The simple design of complement factor H: Looks can be deceiving
Jessy J. Alexander, Richard J. Quigg *

Department of Medicine, University of Chicago, Chicago, IL 60637, USA

Received 8 July 2006; received in revised form 13 July 2006; accepted 13 July 2006

Abstract

The complement system is a powerful component of innate immunity which recognizes and facilitates the elimination of pathogens and unwanted host material. Since complement can also lead to host tissue injury and inflammation, strict regulation of its activation is important. One of the key regulators is complement factor H (CFH), a protein with an ever-expanding list of relevant functions. Inherited mutations in CFH can account for membranoproliferative glomerulonephritis (MPGN) type II, atypical hemolytic uremic syndrome, and age-related macular degeneration. The former can be associated with excessive systemic complement activation from dysfunctional CFH, while the latter two are associated with mutations affecting the ability of CFH to bind to anionic surfaces such as on endothelial cells and glomerular and retinal capillary walls. Mice with targeted deletion of CFH can spontaneously develop MPGN and have increased susceptibility to models of GN. In the rodent, CFH on platelets functions as the immune adherence receptor, analogous to CR1 on primate erythrocytes. In mice, platelets lacking CFH are unable to effectively clear immune complexes which results in their accumulation in glomeruli. The same switch also appears to be true in the rodent podocyte where CFH is present in place of CR1 in human podocytes. Thus, CFH has a variety of functions which can affect the diverse roles the complement system plays in health and disease.

© 2006 Elsevier Ltd. All rights reserved.

Keywords: Rodent; Complement regulators; Factor H; Immune adherence

1. Introduction

1.1. Overview of complement activation regulators

The complement system is a powerful component of innate immunity which recognizes and facilitates the elimination of pathogens and unwanted host material (Walport, 2001). The classical, alternative and lectin activation pathways converge to form C3/C5 convertases which generate C3a, C3b, C5a and C5b, each with substantial biological activity. Complement regulators are necessary to prevent the injudicious production of these mediators and potential injury to self tissue (Liszewski et al., 1996; Morgan and Harris, 1999). The plasma proteins, complement factor H (CFH) and C4-binding protein (C4BP), and the cell membrane proteins complement receptor 1 (CR1, CD35), decay-accelerating factor (DAF, CD55), and membrane cofactor protein (MCP, CD46) are all members of the regulators of complement activation (RCA) gene family on chromosome 1q32 in humans and a comparable genomic location in mice (Rey-Campos et al., 1988; Hourcade et al., 1989; Kingsmore et al., 1989). Each is composed of four to 44 short consensus repeats (SCRs; also known as complement control protein modules) containing conserved amino acids such as four invariant cysteines that form two intra-SCR disulfide bonds. These proteins have natural affinity for C3b and/or C4b which confers upon them the ability to accelerate the intrinsic decay of C3/C5 convertases and/or act as cofactor for the cleavage and inactivation (i) of C3b and C4b by complement factor I (CFI) (Morgan and Harris, 1999).

1.2. Structure and complement regulatory activity of CFH and family members

Human CFH was originally isolated as β1H globulin (Nilsson and Müller-Eberhard, 1965), followed a decade later by an appreciation of its role as a complement regulator (Whaley and Rudd, 1976; Weiler et al., 1976). It is a monomeric protein of ~150 kDa that circulates in human and rodent plasma at relatively high concentrations (~500 μg/ml or 3.3 mmol/L) (Demberg et al., 2002; Rodriguez de Cordoba et al., 2004). Because CFH has affinity for C3b and not C4b, CFH inhibits the...
formation and accelerates the decay of the alternative pathway C3 convertase, C3bBb, and also serves as cofactor for CFI-mediated cleavage and inactivation of C3b to iC3b (Harrison and Lachmann, 1980). As it is the predominant fluid-phase alternative pathway complement regulator, abnormalities in CFH quantity or function result in uncontrolled alternative pathway activation (Pickering et al., 2002; Rodriguez de Cordoba et al., 2004; Zipfel et al., 2006b). CFH also has a role to limit classical pathway C5 convertases on the surface of nucleated cells, reflecting its actions on C3b (Ollert et al., 1995).

