS One* 5(10) (2010) e13519.

1028 [136] N. Friberg, P. Carlson, E. Kentala, P.S. Mattila, P. Kuusela, S. Meri, H. Jarva, Factor H
1029 binding as a complement evasion mechanism for an anaerobic pathogen, *Fusobacterium*
1030 *necrophorum*, *J Immunol* 181(12) (2008) 8624-32.

1031 [137] P. Kraiczy, Hide and Seek: How Lyme Disease Spirochetes Overcome Complement
1032 Attack, *Front Immunol* 7 (2016) 385.

1033 [138] P. Kraiczy, B. Stevenson, Complement regulator-acquiring surface proteins of *Borrelia*
1034 *burgdorferi*: Structure, function and regulation of gene expression, *Ticks Tick Borne Dis* 4(1-
1035 2) (2013) 26-34.

1036 [139] T.R. Fraga, L. Isaac, A.S. Barbosa, Complement Evasion by Pathogenic *Leptospira*,
1037 *Front Immunol* 7 (2016) 623.

1038 [140] B. Stevenson, H.A. Choy, M. Pinne, M.L. Rotondi, M.C. Miller, E. Demoll, P. Kraiczy,
1039 A.E. Cooley, T.P. Creamer, M.A. Suchard, C.A. Brissette, A. Verma, D.A. Haake, *Leptospira*
1040 *interrogans* endostatin-like outer membrane proteins bind host fibronectin, laminin and
1041 regulators of complement, *PLoS One* 2(11) (2007) e1188.

1042 [141] A. Verma, J. Hellwage, S. Artiushin, P.F. Zipfel, P. Kraiczy, J.F. Timoney, B.
1043 Stevenson, LfhA, a novel factor H-binding protein of *Leptospira interrogans*, *Infect Immun*
1044 74(5) (2006) 2659-66.

1045 [142] Y. Yang, C.R. Back, M.A. Grawert, A.A. Wahid, H. Denton, R. Kildani, J. Paulin, K.
1046 Worner, W. Kaiser, D.I. Svergun, A. Sartbaeva, A.G. Watts, K.J. Marchbank, J.M.H. van den

1047 Elsen, Utilization of Staphylococcal Immune Evasion Protein Sbi as a Novel Vaccine
1048 Adjuvant, *Front Immunol* 9 (2019) 3139.

1049 [143] M.C. Schneider, R.M. Exley, H. Chan, I. Feavers, Y.H. Kang, R.B. Sim, C.M. Tang,
1050 Functional significance of factor H binding to *Neisseria meningitidis*, *J Immunol* 176(12)
1051 (2006) 7566-75.

1052 [144] M.C. Schneider, B.E. Prosser, J.J. Caesar, E. Kugelberg, S. Li, Q. Zhang, S. Quoraishi,
1053 J.E. Lovett, J.E. Deane, R.B. Sim, P. Roversi, S. Johnson, C.M. Tang, S.M. Lea, *Neisseria*
1054 *meningitidis* recruits factor H using protein mimicry of host carbohydrates, *Nature* 458(7240)
1055 (2009) 890-3.

1056 [145] S. Davila, V.J. Wright, C.C. Khor, K.S. Sim, A. Binder, W.B. Breunis, D. Inwald, S.
1057 Nadel, H. Betts, E.D. Carrol, R. de Groot, P.W. Hermans, J. Hazelzet, M. Emonts, C.C. Lim,
1058 T.W. Kuijpers, F. Martinon-Torres, A. Salas, W. Zenz, M. Levin, M.L. Hibberd, Genome-
1059 wide association study identifies variants in the CFH region associated with host
1060 susceptibility to meningococcal disease, *Nat Genet* 42(9) (2010) 772-6.

1061 [146] D. Buhlmann, H.U. Eberhardt, A. Medyukhina, W.M. Prodinger, M.T. Figge, P.F.
1062 Zipfel, C. Skerka, FHR3 Blocks C3d-Mediated Coactivation of Human B Cells, *J Immunol*
1063 197(2) (2016) 620-9.

1064 [147] M. Jozsi, A.E. Schneider, E. Karpati, N. Sandor, Complement factor H family proteins
1065 in their non-canonical role as modulators of cellular functions, *Semin Cell Dev Biol* 85
1066 (2019) 122-131.

1067 [148] R. Parente, S.J. Clark, A. Inforzato, A.J. Day, Complement factor H in host defense and
1068 immune evasion, *Cell Mol Life Sci* 74(9) (2017) 1605-1624.

1069 [149] S. Cantsilieris, B.J. Nelson, J. Huddleston, C. Baker, L. Harshman, K. Penewit, K.M.
1070 Munson, M. Sorensen, A.E. Welch, V. Dang, F. Grassmann, A.J. Richardson, R.H. Guymer,
1071 T.A. Graves-Lindsay, R.K. Wilson, B.H.F. Weber, P.N. Baird, R. Allikmets, E.E. Eichler,
1072 Recurrent structural variation, clustered sites of selection, and disease risk for the
1073 complement factor H (CFH) gene family, *Proc Natl Acad Sci U S A* 115(19) (2018) E4433-
1074 E4442.

1075 [150] S.J. Clark, P.N. Bishop, Role of Factor H and Related Proteins in Regulating
1076 Complement Activation in the Macula, and Relevance to Age-Related Macular Degeneration,
1077 *J Clin Med* 4(1) (2015) 18-31.

1078 [151] T.H. Goodship, H.T. Cook, F. Fakhouri, F.C. Fervenza, V. Fremeaux-Bacchi, D.
1079 Kavanagh, C.M. Nester, M. Noris, M.C. Pickering, S. Rodriguez de Cordoba, L.T.
1080 Roumenina, S. Sethi, R.J. Smith, Atypical hemolytic uremic syndrome and C3
1081 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes"
1082 (KDIGO) Controversies Conference, *Kidney Int* 91(3) (2017) 539-551.

1083 [152] N. Maillard, R.J. Wyatt, B.A. Julian, K. Kiryluk, A. Gharavi, V. Fremeaux-Bacchi, J.
1084 Novak, Current Understanding of the Role of Complement in IgA Nephropathy, *J Am Soc*
1085 *Nephrol* 26(7) (2015) 1503-12.

