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Complement control protein factor H: the good, the bad, and the inadequate

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Abstract

The complement system is an essential component of the innate immune system that participates in elimination of pathogens and altered host cells and comprises an essential link between the innate and adaptive immune system. Soluble and membrane-bound complement regulators protect cells and tissues from unintended complement-mediated injury. Complement factor H is a soluble complement regulator essential for controlling the alternative pathway in blood and on cell surfaces. Normal recognition of self cell markers (i.e. polyanions) and C3b/C3d fragments is necessary for factor H function. Inadequate recognition of host cell surfaces by factor H due to mutations and polymorphisms have been associated with complement-mediated tissue damage and disease. On the other hand, unwanted recognition of pathogens and altered self cells (i.e. cancer) by factor H is used as an immune evasion strategy. This review will focus on the current knowledge related to these versatile recognition properties of factor H.

Keywords

Alternative pathway; Complement; Human; Factor H

1. Introduction

The complement system is the major non-cellular component of the innate immune system. It efficiently protects the host from pathogenic microorganisms, contributes to immune complex regulation, and represents an important link between the innate and specific immune system. Complement comprises a group of more than 30 proteins, which participate in a cascade-like activation process, serve as control proteins or act as cellular receptors. Activation of the central component C3, may occur through three different pathways: the classical, the lectin and the alternative pathway. Each of these pathways leads to direct killing, to marking of the target with ligands (C3b, iC3b, C3d) for receptors of the cellular

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innate immune system (CD35, CD21, CR3, etc) and to numerous cellular and humoral responses from systems of acquired immunity (Carroll, 1998; Fearon and Locksley, 1996; Fearon, 1997).

The alternative pathway represents a true safeguard system of the human host and, unlike the classical and lectin pathways that require specific recognition molecules for initiation (C1q or MBL/ficolins, respectively), the alternative pathway is triggered spontaneously and everywhere in an organism. The system is initiated in the fluid phase by the spontaneous hydrolysis of the thioester bond in C3 that allows the generation of a fluid phase initiating protease ($C3(H_2O)Bb$) with the ability to digest C3, generating C3b fragments. These C3b fragments possess a labile thioester group, allowing it to bind covalently to any nearby membranes with exposed amino or hydroxyl groups. Bound C3b can now bind factor B, which is then cleaved by factor D, generating the membrane-bound C3 convertase. This convertase has the ability to greatly amplify the deposition of C3b on the surface of a cell (Muller-Eberhard and Gotze, 1972; Pangburn, 1998; Rother, 1998). Importantly, although deposition of C3b occurs on all cells exposed to activated complement (i.e. pathogenic microorganisms as well as our own host cells), it does not result in continued activation on all surfaces. To prevent unintended injury by our own activated complement, our organism uses a complex set of plasma proteins (factor H, factor I, C4bp, C1 inhibitor) and cell-bound regulators (DAF, CR1, CD59, MCP, and CRIg) (Atkinson et al., 1991; Kim and Song, 2006; Kirkitadze and Barlow, 2001; Liszewski et al., 1996; Morgan and Harris, 1999; Wiesmann et al., 2006) to restrict complement at critical stages of the cascade reaction. This review will focus on the versatile properties of soluble complement control protein factor H.

2. Recognition molecules used by the alternative pathway to identify host

The alternative pathway uses three recognition molecules to identify the host or targets: factor H, properdin, and C3b. Properdin, first identified in 1959 (Lepow et al., 1959) and known to be a stabilizer of the central enzyme in alternative pathway amplification (Muller-Eberhard, 1988), was recently proposed to be a pattern recognition molecule with the ability to initiate complement activation (Kemper et al., 2008; Kemper et al., 2009; Spitzer et al., 2007; Xu et al., 2008; Agarwal et al., 2010). The physiological forms of properdin have been recently shown to be more selective in their recognition than originally proposed (Ferreira et al., 2010).

C3b attaches covalently to targets of complement attack and although this is not normally considered as a target recognition event, C3b attachment shows a strong preference for certain sugars and amino acid hydroxyl groups (Levine and Dodds, 1989; Pangburn et al., 2008; Sahu and Pangburn, 1994; Sahu and Pangburn, 1995; Tack et al., 1980). This selectivity results in more aggressive activation on some surfaces depending on their polysaccharide and protein composition.