CFH solely contains 20 SCRs arranged in tandem, distinguishing it from other RCA members with C-terminal transmembrane and intracytoplasmic regions (MCP, CR1, CR2) or points of attachment to the membrane (DAF) or neighboring molecules in multimers (C4BP). There is a high degree of similarity among human, mouse and rat CFH (Kristensen and Tack, 1986; Kristensen et al., 1986; Demberg et al., 2002). The three C3b-binding sites in CFH are located in SCRs 1-4, 12-14 and 19-20 (Sharma and Pangburn, 1996, 1997; Ram et al., 1998; Pangburn et al., 2000). Testing of factor H SCR deletion mutants in CHO cells has demonstrated that SCRs 1-4 are required for full CFI cofactor activity (Gordon et al., 1995). In addition, SCRs 7, 13 and 19-20 have been found to contain heparin/sialic acid binding sites, which allow CFH to attach to the receptive surfaces (Blackmore et al., 1996, 1998; Jokiranta et al., 2005). CFH is unique among the RCA proteins in using SCRs at its C-terminus to confer its binding specificity.

Structurally, the SCR is a globular ellipsoid of about 35 Å in length created by five short antiparallel β-strands (Barlow et al., 1991, 1992). A wide range of twist angles between adjacent modules is possible, giving the molecule the flexibility that was observed by transmission electron microscopy (DiScipio, 1992). The high density of positively charged residues in SCRs 19 and 20 confers its binding to corresponding negatively charged residues in molecules such as heparin (Jokiranta et al., 2005; Jozsi et al., 2006). It appears that CFH is folded back on itself in its native state (like the Greek σ) but upon binding to a surface bearing C3b and/or heparin (or related anions) it can extend revealing its multiple binding sites and permitting full functionality (Aslam and Perkins, 2001; Oppermann et al., 2006).

A sizable family of CFH-like (FHL) and CFH-related (FHR) proteins have been identified in humans. The former is the product of alternative splicing from the CFH gene, while the latter are products of gene duplications (Zipfel et al., 2001; Rodriguez de Cordoba et al., 2004). Less is known about rodent members of this gene family. In addition to CFH mRNA, three additional species of 3.5, 2.8, and 1.8 kb have been identified in the mouse (Vik et al., 1990) although their exact products remain unclear. We have identified a rat FHR expressed in liver and glomeruli with effective alternative pathway regulatory activity (Ren et al., 2002a); both at a structural and functional level, this is most similar to human FHR-5 (McRae et al., 2000, 2005).

2. Relevance of CFH to human diseases

CFH is an important fluid phase complement regulator. As such, abnormalities in CFH are associated with several diseases. The diseases that have been most actively investigated will be discussed.

2.1. CFH and atypical hemolytic syndrome (aHUS)

Hemolytic uremic syndrome is characterized by consumptive anemia and thrombocytopenia along with acute kidney injury, often in the setting of Shiga toxin-producing *Escherichia coli* diarrheal infections. When not associated with diarrhea or when there is recurrent disease, this is considered to be aHUS (Zipfel et al., 2006b).

A substantial proportion of aHUS cases are attributable to defects in complement regulation (Stuhlinger et al., 1974; Bonnardeaux and Pichette, 2003; Zipfel et al., 2006b). Excessive complement activation occurs on endothelia and erythrocytes under the right genetic and environmental conditions to result in aHUS (Zipfel et al., 2006b). Given the key role of CFH as a complement regulator in the plasma and on particular vascular sites (discussed below), many mutations in CFH have been associated with aHUS (Warwicker et al., 1998; Ying et al., 1999; Buddles et al., 2000; Taylor, 2001; Mathieson, 2002; Caprioli et al., 2003). This is an ever-expanding list, and the interested reader is referred to an excellent website collating these mutations (www.fh-hus.org) (Saunders and Perkins, 2006). Also consistent with the concept that aHUS occurs from abnormal complement regulation is its association with genetic defects in MCP and CFI (Richards et al., 2003; Fremeaux-Bacchi et al., 2004).