1086 [153] R.J.H. Smith, G.B. Appel, A.M. Blom, H.T. Cook, V.D. D'Agati, F. Fakhouri, V.
1087 Fremeaux-Bacchi, M. Jozsi, D. Kavanagh, J.D. Lambris, M. Noris, M.C. Pickering, G.
1088 Remuzzi, S.R. de Cordoba, S. Sethi, J. Van der Vlag, P.F. Zipfel, C.M. Nester, C3
1089 glomerulopathy - understanding a rare complement-driven renal disease, *Nat Rev Nephrol*
1090 15(3) (2019) 129-143.

1091 [154] M.A. Abrera-Abeleda, C. Nishimura, J.L. Smith, S. Sethi, J.L. McRae, B.F. Murphy,
1092 G. Silvestri, C. Skerka, M. Jozsi, P.F. Zipfel, G.S. Hageman, R.J. Smith, Variations in the
1093 complement regulatory genes factor H (CFH) and factor H related 5 (CFHR5) are associated
1094 with membranoproliferative glomerulonephritis type II (dense deposit disease), *J Med Genet*
1095 43(7) (2006) 582-9.

1096 [155] B.H. Ault, B.Z. Schmidt, N.L. Fowler, C.E. Kashtan, A.E. Ahmed, B.A. Vogt, H.R.
1097 Colten, Human factor H deficiency. Mutations in framework cysteine residues and block in H
1098 protein secretion and intracellular catabolism, *J Biol Chem* 272(40) (1997) 25168-75.
1099 [156] C.J. Boon, N.C. van de Kar, B.J. Klevering, J.E. Keunen, F.P. Cremers, C.C. Klaver,
1100 C.B. Hoyng, M.R. Daha, A.I. den Hollander, The spectrum of phenotypes caused by variants
1101 in the CFH gene, *Mol Immunol* 46(8-9) (2009) 1573-94.
1102 [157] M. Cserhalmi, B. Uzonyi, N.S. Merle, D. Csuka, E. Meusburger, K. Lhotta, Z.
1103 Prohaszka, M. Jozsi, Functional Characterization of the Disease-Associated N-Terminal
1104 Complement Factor H Mutation W198R, *Front Immunol* 8 (2017) 1800.
1105 [158] M.A. Dragon-Durey, V. Fremeaux-Bacchi, C. Loirat, J. Blouin, P. Niaudet, G.
1106 Deschenes, P. Coppo, W. Herman Fridman, L. Weiss, Heterozygous and homozygous factor
1107 h deficiencies associated with hemolytic uremic syndrome or membranoproliferative
1108 glomerulonephritis: report and genetic analysis of 16 cases, *J Am Soc Nephrol* 15(3) (2004)
1109 787-95.
1110 [159] S. Hakobyan, A. Tortajada, C.L. Harris, S.R. de Cordoba, B.P. Morgan, Variant-
1111 specific quantification of factor H in plasma identifies null alleles associated with atypical
1112 hemolytic uremic syndrome, *Kidney Int* 78(8) (2010) 782-8.
1113 [160] K. Janssen van Doorn, E. Dirinck, G.A. Verpooten, M.M. Couttenye, Complement
1114 factor H mutation associated with membranoproliferative glomerulonephritis with
1115 transformation to atypical haemolytic uraemic syndrome, *Clin Kidney J* 6(2) (2013) 216-219.
1116 [161] C. Licht, S. Heinen, M. Jozsi, I. Loschmann, R.E. Saunders, S.J. Perkins, R. Waldherr,
1117 C. Skerka, M. Kirschfink, B. Hoppe, P.F. Zipfel, Deletion of Lys224 in regulatory domain 4
1118 of Factor H reveals a novel pathomechanism for dense deposit disease (MPGN II), *Kidney*
1119 *Int* 70(1) (2006) 42-50.
1120 [162] T.K. Maga, C.J. Nishimura, A.E. Weaver, K.L. Frees, R.J. Smith, Mutations in
1121 alternative pathway complement proteins in American patients with atypical hemolytic
1122 uremic syndrome, *Hum Mutat* 31(6) (2010) E1445-60.
1123 [163] A.J. Osborne, M. Breno, N.G. Borsa, F. Bu, V. Fremeaux-Bacchi, D.P. Gale, L.P. van
1124 den Heuvel, D. Kavanagh, M. Noris, S. Pinto, P.M. Rallapalli, G. Remuzzi, S. Rodriguez de
1125 Cordoba, A. Ruiz, R.J.H. Smith, P. Vieira-Martins, E. Volokhina, V. Wilson, T.H.J.
1126 Goodship, S.J. Perkins, Statistical Validation of Rare Complement Variants Provides Insights
1127 into the Molecular Basis of Atypical Hemolytic Uremic Syndrome and C3 Glomerulopathy, *J*
1128 *Immunol* 200(7) (2018) 2464-2478.
1129 [164] I.C. Pechtl, D. Kavanagh, N. McIntosh, C.L. Harris, P.N. Barlow, Disease-associated
1130 N-terminal complement factor H mutations perturb cofactor and decay-accelerating activities,
1131 *J Biol Chem* 286(13) (2011) 11082-90.
1132 [165] D. Perez-Caballero, C. Gonzalez-Rubio, M.E. Gallardo, M. Vera, M. Lopez-Trascasa,
1133 S. Rodriguez de Cordoba, P. Sanchez-Corral, Clustering of missense mutations in the C-
1134 terminal region of factor H in atypical hemolytic uremic syndrome, *Am J Hum Genet* 68(2)
1135 (2001) 478-84.
1136 [166] S. Rodriguez de Cordoba, J. Esparza-Gordillo, E. Goicoechea de Jorge, M. Lopez-
1137 Trascasa, P. Sanchez-Corral, The human complement factor H: functional roles, genetic
1138 variations and disease associations, *Mol Immunol* 41(4) (2004) 355-67.
1139 [167] P. Sanchez-Corral, D. Perez-Caballero, O. Huarte, A.M. Simckes, E. Goicoechea, M.
1140 Lopez-Trascasa, S.R. de Cordoba, Structural and functional characterization of factor H
1141 mutations associated with atypical hemolytic uremic syndrome, *Am J Hum Genet* 71(6)
1142 (2002) 1285-95.
1143 [168] N. Szarvas, A. Szilagy, D. Csuka, B. Takacs, K. Rusai, T. Muller, K. Arbeiter, M.
1144 Reti, A. Haris, L. Wagner, S. Torok, K. Kelen, A.J. Szabo, G.S. Reusz, B.P. Morgan, Z.