Factor H (formerly known as β1H) is an abundant serum glycoprotein that is expressed constitutively in the liver (Adinolfi et al., 1981; Schwaeble et al., 1987) and can be also expressed locally by a variety of cell types including retinal pigment epithelial cells, endothelial cells, epithelial cells, platelets, and mesenchymal stem cells, among others (Brooimans et al., 1990; Chen et al., 2007; Licht et al., 2009; Sakaue et al., 2010; Tu et al., 2010). The serum concentration of factor H is ~ 500 μg/ml, although it can vary widely from 116–562 μg/ml depending on genetic and environmental factors (Esparza-Gordillo et al., 2004; de Cordoba and de Jorge, 2008). Factor H accelerates the decay of the alternative pathway C3 convertase (C3b,Bb) and is also a cofactor for factor I-mediated cleavage and inactivation of C3b (Harrison and Lachmann, 1980; Pangburn et al., 1977; Weiler et al., 1976; Whaley and Ruddy, 1976). In the absence of factor H, spontaneous activation of the

alternative pathway of complement occurs in plasma, which leads to consumption of complement components C3 and factor B (Schreiber et al., 1978). In addition to its function as a regulator of alternative pathway activation in fluid phase, factor H can recognize specific markers on host cells and control complement on self surfaces. The alternative pathway can activate and efficiently amplify on any surface that is not protected by soluble or membrane bound complement regulatory proteins. Factor H is essential in this “reverse recognition” because it detects and binds to initial C3b deposits in combination with specific markers on host cells. This inhibits further deposition of C3b, while allowing alternative pathway activation to proceed on any other surface to which factor H cannot bind efficiently due to lack of host or host-like markers (Joiner, 1988; Pangburn and Muller-Eberhard, 1984; Pangburn, 1987; Pangburn et al., 2008). The specific chemical nature of human host markers has not been identified, but they are assumed to be polyanionic because sheep cells, which bind factor H and are protected from human complement, activate the alternative pathway after surface sialic acid is removed (Fearon, 1978; Pangburn and Muller-Eberhard, 1978). In addition, the 10-fold higher affinity of factor H for C3b on host cells and other non-activators (i.e. normal factor H recognition) requires the presence of sialic acid clusters or other polyanions on the surface (Pangburn and Muller-Eberhard, 1978; Meri and Pangburn, 1990; Fearon, 1978). Other polyanionic structures such as the highly sulfated heparin and glycosaminoglycan (GAG) chains of proteoglycans (i.e. heparan sulfate (HS) and dermatan sulfate (DS)) have also been shown to enhance factor H-mediated control of complement activation on surfaces (Carreno et al., 1989; Kazatchkine et al., 1979).

3. Factor H as an alternative pathway host recognition molecule and complement regulator

3.1. Normal recognition of cells by factor H

The factor H gene is located in the regulators of complement activation (RCA) gene cluster on human chromosome 1(Rodriguez de et al., 1985; Vik et al., 1990). Ripoche et al (1988) deduced the amino acid sequence from 3 overlapping cDNA clones. In addition to the 150-kD factor H protein, a second gene product, a 43-kD factor H-like molecule (FHL-1), has been identified in human plasma (Schwaeble et al., 1987). There are also a number of factor H-related (FHR) molecules, reviewed elsewhere (Skerka and Zipfel, 2008), which share homology with factor H and FHL-1, although they are not transcribed from the factor H gene. A common structural motif of the genes in the RCA cluster is the complement control protein (CCP) unit (also known as the short consensus repeat or SCR), a highly conserved unit of about 60 amino acids in length with three to eight amino acid spacers between the domains (Klickstein et al., 1987). Factor H is composed of 20 homologous CCP domains (Kristensen and Tack, 1986; Ripoche et al., 1988) that in the electron microscope give factor H the appearance of flexible `beads on a string' with the ability to fold back on itself (Aslam and Perkins, 2001; Discipio, 1992; Perkins et al., 1991; Sim and Perkins, 1989). The actual conformation of factor H may be affected by the ionic strength and pH of its local microenvironment (Okemefuna et al., 2009b).