Genetic abnormalities in CFH include type I mutations associated with low CFH plasma levels and type II mutations, the majority of which are single amino acid substitutions (Zipfel et al., 2006b). The latter have been extremely informative in aHUS, as they cluster in SCRs 19-20 of CFH and are associated with impaired binding to anionic molecules including those on endothelial cells (Pangburn, 2002; Manuelian et al., 2003; Jokiranta et al., 2005; Oppermann et al., 2006; Jozsi et al., 2006). Although CFH is a fluid-phase protein, it associates with tissue sites bearing appropriate anions where it protects against alternative pathway activation. The data from aHUS have clearly shown that many of the CFH mutants have impaired ability to perform this function. The initiator that tips complement activation over in aHUS has been elusive.

Although there is not a uniformly accepted model of aHUS, we generated a rat model with features of aHUS, namely thrombocytopenia, anemia and renal disease, using a complement-fixing antibody to endothelial cells (Ren et al., 2002b). This disease had all features one would expect of a complement-dependent disease state, in that it was prevented by complement depletion and worsened by blockade of complement regulation, in this case Cry (Ren et al., 2002b). A related rat model was developed in the Couser lab using antibodies to glomerular endothelial cells (Nangaku et al., 1997). This was informative in showing a key role for C5b-9 mediated endothelial cell apoptosis in this disease model (Hughes et al., 2000). In our studies in mice with this antibody, we showed renal disease could be blocked by constitutive expression of soluble Cry in the kidney (Schiller et al., 2001).
A relative obstacle for those of us who model human diseases in the rodent is the difference between complement regulators among the species. For instance, the potent and widely distributed rodent complement regulator, Crry, is absent in humans (Holers et al., 1992; Foley et al., 1993; Li et al., 1993; Kim et al., 1995). In many sites, Crry serves the function of human DAF and MCP, which is to inhibit, decay and inactivate C3 convertases. The absence of Crry is embryonic lethal in mice because of unrestricted complement activation (Xu et al., 2000), while the absence of DAF or MCP has no apparent systemic consequence (Sogabe et al., 2001; Lin et al., 2002; Inoue et al., 2003). For example, the studies from the Song lab have shown mouse erythrocytes require Crry to prevent hemolysis, while DAF (and CD59) is dispensable (Miwa et al., 2002b). This is not universal though; for instance, skin has a relative dependency on DAF (Miwa et al., 2002a).

Insights into what happens when an important vascular complement regulator is dysfunctional or absent have come from studies at Matsuo, Okada and colleagues using a Crry inhibiting antibody (Matsuo et al., 1994; Mizuno et al., 1999). When Crry is inhibited, marked complement activation can occur leading to systemic and intrarenal events. As noted, the remarkable observation of unrestricted maternal complement activation on Crry-deficient fetuses has provided additional evidence for the importance of having a functional vascular complement regulator; this can be averted by coexistent deficiency of C3 (Xu et al., 2000). Therefore, it has been difficult to date to examine the role for Crry on vascular endothelium in vivo; for instance, as a model for MCP abnormalities in aHUS. In our recent studies, we have transplanted Crry/C3-deficient kidneys into wildtype hosts, in which there was marked inflammation in the tubulointerstitium and complete failure of the kidney within weeks, while the appropriate controls were normal (Bao et al., 2006). That renal Crry deficiency can lead to unrestricted alternative pathway activation has been clearly shown by a series of insightful studies from the Thurman and Holers group (Thurman et al., 2003, 2006a,b).

2.2. CFH and MPGN type II

MPGN type II is a kidney disease characterized by accumulation of dense deposits of unknown composition in the glomerular capillary wall (GCW), associated with impaired glomerular function to filter plasma and generate a largely protein-free ultrafiltrate (Appel et al., 2005). There are similarities and differences between MPGN type II and aHUS. Distinct from aHUS is the consistent appearance of systemic complement consumption leading to acquired hypocomplementemia in MPGN type II (Varade et al., 1990). While both are associated with defects in CFH, as of this writing there are 77 CFH mutations associated with aHUS, while only six have been identified for MPGN type II (Ault et al., 1997; Dragon-Durey et al., 2004; Licht et al., 2006). Much more common than defects in CFH is the association of MPGN type II with nephritic factor, an autoantibody that binds and stabilizes the alternative pathway C3 convertase, C3bBb, leading to unrestricted C3 activation (Daha et al., 1976).