1145 Prohaszka, Genetic analysis and functional characterization of novel mutations in a series of
 1146 patients with atypical hemolytic uremic syndrome, *Mol Immunol* 71 (2016) 10-22.
 1147 [169] V.P. Ferreira, A.P. Herbert, C. Cortes, K.A. McKee, B.S. Blaum, S.T. Esswein, D.
 1148 Uhrin, P.N. Barlow, M.K. Pangburn, D. Kavanagh, The binding of factor H to a complex of
 1149 physiological polyanions and C3b on cells is impaired in atypical hemolytic uremic
 1150 syndrome, *J Immunol* 182(11) (2009) 7009-18.
 1151 [170] E. Gnappi, M. Allinovi, A. Vaglio, E. Bresin, A. Sorosina, F.P. Pilato, L. Allegri, L.
 1152 Manenti, Membrano-proliferative glomerulonephritis, atypical hemolytic uremic syndrome,
 1153 and a new complement factor H mutation: report of a case, *Pediatr Nephrol* 27(10) (2012)
 1154 1995-9.
 1155 [171] A.P. Herbert, D. Kavanagh, C. Johansson, H.P. Morgan, B.S. Blaum, J.P. Hannan, P.N.
 1156 Barlow, D. Uhrin, Structural and functional characterization of the product of disease-related
 1157 factor H gene conversion, *Biochemistry* 51(9) (2012) 1874-84.
 1158 [172] M. Jozsi, S. Heinen, A. Hartmann, C.W. Ostrowicz, S. Halbich, H. Richter, A. Kunert,
 1159 C. Licht, R.E. Saunders, S.J. Perkins, P.F. Zipfel, C. Skerka, Factor H and atypical hemolytic
 1160 uremic syndrome: mutations in the C-terminus cause structural changes and defective
 1161 recognition functions, *J Am Soc Nephrol* 17(1) (2006) 170-7.
 1162 [173] H. Kerr, E. Wong, E. Makou, Y. Yang, K. Marchbank, D. Kavanagh, A. Richards, A.P.
 1163 Herbert, P.N. Barlow, Disease-linked mutations in factor H reveal pivotal role of cofactor
 1164 activity in self surface-selective regulation of complement activation, *J Biol Chem* (2017).
 1165 [174] T. Manuelian, J. Hellwage, S. Meri, J. Caprioli, M. Noris, S. Heinen, M. Jozsi, H.P.
 1166 Neumann, G. Remuzzi, P.F. Zipfel, Mutations in factor H reduce binding affinity to C3b and
 1167 heparin and surface attachment to endothelial cells in hemolytic uremic syndrome, *J Clin*
 1168 *Invest* 111(8) (2003) 1181-90.
 1169 [175] H.M. Merinero, S.P. Garcia, J. Garcia-Fernandez, E. Arjona, A. Tortajada, S.
 1170 Rodriguez de Cordoba, Complete functional characterization of disease-associated genetic
 1171 variants in the complement factor H gene, *Kidney Int* 93(2) (2018) 470-481.
 1172 [176] S. Recalde, A. Tortajada, M. Subias, J. Anter, M. Blasco, R. Maranta, R. Coco, S.
 1173 Pinto, M. Noris, A. Garcia-Layana, S. Rodriguez de Cordoba, Molecular Basis of Factor H
 1174 R1210C Association with Ocular and Renal Diseases, *J Am Soc Nephrol* 27(5) (2016) 1305-
 1175 11.
 1176 [177] P. Sanchez-Corral, C. Gonzalez-Rubio, S. Rodriguez de Cordoba, M. Lopez-Trascasa,
 1177 Functional analysis in serum from atypical Hemolytic Uremic Syndrome patients reveals
 1178 impaired protection of host cells associated with mutations in factor H, *Mol Immunol* 41(1)
 1179 (2004) 81-4.
 1180 [178] A. Tortajada, T. Montes, R. Martinez-Barricarte, B.P. Morgan, C.L. Harris, S.R. de
 1181 Cordoba, The disease-protective complement factor H allotypic variant Ile62 shows increased
 1182 binding affinity for C3b and enhanced cofactor activity, *Hum Mol Genet* 18(18) (2009) 3452-
 1183 61.
 1184 [179] A. Tortajada, S. Pinto, J. Martinez-Ara, M. Lopez-Trascasa, P. Sanchez-Corral, S.R. de
 1185 Cordoba, Complement factor H variants I890 and L1007 while commonly associated with
 1186 atypical hemolytic uremic syndrome are polymorphisms with no functional significance,
 1187 *Kidney Int* 81(1) (2012) 56-63.
 1188 [180] E.K. Wong, H.E. Anderson, A.P. Herbert, R.C. Challis, P. Brown, G.S. Reis, J.O.
 1189 Tellez, L. Strain, N. Fluck, A. Humphrey, A. Macleod, A. Richards, D. Ahlert, M.
 1190 Santibanez-Koref, P.N. Barlow, K.J. Marchbank, C.L. Harris, T.H. Goodship, D. Kavanagh,
 1191 Characterization of a factor H mutation that perturbs the alternative pathway of complement
 1192 in a family with membranoproliferative GN, *J Am Soc Nephrol* 25(11) (2014) 2425-33.

1193 [181] A.O. Edwards, R. Ritter, 3rd, K.J. Abel, A. Manning, C. Panhuysen, L.A. Farrer,
1194 Complement factor H polymorphism and age-related macular degeneration, *Science*
1195 308(5720) (2005) 421-4.

1196 [182] G.S. Hageman, D.H. Anderson, L.V. Johnson, L.S. Hancox, A.J. Taiber, L.I. Hardisty,
1197 J.L. Hageman, H.A. Stockman, J.D. Borchardt, K.M. Gehrs, R.J. Smith, G. Silvestri, S.R.
1198 Russell, C.C. Klaver, I. Barbazetto, S. Chang, L.A. Yannuzzi, G.R. Barile, J.C. Merriam,
1199 R.T. Smith, A.K. Olsh, J. Bergeron, J. Zernant, J.E. Merriam, B. Gold, M. Dean, R.
1200 Allikmets, A common haplotype in the complement regulatory gene factor H (HF1/CFH)
1201 predisposes individuals to age-related macular degeneration, *Proc Natl Acad Sci U S A*
1202 102(20) (2005) 7227-32.