Structure-function analysis have determined that a C3b-binding site located in the N-terminal four CCP domains possesses the decay accelerating and cofactor activities (Alsenz et al., 1984; Gordon et al., 1995; Kühn et al., 1995; Kuhn and Zipfel, 1996; Pangburn et al., 1977). Two additional binding sites for C3b have been mapped to varying regions within CCPs 7–15 and to CCPs 19–20 (Jokiranta et al., 1996; Jokiranta et al., 2000; Schmidt et al., 2008b; Sharma and Pangburn, 1996). The site on CCP 19–20 interacts with C3b, iC3b, and C3d (Gordon et al., 1995; Jokiranta et al., 2000; Pangburn et al., 2004) (Figure 1).

Factor H has at least three binding sites for heparin and other polyanions, located in CCP 7, CCP 20, and in the CCP 9–15 region (Blackmore et al., 1996; Blackmore et al., 1998b; Jokiranta et al., 2000; Ormsby et al., 2006; Pangburn et al., 1991; Prodinger et al., 1998; Sharma and Pangburn, 1996), although recent evidence challenges the existence of the latter site (Schmidt et al., 2008b). The C-terminal site has also been shown to bind sialic acids (Blackmore and Gordon, 1996; Ram et al., 1998b). Importantly, the C3b and polyanion binding sites in CCP 19–20 are key for factor H interactions with host surfaces (Ferreira et al., 2006; Jokiranta et al., 2000; Jokiranta et al., 2005; Jozsi et al., 2007; Pangburn, 2002; Pickering et al., 2007; Ram et al., 1998b). Thus, a recombinant form of these C-terminal CCPs (rH19–20) has been shown to compete with full-length factor H for binding to C3b and host polyanions (Ferreira et al., 2006; Ferreira and Pangburn, 2007), resulting in increased complement activation on host surfaces *in vitro* (Ferreira et al., 2006). Full-length factor H and isolated rH19–20 each bind 7 fold better to cells bearing C3b and polyanions than to cells bearing C3b but lacking polyanions (Ferreira et al., 2006). A maximum difference of 10-fold for this effect has been reported for full-length factor H (Meri and Pangburn, 1990; Pangburn and Muller-Eberhard, 1978). In addition, studies analyzing the functions of deletion mutants of factor H (Pangburn et al., 2000) showed that deletion of the C-terminal five domains caused a 50-fold reduction in binding to C3b-coated, polyanion-bearing cells. Likewise, a transgenic mouse lacking the four C-terminal domains of factor H loses its ability to effectively protect renal tissues from complement attack (Pickering et al., 2007). It was additionally shown in these studies that the lack of the C-terminal domains does not seem to affect the ability of factor H to control complement in the fluid phase of plasma (Ferreira et al., 2006; Pickering et al., 2007). Taken together, these observations suggest that the two C-terminal domains may account for most of the host cell recognition/discrimination abilities of factor H.

Much effort has been invested in trying to elucidate the molecular details of how the C-terminal 19–20 domains of factor H interact with C3b and polyanions on the cell surface. Although discrepancies exist in the exact location of the C-terminal C3b and polyanion sites, the structure/function studies do agree that both binding sites are indeed overlapping, yet distinct (Ferreira et al., 2009; Lehtinen et al., 2009). Binding of the C-terminus of factor H to a cell appears to rely on an optimal combination of affinities for both C3b and polyanion ligands on the non-activating surface. Thus, certain mutations in CCP 20 that do not alter the overall structure of the domain, but actually increase their ability to bind either a polyanion (heparin) and/or C3b when measured separately, largely diminish the ability of the C-terminus to bind to the combination of both markers on a cell surface (Ferreira et al., 2009).

Adding to the complexity of how factor H interacts with host markers on cell surfaces, factor H has been shown to self-associate into dimers and tetramers in the presence of polyanionic molecules and this polyanion-induced self-association is mediated, at least in part, by C-terminus to C-terminus complex formation, specifically through CCP 18–20 (Pangburn et al., 2009). This is consistent with the tetramer structure seen in crystals of domains CCP 19–20 (Jokiranta et al., 2005) and the weak self association seen with CCP 16–20 (Nan et al., 2008; Okemefuna et al., 2008) suggesting that the C-terminal domain of factor H, may form a contact point for tetramer formation. In addition, the C-terminus of factor H has also been shown recently to form multimeric complexes with C3d, composed of dimers of each molecule (Okemefuna et al., 2009b). Therefore, the interaction with surface markers (polyanions) and C3b/C3d may induce the formation of defined clusters of factor H that would protect broad regions of the surface due to the flexibility and extended shape of factor H (Figure 2).