As a generalization, MPGN type II is associated with absent CFH due to type I mutations resulting in unrestricted systemic alternative pathway activation, while aHUS is attributable to type II mutations clustering in the terminalSCRs leading to impaired ability of CFH to bind anionic sites such as on endothelium and provide local protection against complement activation (Rodriguez de Cordoba et al., 2004). A fascinating exception to this “rule” is the recently reported Lys224 deletion in SCR4 of CFH; two patients homozygous for this allele (from heterozygous parents) developed MPGN type II with hypocomplementemia, yet had CFH plasma levels in the normal range (Licht et al., 2006). Consistent with the location of the defect, the abnormal CFH protein had impaired complement regulatory activity (C3b binding, decay-accelerating activity, and CFI cofactor activity) yet bound anionic surfaces normally. Related to this is the report from the Meri group of a patient with MPGN type II (with features of type I as well) who had a mini-autoantibody to SCR3 of CFH (Jokiranta et al., 1999).

2.3. CFH and age-related macular degeneration (AMD)

AMD is a leading cause of visual impairment and blindness in the elderly, with a complex underlying etiology, involving both genetic and environmental factors. Drusen are the hallmark deposits associated with AMD and contain complement activators, inhibitors, activation-specific complement fragments including C5b-9 (Baudouin et al., 1992; Mullins et al., 2000). There are also similarities between drusen and the glomerular dense deposits in MPGN type II (Mullins et al., 2000). These findings led to the hypothesis that AMD was an inflammatory disease (Hageman et al., 2001). However, the field was changed forever last year when four groups of investigators independently showed genetic linkage of CFH with AMD (Klein et al., 2005; Haines et al., 2005; Hageman et al., 2005; Edwards et al., 2005). Subsequent work has identified this allotypic variation to be attributable to a His384Tyr polymorphism; this is in a polyanion binding region in the 7th SCR of CFH and leads to reduced affinity for heparin (Clark et al., 2006). Thus, AMD appears to have similarities to aHUS in altered anion binding capacity of CFH, with reduced CFH binding to Bruch’s membrane in the eye and the GCW in the kidney (Zipfel et al., 2006a).

3. Importance of CFH as a complement regulator—lessons from animals

Animal models of spontaneous and targeted deficiencies of CFH have added considerably to our understanding of the physiological and pathophysiological roles of CFH. These will be discussed in this and the next section.

3.1. Spontaneous disease in animals with defects in CFH

Yorkshire pigs with homozygous CFH deficiency developed a disease similar to MPGN type II which can be rescued by infusion of CFH (Hogasen et al., 1995). This has been shown to be due to a type I mutation in the 20th SCR (Ile1166 Arg) preventing extracellular release of CFH (Hegasy et al., 2002).
Although those involved in revolutionary medical genetic and molecular modeling studies might argue, the CFH-deficient mouse strain developed by the Botto group (Picking et al., 2002) may be the one single advance that has allowed the most insight into the truly remarkable CFH protein. These mice have marked systemic alternative pathway complement activation as shown by absent plasma C3 which was dependent upon the presence of complement factor B (CFB). These mice developed glomerular disease with features of MPGN type II later in life, which was fatal in some animals. Complement deposition in the glomerular capillary wall (a feature of MPGN type II) preceded immune complex deposition (which is a feature of MPGN type I but not type II). As could be anticipated, the glomerular disease phenotype was also dependent on the alternative pathway, as it was not present in CFH-deficient mice with coexisting CFB deficiency (Picking et al., 2002). In more recent studies, this group has gone on to show a partial C5 dependence of MPGN disease (Pickering et al., 2006). In other studies, it was not present in CFH-deficient mice with coexisting CFB deficiency. In CSS induced with native apoferritin, circulating immune complexes (ICs) bound to erythrocytes, but not type II. As could be anticipated, the glomerular disease phenotype was also dependent on the alternative pathway, as it was not present in CFH-deficient mice with coexisting CFB deficiency (Picking et al., 2002). In our studies with CSS induced with native apoferritin, circulating immune complexes (ICs) become trapped in the GCW, where they incite an inflammatory response. To examine the relevance of a complement regulator like CFH and the informative CFH−/− mouse strain, a useful experimental approach has been to induce a disease model in which wildtype mice get little in the way of disease features. This is possible for both NSN and CSS as disease features in both models depend upon the dose of administered protein and the background strain in mice (Noble et al., 1981; Iskandar et al., 1982; Boyce and Holdsworth, 1985; Quigg et al., 1998a).