1203 [183] J.L. Haines, M.A. Hauser, S. Schmidt, W.K. Scott, L.M. Olson, P. Gallins, K.L.
1204 Spencer, S.Y. Kwan, M. Noureddine, J.R. Gilbert, N. Schnetz-Boutaud, A. Agarwal, E.A.
1205 Postel, M.A. Pericak-Vance, Complement factor H variant increases the risk of age-related
1206 macular degeneration, *Science* 308(5720) (2005) 419-21.

1207 [184] R.J. Klein, C. Zeiss, E.Y. Chew, J.Y. Tsai, R.S. Sackler, C. Haynes, A.K. Henning, J.P.
1208 SanGiovanni, S.M. Mane, S.T. Mayne, M.B. Bracken, F.L. Ferris, J. Ott, C. Barnstable, J.
1209 Hoh, Complement factor H polymorphism in age-related macular degeneration, *Science*
1210 308(5720) (2005) 385-9.

1211 [185] S.J. Clark, S. McHarg, V. Tilakaratna, N. Brace, P.N. Bishop, Bruch's Membrane
1212 Compartmentalizes Complement Regulation in the Eye with Implications for Therapeutic
1213 Design in Age-Related Macular Degeneration, *Front Immunol* 8 (2017) 1778.

1214 [186] S.J. Clark, R. Perveen, S. Hakobyan, B.P. Morgan, R.B. Sim, P.N. Bishop, A.J. Day,
1215 Impaired binding of the age-related macular degeneration-associated complement factor H
1216 402H allotype to Bruch's membrane in human retina, *J Biol Chem* 285(39) (2010) 30192-
1217 202.

1218 [187] M. Laine, H. Jarva, S. Seitsonen, K. Haapasalo, M.J. Lehtinen, N. Lindeman, D.H.
1219 Anderson, P.T. Johnson, I. Jarvela, T.S. Jokiranta, G.S. Hageman, I. Immonen, S. Meri,
1220 Y402H polymorphism of complement factor H affects binding affinity to C-reactive protein,
1221 *J Immunol* 178(6) (2007) 3831-6.

1222 [188] C. Skerka, N. Lauer, A.A. Weinberger, C.N. Keilhauer, J. Suhnel, R. Smith, U.
1223 Schlotzer-Schrehardt, L. Fritsche, S. Heinen, A. Hartmann, B.H. Weber, P.F. Zipfel,
1224 Defective complement control of factor H (Y402H) and FHL-1 in age-related macular
1225 degeneration, *Mol Immunol* 44(13) (2007) 3398-406.

1226 [189] R. Martinez-Barricarte, S. Recalde, P. Fernandez-Robredo, I. Millan, L. Olavarrieta, A.
1227 Vinuela, J. Perez-Perez, A. Garcia-Layana, S. Rodriguez de Cordoba, Relevance of
1228 complement factor H-related 1 (CFHR1) genotypes in age-related macular degeneration,
1229 *Invest Ophthalmol Vis Sci* 53(3) (2012) 1087-94.

1230 [190] G. Monteferrante, S. Brioschi, J. Caprioli, G. Pianetti, P. Bettinaglio, E. Bresin, G.
1231 Remuzzi, M. Noris, Genetic analysis of the complement factor H related 5 gene in
1232 haemolytic uraemic syndrome, *Mol Immunol* 44(7) (2007) 1704-8.

1233 [191] U. Narendra, G.J. Pauer, S.A. Hagstrom, Genetic analysis of complement factor H
1234 related 5, CFHR5, in patients with age-related macular degeneration, *Mol Vis* 15 (2009) 731-
1235 6.

1236 [192] D. Westra, K.A. Vernon, E.B. Volokhina, M.C. Pickering, N.C. van de Kar, L.P. van
1237 den Heuvel, Atypical hemolytic uremic syndrome and genetic aberrations in the complement
1238 factor H-related 5 gene, *J Hum Genet* 57(7) (2012) 459-64.

1239 [193] Y.L. Zhai, S.J. Meng, L. Zhu, S.F. Shi, S.X. Wang, L.J. Liu, J.C. Lv, F. Yu, M.H.
1240 Zhao, H. Zhang, Rare Variants in the Complement Factor H-Related Protein 5 Gene
1241 Contribute to Genetic Susceptibility to IgA Nephropathy, *J Am Soc Nephrol* 27(9) (2016)
1242 2894-905.

1243 [194] X.F. Huang, Y. Wang, F.F. Li, D. Lin, M.L. Dai, Q.F. Wang, Z.B. Jin, CFHR2-
1244 rs2986127 as a genetic protective marker for acute anterior uveitis in Chinese patients, *J*
1245 *Gene Med* 18(8) (2016) 193-8.

1246 [195] L. Lores-Motta, C.C. Paun, J. Corominas, M. Pauper, M.J. Geerlings, L. Altay, T.
1247 Schick, M.R. Daha, S. Fauser, C.B. Hoyng, A.I. den Hollander, E.K. de Jong, Genome-Wide
1248 Association Study Reveals Variants in CFH and CFHR4 Associated with Systemic
1249 Complement Activation: Implications in Age-Related Macular Degeneration, *Ophthalmology*
1250 125(7) (2018) 1064-1074.

1251 [196] S.R. de Cordoba, E.G. de Jorge, Translational mini-review series on complement factor
1252 H: genetics and disease associations of human complement factor H, *Clin Exp Immunol*
1253 151(1) (2008) 1-13.

1254 [197] G.S. Hageman, L.S. Hancox, A.J. Taiber, K.M. Gehrs, D.H. Anderson, L.V. Johnson,
1255 M.J. Radeke, D. Kavanagh, A. Richards, J. Atkinson, S. Meri, J. Bergeron, J. Zernant, J.
1256 Merriam, B. Gold, R. Allikmets, M. Dean, Extended haplotypes in the complement factor H
1257 (CFH) and CFH-related (CFHR) family of genes protect against age-related macular
1258 degeneration: characterization, ethnic distribution and evolutionary implications, *Ann Med*
1259 38(8) (2006) 592-604.