An additional way that factor H participates in normal recognition of host cells is through binding to cell markers that are exposed on cells undergoing apoptosis (programmed cell

death). The cell markers identified to date that are translocated onto apoptotic cell surfaces, and can be recognized by factor H, are DNA and annexin II (Leffler et al., 2010). DNA was first identified as having two major binding proteins, factor H and factor B over 30 years ago, when human serum was fractionated by affinity chromatography on DNA-cellulose (Gardner et al., 1980). Annexin II, an abundant phospholipid binding protein that is present in the cytosol and on the cytoplasmic face of plasma membrane and early endosomes (Moss, 1992), was initially suggested as a possible ligand for factor H that is expressed in the post-ischemic kidney (Coleman et al., 2010). In addition, soluble acute phase proteins, C-reactive protein (Mold et al., 1999; Okemefuna et al., 2010) and pentraxin 3 (Deban et al., 2008) have been reported to have the ability to bind to apoptotic cells and recruit factor H to that cell surface (Deban et al., 2008; Gershov et al., 2000). Although the interaction between factor H and CRP has been proposed to be an artifact due to interaction between denatured CRP and factor H (Hakobyan et al., 2008), additional recent studies report its validity (Okemefuna et al., 2010). These acute phase proteins appear to serve as soluble molecules that assist factor H in normal recognition of dying host cells. Dying cells are known to activate complement in order to achieve proper opsonization for efficient removal, and binding of factor H may be important for limiting excessive complement activation during this process (Trouw et al., 2008). The binding of factor H to host markers on dying cells may also contribute to restricting complement activation so that it will not proceed beyond C3b deposition. Thus, by not allowing complete cell destruction, the release of dangerous autoantigens would be avoided.

Certain host cells (neutrophils, B lymphocytes, monocytes, and platelets) have been reported to express receptors for factor H on their surface, including complement receptor 3 (CR3; CD11b/CD18; integrin αMβ2), other integrins (αvβ3, αIIbβ3), and L-selectin (Ault, 2000; Discipio et al., 1998; Malhotra et al., 1999; Mnjoyan et al., 2008). These interactions appear to mediate functions additional to those involved in host recognition and complement regulation (including cell adhesion and cytokine induction) and are beyond the scope this review.

It is important to note that normal factor H, by recognizing host cell markers, not only controls complement during normal homeostasis, but also plays an important role by limiting complement-mediated damage of diseased cells and tissues. For example, normal factor H (if expressed at normal levels) may play an important role in protection of cells and tissues undergoing pathological processes in which alternative pathway-mediated damage participates in the pathogenesis. Examples of such diseases are reviewed elsewhere (Holers, 2008). One of the causes of alternative pathway-mediated damage to self tissues is a lapse in proper regulation of complement. An example of how normal factor H may in part correct this lapse in complement control is illustrated in the PNH model (paroxysmal nocturnal hemoglobinuria). PNH is an acquired stem-cell disorder that results in little to no synthesis of glycosylphosphatidylinositol (GPI) leading to partial or complete deficiency of GPI-linked membrane proteins including the complement regulatory molecules decay-accelerating factor (DAF; CD55) and CD59 (Luzzatto, 2006; Rosse, 2001). The loss of these complement regulators on host red cells leads to complement-mediated pathology in the disease. The *in vivo* lifespan of normal human red cells is between 60 to 120 days, however abnormal PNH cells are lysed in 6–60 days (Navenot et al., 1998; Rosse, 1971) due to low level complement activation on their surface (Luzzatto, 2006; Navenot et al., 1998; Rosse, 2001). These cells are not lysed in a shorter period of time (i.e. minutes) due to cell surface protection provided by factor H (Ferreira and Pangburn, 2007).