CFH-deficient mice receiving relatively low (“subnephritogenic”) doses of sheep NS were more susceptible than wildtype controls to acute features (occurring over several days) of NSN (Picking et al., 2002). In these studies, all mice had been primunized with sheep IgG to accelerate this passive model. This susceptibility required intact CFB as CFB-deficient mice were largely protected from disease. While these are relatively simple data, they are also very informative in showing that presumed classical pathway complement activation by ICs (in this case, sheep and mouse IgG bound directly to their GCW antigens) can recruit the alternative pathway if it is not effectively regulated in the GCW by CFH. A similar key role for the alternative pathway in IC-mediated GCW disease has been shown by the Gilkeson group in experimental lupus nephritis (Elliott et al., 2004). Further dissection of which complement components were relevant to CFH-dependent acute NSN was provided through the use of naturally C5- and C6-deficient mice and an inhibitory anti-C5 antibody (Picking et al., 2006). In these studies, disease features of albuminuria and neutrophil accumulation appeared dependent upon the cleavage of C5, as they were largely abrogated in C5-deficient mice and in wildtype mice treated with anti-C5. That C6-deficient mice appeared to be unproctected implicated C5a as the major factor accounting for these findings. These studies allowed the following paradigm to be constructed for NSN. Animals receiving low-doses of NSN (arguably, most relevant to human disease) were protected from alternative pathway activation by the actions of CFH. In the absence of CFH, unrestricted complement activation led to the generation of the potent C5a anaphylatoxin with subsequent glomerular inflammation.

In our studies with CFH−/− mice, we have exploited the fact that CSS leads to GN with many features relevant to human disease in some strains of mice; however, the C57BL/6 strain is completely resistant to GN (Quigg et al., 1998b). Therefore, C57BL/6 CFH−/− mice and wildtype controls were immunized daily with heterologous apoferritin. All animals developed an immune response to apoferritin with deposition of ICs in glomeruli (Alexander et al., 2005). However, CFH−/− mice had a greater quantity of mesangial ICs as well as their extension to the GCW for which several explanations were possible, as will be discussed below. Consistent with the increase in glomerul ICs and the role of CFH to limit complement activation, CFH−/− mice had a marked increase in glomerular C3 deposition. In keeping with the known strain dependence of this model, wild-type mice immunized with apoferritin did not develop glomerular pathology, nor did wildtype or CFH−/− mice immunized with saline. In contrast, CFH−/− mice immunized with apoferritin developed diffuse proliferative GN, focal crescentic GN, and focal and segmental sclerosis/hyalinosis, associated with increases in mRNA for laminin, fibronectin and collagen type IV (Alexander et al., 2005). These data affirmed the importance of CFH as a protector of the GCW.

4. Cell-associated CFH—the rodent analogue to CR1?

4.1. Immune adherence and CR1

Complement activation in ICs leads to their incorporating C3b which bind to cells with specific membrane receptors. This phenomenon was called immune adherence (IA) by Nelson (1963). In contrast to erythrocytes in primates, the IA function in non-primates, including rodents, is served by platelets bearing immune adherence receptors (IARs). This indicates an evolutionary divergence from platelets to erythrocytes for this particular immune function. ICs bound to erythrocyte or platelet IARs are transported to CR3 and FcγR-bearing cells
of the mononuclear phagocyte system in liver for elimination (Schifferli and Taylor, 1989; Hebert, 1991).

The glomerular podocyte is also capable of IA (Gelfand et al., 1975). In humans, the podocyte IAR is CR1 as it is on erythrocytes (Kazatchkine et al., 1982). Notably, CR1 protein quantities are decreased on both erythrocytes and podocytes in IC diseases such as systemic lupus erythematosus (Emancipator et al., 1983; Ross et al., 1985). The work of Schifferli and colleagues has shown that this is attributable to loss of the entire CR1 molecule and not just its extracellular domain (Moll et al., 2001). CR1 is also produced as a soluble urinary form which retains its IC-binding capacity (Pascual et al., 1994). In spite of a significant amount of data on its appearance in normal and diseased states, the role for the podocyte IAR is unknown.