1260 [198] A.G. Gharavi, K. Kiryluk, M. Choi, Y. Li, P. Hou, J. Xie, S. Sanna-Cherchi, C.J. Men,
1261 B.A. Julian, R.J. Wyatt, J. Novak, J.C. He, H. Wang, J. Lv, L. Zhu, W. Wang, Z. Wang, K.
1262 Yasuno, M. Gunel, S. Mane, S. Umlauf, I. Tikhonova, I. Beeraman, S. Savoldi, R. Magistroni,
1263 G.M. Ghiggeri, M. Bodria, F. Lugani, P. Ravani, C. Ponticelli, L. Allegri, G. Boscutti, G.
1264 Frasca, A. Amore, L. Peruzzi, R. Coppo, C. Izzi, B.F. Viola, E. Prati, M. Salvadori, R.
1265 Mignani, L. Gesualdo, F. Bertinetto, P. Mesiano, A. Amoroso, F. Scolari, N. Chen, H. Zhang,
1266 R.P. Lifton, Genome-wide association study identifies susceptibility loci for IgA
1267 nephropathy, *Nat Genet* 43(4) (2011) 321-7.

1268 [199] J. Zhao, H. Wu, M. Khosravi, H. Cui, X. Qian, J.A. Kelly, K.M. Kaufman, C.D.
1269 Langefeld, A.H. Williams, M.E. Comeau, J.T. Ziegler, M.C. Marion, A. Adler, S.B. Glenn,
1270 M.E. Alarcon-Riquelme, B.A. Pons-Estel, J.B. Harley, S.C. Bae, S.Y. Bang, S.K. Cho, C.O.
1271 Jacob, T.J. Vyse, T.B. Niewold, P.M. Gaffney, K.L. Moser, R.P. Kimberly, J.C. Edberg, E.E.
1272 Brown, G.S. Alarcon, M.A. Petri, R. Ramsey-Goldman, L.M. Vila, J.D. Reveille, J.A. James,
1273 G.S. Gilkeson, D.L. Kamen, B.I. Freedman, J.M. Anaya, J.T. Merrill, L.A. Criswell, R.H.
1274 Scofield, A.M. Stevens, J.M. Guthridge, D.M. Chang, Y.W. Song, J.A. Park, E.Y. Lee, S.A.
1275 Boackle, J.M. Grossman, B.H. Hahn, T.H. Goodship, R.M. Cantor, C.Y. Yu, N. Shen, B.P.
1276 Tsao, Association of genetic variants in complement factor H and factor H-related genes with
1277 systemic lupus erythematosus susceptibility, *PLoS Genet* 7(5) (2011) e1002079.

1278 [200] L. Zhu, Y.L. Zhai, F.M. Wang, P. Hou, J.C. Lv, D.M. Xu, S.F. Shi, L.J. Liu, F. Yu,
1279 M.H. Zhao, J. Novak, A.G. Gharavi, H. Zhang, Variants in Complement Factor H and
1280 Complement Factor H-Related Protein Genes, CFHR3 and CFHR1, Affect Complement
1281 Activation in IgA Nephropathy, *J Am Soc Nephrol* 26(5) (2015) 1195-204.

1282 [201] P.F. Zipfel, M. Edey, S. Heinen, M. Jozsi, H. Richter, J. Misselwitz, B. Hoppe, D.
1283 Routledge, L. Strain, A.E. Hughes, J.A. Goodship, C. Licht, T.H. Goodship, C. Skerka,
1284 Deletion of complement factor H-related genes CFHR1 and CFHR3 is associated with
1285 atypical hemolytic uremic syndrome, *PLoS Genet* 3(3) (2007) e41.

1286 [202] I. Moore, L. Strain, I. Pappworth, D. Kavanagh, P.N. Barlow, A.P. Herbert, C.Q.
1287 Schmidt, S.J. Staniforth, L.V. Holmes, R. Ward, L. Morgan, T.H. Goodship, K.J. Marchbank,
1288 Association of factor H autoantibodies with deletions of CFHR1, CFHR3, CFHR4, and with
1289 mutations in CFH, CFI, CD46, and C3 in patients with atypical hemolytic uremic syndrome,
1290 *Blood* 115(2) (2010) 379-87.

1291 [203] M.A. Dragon-Durey, C. Blanc, F. Marliot, C. Loirat, J. Blouin, C. Sautes-Fridman,
1292 W.H. Fridman, V. Fremeaux-Bacchi, The high frequency of complement factor H related

1293 CFHR1 gene deletion is restricted to specific subgroups of patients with atypical haemolytic
1294 uraemic syndrome, *J Med Genet* 46(7) (2009) 447-50.

1295 [204] M. Jozsi, C. Licht, S. Strobel, S.L. Zipfel, H. Richter, S. Heinen, P.F. Zipfel, C. Skerka,
1296 Factor H autoantibodies in atypical hemolytic uremic syndrome correlate with
1297 CFHR1/CFHR3 deficiency, *Blood* 111(3) (2008) 1512-4.

1298 [205] A. Bhattacharjee, S. Reuter, E. Trojnar, R. Kolodziejczyk, H. Seeberger, S. Hyvarinen,
1299 B. Uzonyi, A. Szilagyi, Z. Prohaszka, A. Goldman, M. Jozsi, T.S. Jokiranta, The major
1300 autoantibody epitope on factor H in atypical hemolytic uremic syndrome is structurally
1301 different from its homologous site in factor H-related protein 1, supporting a novel model for
1302 induction of autoimmunity in this disease, *J Biol Chem* 290(15) (2015) 9500-10.

1303 [206] M. Jozsi, S. Strobel, H.M. Dahse, W.S. Liu, P.F. Hoyer, M. Oppermann, C. Skerka,
1304 P.F. Zipfel, Anti factor H autoantibodies block C-terminal recognition function of factor H in
1305 hemolytic uremic syndrome, *Blood* 110(5) (2007) 1516-8.

1306 [207] P. Nozal, M.E. Bernabeu-Herrero, B. Uzonyi, A. Szilagyi, S. Hyvarinen, Z. Prohaszka,
1307 T.S. Jokiranta, P. Sanchez-Corral, M. Lopez-Trascasa, M. Jozsi, Heterogeneity but individual
1308 constancy of epitopes, isotypes and avidity of factor H autoantibodies in atypical hemolytic
1309 uremic syndrome, *Mol Immunol* 70 (2016) 47-55.