Factor H is a contributor to the normal regulatory redundancy at host cell surfaces and has been shown to be important to other disease scenarios such as experimental autoimmune encephalomyelitis (Griffiths et al., 2009), atherosclerosis (Haskard et al., 2008), insulin

resistance (Moreno-Navarrete et al., 2010), IgA nephropathy (Zhang et al., 2009), and cisplatin nephropathy (Fuke et al., 2009). In agreement with an important role of factor H in the protection of host tissues is the successful use of a factor H-CR2 chimeric molecule (fH-CR2) as a targeted therapeutic agent for complement inhibition in alternative pathway-dependent murine models of collagen antibody-induced arthritis (Banda et al., 2009), intestinal ischemia-reperfusion injury (Huang et al., 2008), and choroidal neovascularization (Rohrer et al., 2009). Factor H-CR2 is also capable of reducing oxidative stress-induced, complement-mediated injury of retinal pigment epithelial cells *in vitro* (Rohrer et al., 2009; Thurman et al., 2009). This inhibitor uses the CR2 domain for targeting to sites of initial iC3b/C3d deposition, and the amino terminal five SCRs of factor H, which encode the regulatory domain of the molecule.

3.2. Inadequate recognition of cells by factor H

Clinical evidence indicates that alleles and mutations that affect host cell recognition domains in factor H result in pathology involving complement activation, as evidenced by inherited atypical hemolytic uremic syndrome (aHUS) (de Cordoba and de Jorge, 2008; Holers, 2008), age-related macular degeneration (ARMD) (Holers, 2008), and dense deposit disease (membranoproliferative glomerulonephritis type II) (Pickering and Cook, 2008; de Cordoba and de Jorge, 2008). Atypical hemolytic uremic syndrome is a disease characterized by hemolytic anemia, thrombocytopenia and acute renal failure (Kavanagh et al., 2008). The study of genetics of aHUS focused attention on the C-terminal domains of factor H bearing C3d and sialic acid/polyanion-binding sites (Bettinaglio et al., 2001; Buddles et al., 2000; Dragon-Durey et al., 2004; Heinen et al., 2006; Manuelian et al., 2003; Pichette et al., 1994; Richards et al., 2001; Rodriguez de Cordoba et al., 2004; Warwicker et al., 1998; Ying et al., 1999; Zipfel et al., 1999). Moreover, age-related macular degeneration suggested a similar role might exist for the polyanion-binding site in CCP 7 (Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005; Klein et al., 2005). The association of factor H mutations and polymorphisms with disease has contributed significantly to elucidating what regions of factor H are important for host recognition, as described in the previous section.

Mutational analyses demonstrated that the majority of the mutations associated with aHUS clustered at or indirectly affected the C-terminal end, specifically domain 20, of complement factor H (Bettinaglio et al., 2001; Herbert et al., 2006; Jokiranta et al., 2006; Perez-Caballero et al., 2001; Perkins and Goodship, 2002; Richards et al., 2001). Molecules carrying these mutations in domain 20 have been shown to be defective in their ability to bind either C3b, polyanions, or both (Ferreira et al., 2009; Kavanagh et al., 2006; Lehtinen et al., 2009; Schmidt et al., 2008a), or surprisingly, in some cases to have an increased affinity for C3b, for both C3b and polyanions (Ferreira et al., 2009) or polyanions only (Lehtinen et al., 2009). In one study (Ferreira et al., 2009), the affinity for C3b, as measured by Biacore, correlated well with binding to C3b-coated zymosan (which lacks polyanions). Nevertheless, affinities for C3b and heparin (when measured separately) did not correlate consistently with the strength of binding to polyanion-rich human and sheep erythrocyte surfaces on which C3b has been deposited; nor did they correlate with the disease-risk phenotype. Others (Lehtinen et al., 2009) have observed a correlation between the ability of certain aHUS mutants to bind with increased affinity to heparin and to TNF-activated murine glomerular endothelial cells, while maintaining normal affinity of C3b. Taken together, the many aHUS-associated mutant studies (Ferreira et al., 2009; Lehtinen et al., 2009; Schmidt et al., 2008a) seem to suggest that a defect in binding (negative or positive) to either of its known cell recognition ligands (C3b/C3d, polyanions), can lead to a defect in binding to a combination of these ligands on a cell surface. Therefore, aHUS-linked

mutations may disturb a complex relationship between affinities of factor H for both individual ligands needed for cell recognition.

Additional factors may be playing a role in susceptibility to aHUS including that the mutations may interfere with a third functional site in CCPs 19–20, perhaps different from those involved in C3b or polyanion binding. For example, a mutation could affect the region involved in the formation of putative dimers or tetramers (Nan et al., 2008; Okemefuna et al., 2008; Okemefuna et al., 2009a; Pangburn et al., 2009), which may be important for factor H binding/function on the cell surface. Autoantibodies to factor H have also been identified in aHUS patients and their specificity has been mapped to the C-terminus, within the region considered to be a hot spot for aHUS-associated mutations (Skerka et al., 2009; Strobel et al., 2010), which is the same region that is essential for factor H recognition functions.