4.2. Studies in vitro

Until recently, the non-primate IAR remained unknown. The Atkinson lab identified a 150-kDa C3b/iC3-binding protein on rabbit platelets which was absent from erythrocytes, but did not characterize this further (Manthei et al., 1988). We isolated a group of C3-binding proteins from rodent platelets, including those of 150- and 125-kDa (Quigg and Holers, 1995; Quigg et al., 1997). Still, it was not until we were able to do mass spectroscopic analysis of these proteins that we realized they had identity to CFH (Alexander et al., 2001). In follow-up studies, we provided evidence using functional, biochemical, immunoochemical, and molecular biological approaches that this C3b-binding protein on rodent platelets was CFH.

Megakaryocytes from wildtype mice cultured in CFH-deficient medium contained CFH mRNA and protein (Fig. 1) (Alexander et al., 2006a). The same was true of differentiated platelets released by megakaryocytes into the supernatant. Platelet-associated CFH was plasma membrane-bound as shown by flow cytometry. Not surprisingly, megakaryocytes and platelets from CFH−/− mice lacked CFH mRNA and protein. These results provided proof that platelets and their precursors have the intrinsic capacity to produce CFH as a plasma membrane protein.

Because human podocytes also bear CR1 (Kazatchkine et al., 1982), we reasoned that rodent podocytes would have CFH. Therefore, using a combination of antibody- and polymerase chain reaction-based strategies, we cloned the cDNA for CFH from cultured rat podocytes and showed that like platelets, podocytes produce CFH and display it on their plasma membrane (Ren et al., 2003). During these studies, we found that comparable to many of the RCA proteins, there was an alternatively spliced CFH transcript from podocyte cDNA, termed FHR (Ren et al., 2002a). Complement activation by anti-FxIa on podocytes in vitro (and in vivo in experimental membranous nephropathy) led to upregulated production of both CFH and FHRP, indicating a functional “protective” response by this cell.

4.3. Studies in vivo

To dissect the roles of plasma and platelet-associated CFH, we created bone marrow (BM) chimeras between CFH−/− and wildtype C57BL/6 mice (Alexander et al., 2006a). Plasma and platelet CFH protein largely tracked with the CFH status of recipient and BM donors. These results were consistent with those from cultured megakaryocytes in showing the intrinsic origin of platelet CFH. That wildtype recipients of CFH−/− BM had some platelet-associated CFH could reflect incomplete chimerism and/or passive adsorption from plasma rich in CFH, as is known to occur (Vaziri-Sani et al., 2005).

Further studies were performed in which CSS was induced in these BM chimeric mice. After 5 weeks of daily immunization with apoferritin, there were no differences in antibody titters between groups. As a measure of ICs bound to platelets, platelet-associated IgG was significantly increased only in CSS and only in animals with wildtype platelets (wildtype animals without BM transfer, and wildtype and CFH−/− recipients of wildtype BM) (Fig. 2), consistent with the paradigm that platelet CFH originates intrinsically and functions as the IAR to bind ICs. Further support for this was the significant correlation between platelet-associated CFH and IgG levels (r = 0.68, p = 0.03). Wildtype mice with CFH−/− BM had extensive glomerular deposition of complement-activating ICs but did not develop glomerular pathology. In contrast, CFH−/− mice reconstituted with wildtype BM had substantially less glomerular deposition of ICs and complement activation than mice with global or platelet CFH.