1310 [208] E. Trojnar, M. Jozsi, K. Uray, D. Csuka, A. Szilagyi, D. Milosevic, V.D. Stojanovic, B.
1311 Spasojevic, K. Rusai, T. Muller, K. Arbeiter, K. Kelen, A.J. Szabo, G.S. Reusz, S.
1312 Hyvarinen, T.S. Jokiranta, Z. Prohaszka, Analysis of Linear Antibody Epitopes on Factor H
1313 and CFHR1 Using Sera of Patients with Autoimmune Atypical Hemolytic Uremic Syndrome,
1314 *Front Immunol* 8 (2017) 302.

1315 [209] R.C. Challis, G.S. Araujo, E.K. Wong, H.E. Anderson, A. Awan, A.M. Dorman, M.
1316 Waldron, V. Wilson, V. Brocklebank, L. Strain, B.P. Morgan, C.L. Harris, K.J. Marchbank,
1317 T.H. Goodship, D. Kavanagh, A De Novo Deletion in the Regulators of Complement
1318 Activation Cluster Producing a Hybrid Complement Factor H/Complement Factor H-Related
1319 3 Gene in Atypical Hemolytic Uremic Syndrome, *J Am Soc Nephrol* 27(6) (2016) 1617-24.

1320 [210] S.J. Eyler, N.C. Meyer, Y. Zhang, X. Xiao, C.M. Nester, R.J. Smith, A novel hybrid
1321 CFHR1/CFH gene causes atypical hemolytic uremic syndrome, *Pediatr Nephrol* 28(11)
1322 (2013) 2221-5.

1323 [211] N.J. Francis, B. McNicholas, A. Awan, M. Waldron, D. Reddan, D. Sadlier, D.
1324 Kavanagh, L. Strain, K.J. Marchbank, C.L. Harris, T.H. Goodship, A novel hybrid
1325 CFH/CFHR3 gene generated by a microhomology-mediated deletion in familial atypical
1326 hemolytic uremic syndrome, *Blood* 119(2) (2012) 591-601.

1327 [212] S. Heinen, P. Sanchez-Corral, M.S. Jackson, L. Strain, J.A. Goodship, E.J. Kemp, C.
1328 Skerka, T.S. Jokiranta, K. Meyers, E. Wagner, P. Robitaille, J. Esparza-Gordillo, S.
1329 Rodriguez de Cordoba, P.F. Zipfel, T.H. Goodship, De novo gene conversion in the RCA
1330 gene cluster (1q32) causes mutations in complement factor H associated with atypical
1331 hemolytic uremic syndrome, *Hum Mutat* 27(3) (2006) 292-3.

1332 [213] T.K. Maga, N.C. Meyer, C. Belsha, C.J. Nishimura, Y. Zhang, R.J. Smith, A novel
1333 deletion in the RCA gene cluster causes atypical hemolytic uremic syndrome, *Nephrol Dial
1334 Transplant* 26(2) (2011) 739-41.

1335 [214] E. Valoti, M. Alberti, A. Tortajada, J. Garcia-Fernandez, S. Gastoldi, L. Besso, E.
1336 Bresin, G. Remuzzi, S. Rodriguez de Cordoba, M. Noris, A novel atypical hemolytic uremic
1337 syndrome-associated hybrid CFHR1/CFH gene encoding a fusion protein that antagonizes
1338 factor H-dependent complement regulation, *J Am Soc Nephrol* 26(1) (2015) 209-19.

1339 [215] J.P. Venables, L. Strain, D. Routledge, D. Bourn, H.M. Powell, P. Warwicker, M.L.
1340 Diaz-Torres, A. Sampson, P. Mead, M. Webb, Y. Pirson, M.S. Jackson, A. Hughes, K.M.
1341 Wood, J.A. Goodship, T.H. Goodship, Atypical haemolytic uraemic syndrome associated
1342 with a hybrid complement gene, *PLoS Med* 3(10) (2006) e431.

1343 [216] D.P. Gale, E.G. de Jorge, H.T. Cook, R. Martinez-Barricarte, A. Hadjisavvas, A.G.
1344 McLean, C.D. Pusey, A. Pierides, K. Kyriacou, Y. Athanasiou, K. Voskarides, C. Deltas, A.
1345 Palmer, V. Fremeaux-Bacchi, S.R. de Cordoba, P.H. Maxwell, M.C. Pickering, Identification
1346 of a mutation in complement factor H-related protein 5 in patients of Cypriot origin with
1347 glomerulonephritis, *Lancet* 376(9743) (2010) 794-801.
1348 [217] T.H. Malik, P.J. Lavin, E. Goicoechea de Jorge, K.A. Vernon, K.L. Rose, M.P. Patel,
1349 M. de Leeuw, J.J. Neary, P.J. Conlon, M.P. Winn, M.C. Pickering, A hybrid CFHR3-1 gene
1350 causes familial C3 glomerulopathy, *J Am Soc Nephrol* 23(7) (2012) 1155-60.
1351 [218] N. Medjeral-Thomas, T.H. Malik, M.P. Patel, T. Toth, H.T. Cook, C. Tomson, M.C.
1352 Pickering, A novel CFHR5 fusion protein causes C3 glomerulopathy in a family without
1353 Cypriot ancestry, *Kidney Int* 85(4) (2014) 933-7.
1354 [219] S.K. Togarsimalemath, S.K. Sethi, R. Duggal, M.L. Quintrec, P. Jha, R. Daniel, F.
1355 Gonnet, S. Bansal, L.T. Roumenina, V. Fremeaux-Bacchi, V. Kher, M.A. Dragon-Durey, A
1356 novel CFHR1-CFHR5 hybrid leads to a familial dominant C3 glomerulopathy, *Kidney Int*
1357 (2017).
1358 [220] A. Tortajada, J. Gutierrez-Tenorio, A. Saiz Gonzalez, R. Marcen Letosa, A. Bouthelier,
1359 P. Sanchez-Corral, E. Goicochea de Jorge, S. Rodriguez de Cordoba, Novel duplication of
1360 the FHRs dimerization domain associated with C3G., *Mol Immunol* 89 (2017) 181.
1361 [221] X. Xiao, C. Ghossein, A. Tortajada, Y. Zhang, N. Meyer, M. Jones, N.G. Borsa, C.M.
1362 Nester, C.P. Thomas, S.R. de Cordoba, R.J. Smith, Familial C3 glomerulonephritis caused by
1363 a novel CFHR5-CFHR2 fusion gene, *Mol Immunol* 77 (2016) 89-96.
1364 [222] N. Schafer, A. Grosche, J. Reinders, S.M. Hauck, R.B. Pouw, T.W. Kuijpers, D.
1365 Wouters, B. Ehrenstein, V. Enzmann, P.F. Zipfel, C. Skerka, D. Pauly, Complement
1366 Regulator FHR-3 Is Elevated either Locally or Systemically in a Selection of Autoimmune
1367 Diseases, *Front Immunol* 7 (2016) 542.
1368 [223] N.R. Medjeral-Thomas, A. Trolborg, N. Constantinou, H.J. Lomax-Browne, A.G.
1369 Hansen, M. Willicombe, C.D. Pusey, H.T. Cook, S. Thiel, M.C. Pickering, Progressive IgA
1370 Nephropathy Is Associated With Low Circulating Mannan-Binding Lectin-Associated Serine
1371 Protease-3 (MASP-3) and Increased Glomerular Factor H-Related Protein-5 (FHR5)
1372 Deposition, *Kidney Int Rep* 3(2) (2018) 426-438.
1373

1374 **Figure legends**

1375 **Figure 1. Overview of complement activation and its regulation by factor H.**

1376 Complement is activated through three main pathways, initiated by the binding of recognition
1377 molecules, such as C1q in the classical pathway and mannose-binding lectin and ficolins in the
1378 lectin pathway, as well as by the spontaneous hydrolysis of C3b in the alternative pathway.
1379 The activation cascades generate C3 convertases that cleave C3 and produce active C3b
1380 molecules, which covalently bind to target surfaces and opsonize them for enhanced
1381 phagocytosis; further activation and the deposition of additional C3b molecules generate C5
1382 convertases that trigger the terminal pathway, which may ultimately lead to target cell lysis.
1383 FH inhibits complement activation at the level of the central C3b molecule, thus also blocks
1384 the amplification loop and the terminal pathway.

1385

1386 **Figure 2. The human factor H protein family.**

1387 Members of the FH protein family are exclusively built up from complement control protein
1388 (CCP) domains. FH is composed of 20 CCPs, of which the N-terminal CCPs 1-4 mediate the
1389 complement regulatory (cofactor and convertase decay acceleration) activities. Major ligand
1390 binding and surface recognition sites are located in CCPs 6-7 and 19-20. FHL-1 is derived by
1391 alternative splicing from the *CFH* gene and essentially contains the N-terminal seven CCPs,
1392 thus shares complement regulatory activity with FH, as well as the N-terminal ligand/surface
1393 recognition site (CCPs 6-7). By contrast, the FHR proteins lack homologs of the complement
1394 regulatory domains, but do include domains that display variable degree of sequence identity
1395 to the ligand- and surface recognition domains of FH. In addition, FHR-1, FHR-2 and FHR-5
1396 contain unique N-terminal domains that mediate homo- and heterooligomerization of these
1397 proteins.

1398 Each CCP is represented by a circle, the major binding and activity sites are indicated
1399 by color coding. The CCPs of the molecules are aligned vertically based on highest sequence
1400 similarity to each other. Numbers indicate the percentage of amino acid sequence identity to
1401 the corresponding FH domains or, in the case of the dimerization domains, to each other.

1402

1403 **Figure 3. Roles of factor H family proteins under physiological and disease conditions.**

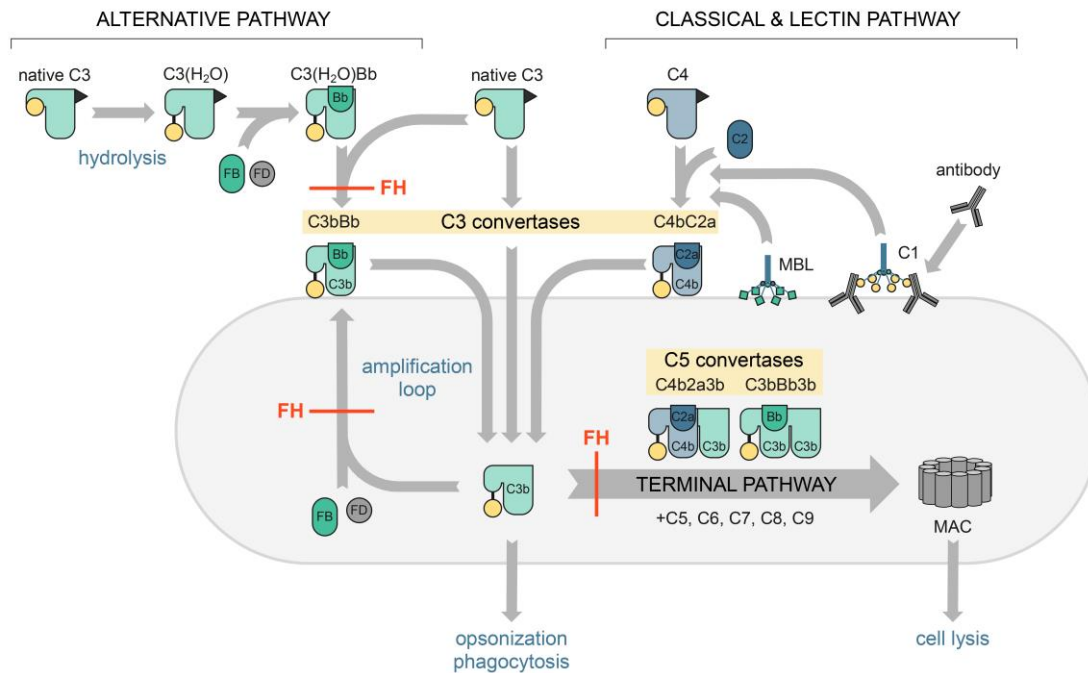
1404 The figure shows a schematic overview of the roles of FH versus FHR proteins in complement
1405 regulation and activation on various surfaces in light of the latest data [9, 11, 115]. The
1406 alternative pathway is continuously active and probes any surface by generating and depositing
1407 active C3b fragments at a low rate. The nature of the surfaces and the relative concentrations
1408 of functionally active FH and FHRs influence the degree of complement activation.

1409 (A) Healthy host cells are recognized by FH via cell surface glycosaminoglycans or sialic acids
1410 (indicated by the brown dots), which engage the C-terminal C3b/C3d binding site to anchor
1411 FH to the surface when C3b is deposited in low density due to the continuous, low-level
1412 activation of the alternative pathway. Surface-bound FH promotes inactivation of C3b and the
1413 C3bBb convertase, and thus down-regulates local complement activation. There is no
1414 significant competition between FH and the FHRs under these conditions.