Fig. 1. Flow cytometric analyses of cultured platelets from wildtype (blue) and CFH−/− mice (red) using anti-thrombocyte (A) or anti-CFH Abs (B). When overlap occurs between wildtype and CFH−/− platelets, the color is purple. Irrelevant antibodies as controls are in green. In (C) is RT-PCR for CFH in blood platelets, cultured megakaryocytes, and platelets from cultured megakaryocytes from wildtype and CFH−/− mice. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

J.J. Alexander, R.J. Quigg / Molecular Immunology 44 (2007) 123–132
deficiency, yet, these mice still developed glomerular inflammation and sclerosis/hyalinosis. Western blotting of isolated glomeruli confirmed that wildtype mice with $CFH^{-/-}$ BM had a large quantity of glomerular C3 protein which was exclusively in the form of iC3b, while $CFH^{-/-}$ mice with wildtype BM had much less C3, but some remained as intact C3b $\alpha$ chain. These data show that plasma and platelet CFH have distinct and separable roles. Plasma CFH limits complement activation in the circulation and other accessible sites such as the glomerulus, while platelet CFH is responsible for IC processing. Even if excessive IC deposition occurs in glomeruli, such as when platelet CFH is absent, the presence of plasma CFH is sufficient to limit the generation of proinflammatory complement activation products.

We have also examined the role of CFH intrinsic to the kidney through the use of renal transplants between wildtype and $CFH^{-/-}$ mice (Alexander et al., 2006b). These have shown that wildtype kidneys in a CFH-deficient host bear CFH in the GCW (Fig. 3), which, by several lines of evidence is likely to originate from the podocyte. In addition, the data imply that locally produced podocyte CFH is important to process ICs in the subepithelial space. Overall, it is our contention that CFH also replaces CR1 on the podocyte.

There is a growing understanding of how the complement system can affect glomerular IC processing. Besides our studies in the CSS model showing the C4- and C3-dependence of IC localization in the glomerular capillary wall (Quigg et al., 1998b), a number of revealing studies have used active ICGN models in which cationized heterologous proteins serve as “planted” antigens in the glomerular capillary wall (as opposed to the highly anionic native apoferritin which clearly generates circulating ICs). These ICs follow an “orderly” progression through subendothelial, intramembranous, subepithelial, and intrapodocyte sites; C3 is apparent in subendothelial ICs, is not found in those within the glomerular basement membrane, and then again appears in subepithelial ICs; C5b-9 only becomes apparent in the subepithelial location (Fujigaki et al., 1997). Consistent with these ultrastructural findings is that an active complement system is required for most ICs to progress beyond the subendothelial site (Sheerin et al., 1999). The presence of subendothelial ICs leads to complement-dependent inflammatory cell infiltration (Johnson et al., 1988, 1989), which also presumably clear these ICs (Fujigaki et al., 1997). The ability of the podocyte to actively process ICs has been shown in ultrastructural studies and in culture models (Lewis et al., 1978; Singh and Rahman, 1994; Haymann et al., 2004); yet, further details, including the role for CR1 remain unknown. Taken together, wildtype mice with CSS have a balance of ICs present in the mesangium and glomerular capillary, with the latter undergoing a directed movement towards the podocyte (Quigg et al., 1998b). This is markedly affected by plasma, platelet or podocyte CFH individually. The composition and location of complement activation products has a major impact on the outcome in glomerular diseases.

5. Summary

CFH is a fascinating molecule that is very active in the complement system. It has a high degree of evolutionary conservation, presumably indicating its “design” is already quite functional and hard to improve upon. CFH is a simple molecule composed of only SCRs arranged in tandem, which it puts to good use to bind C3b and polyanions; this binding reveals its functions. CFH is a necessary fluid-phase regulator of the complement alternative pathway, which would otherwise be active by its very design. The capacity to bind polyanions expands the sites of CFH’s complement regulatory activity to tissue surfaces bearing appropriate molecules. Genetic defects at different positions in CFH interfere with these actions, and can result in diseases affecting the endothelium (aHUS), GCW (MPGN type II) and retina (AMD). Lastly, its role is even more expanded in rodents to include those served by CR1 in human erythrocytes and podocytes. Seemingly this is because they have overlapping activities in the complement pathways. How CFH, lacking the transmembrane region of CR1, is attached to rodent platelets and podocytes, and whether its roles in those sites is truly analogous...
to human CR1, is the subject of future investigations. The studies of CFH carry out by a large number of investigators over the years, of which only a minority were cited because of constraints of space, have proven the relevance of the complement system to human health and disease.

References


tor H variant increases the risk of age-related macular degeneration. Science 308, 419–421.