1415 (B) Changes in their relative amounts or avidity influence binding of FH and FHRs to host cells
1416 and may associate with diseases. Mutations in FH or the generation of autoantibodies that affect
1417 the recognition of host glycans and/or surface-bound C3b/C3d, can cause insufficient
1418 complement control on surfaces. In addition, FHR proteins – particularly when their avidities
1419 increase due to nonphysiological oligomerization caused by e.g. duplication of their
1420 dimerization domains, or due to the appearance of new ligands (indicated by orange triangles)
1421 on altered cells – may compete with FH for ligand and surface binding and, similarly, result in
1422 enhanced complement activation. Moreover, some FHRs may propagate alternative pathway
1423 activation by binding C3b and thus recruiting C3 convertase to the surface (indicated by black

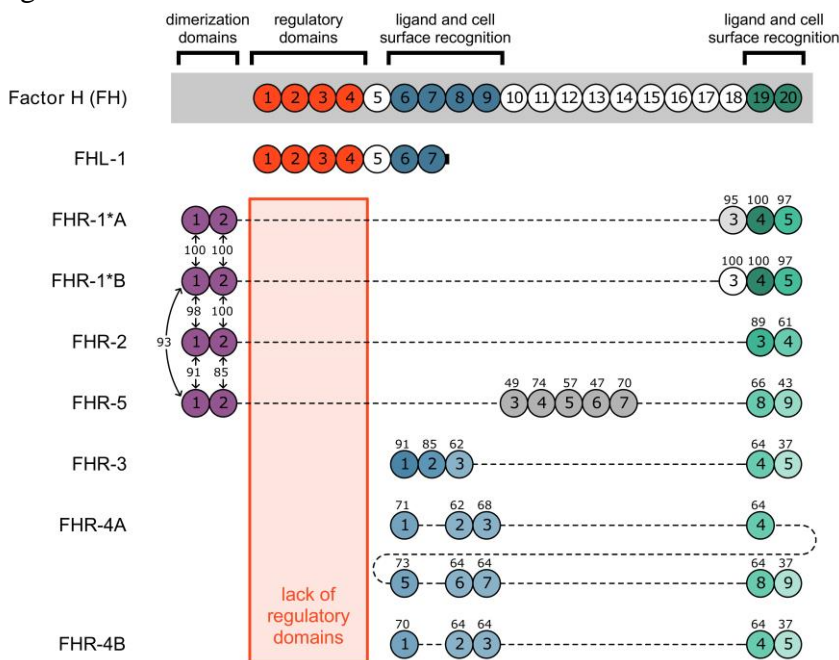
1424 arrow). While enhancing C3 fragment deposition and thus opsonization, FHRs may inhibit the
 1425 terminal pathway and membrane attack complex (MAC) formation, a potential activity that
 1426 needs further clarification (indicated by dotted line).
 1427 (C) Pathogens, even though generally lacking host-like glycosaminoglycans/sialic acid, may
 1428 sequester host FH by expressing FH binding surface proteins (schematically shown in black),
 1429 thus disguising themselves as “self” and reducing complement activation on their surface.
 1430 (D) FHR proteins may bind to FH-binding microbial proteins and competitively inhibit the
 1431 recruitment of this host complement inhibitor, as shown for FHR-3 and FHR-1. Consequently,
 1432 complement activation is enhanced on the microbial surface.
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 1434

Fig. 1.



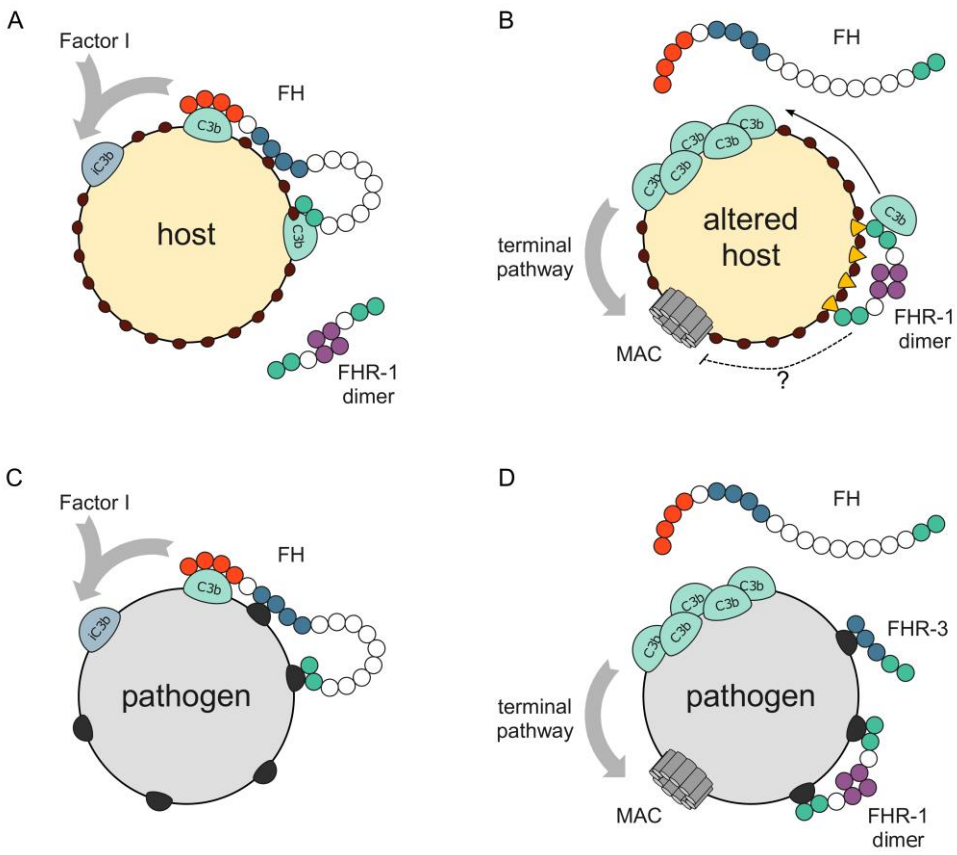
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Fig. 2.



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1440 Fig. 3.



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