ARMD is the leading cause of blindness in the elderly (Klein et al., 2004) and appears to be another example of a disease caused by inadequately controlled activation of the complement cascade, although the exact molecular mechanisms have yet to be defined. ARMD is strongly linked to a single amino acid variant in the and seventh (Y402H) domains of factor H, while the presence of Ile62 in factor H CCP1 is associated with a lower risk of ARMD and of dense deposit disease (Edwards et al., 2005; Hageman et al., 2005; Haines et al., 2005; Klein et al., 2005). Recombinant fragments of factor H, encompassing the Y402H polymorphism, have been shown to be impaired in their ability to interact with various ligands including heparin, C reactive protein, and fibromodulin (Clark et al., 2006; Herbert et al., 2007; Laine et al., 2007; Sjoberg et al., 2007; Skerka et al., 2007), while displaying increased binding to DNA and necrotic cells (Sjoberg et al., 2007). FHL-1 variant Y402H has been shown to have reduced cofactor activity on the surface of CHO cells (Skerka et al., 2007). In addition, factor H purified from individuals homozygous for either the Ile62 or Val62 variants and identical at all other amino acid residues, showed that the protective variant (Ile62) exhibits increased binding to C3b and is a more efficient cofactor for factor I *versus* the ARMD-linked variant (Tortajada et al., 2009).

Dense deposit disease (membranoproliferative glomerulonephritis.type II) is accompanied by massive complement activation via the alternative pathway due to uncontrolled fluid phase activation and inadequately controlled surface activation. This can lead to complete organ failure (Pickering and Cook, 2008; Pickering et al., 2002). In a factor H-deficient line of pigs, homozygous individuals die soon after birth from complement-mediated acute renal failure (Hogasen et al., 1995) and factor H deficient mice spontaneously develop membranoproliferative glomerulonephritis (Pickering et al., 2002).

As mentioned above, factor H mutations and polymorphisms have been associated with diseases that affect different tissues (i.e. kidney, eye). Likewise, there is a growing body of evidence that each polyanion-binding site on factor H has unique specificities. For instance, domain 7 has been shown to exhibit a polyanion recognition profile different from that of CCP 19–20 (Ormsby et al., 2006). It is thus probable that factor H exhibits cell-type specific recognition depending on the array of polyanions that the particular cell expresses on its surface.

Interestingly, certain cell stress conditions can lead to down-regulation of factor H expression, such as hypoxia (Okroj et al., 2009) and metal-sulfate-induced stress (Pogue et al., 2009). The down-regulation of factor H expression observed in neural cells due to the latter may lead to inadequate protection by factor H, contributing to inflammatory responses observed in neurodegenerative disease processes, such as Alzheimer's disease (Pogue et al., 2009).

Therapeutic strategies based on complement inhibition should contribute to reducing complement mediated damage of cells and tissues due to inadequate protection by factor H. Recently, Eculizumab (anti-C5 monoclonal antibody from Alexion), the first approved complement inhibitor drug for the human disease PNH, has been tested with positive results in aHUS patients (Davin et al., 2009; De et al., 2010) and has been recommended for dense deposit disease (Smith et al., 2007). Additional complement inhibition strategies, such as the use of Compstatin, a peptide that binds to C3 and inhibits all three complement pathways (Sahu et al., 1996) have been reviewed elsewhere (Qu et al., 2009). For the diseases due to inadequate factor H protection at cell surfaces, more targeted strategies, such as the use of the fH-CR2 chimeric protein described in the previous section, could prove to be promising.

3.3 Unwanted protection of cells by factor H (immune evasion strategy)

Some cancer cells and pathogenic microorganisms have developed immune evasion strategies whereby they use factor H to increase complement control in their microenvironment, thus disguising themselves as normal host cells and escaping elimination by the alternative pathway of complement. In the case of cancer cells, they have developed various strategies to evade complement attack including, among others: a) upregulation of complement regulatory proteins including factor H expression, which leads to increased levels of factor H in their local microenvironment; b) secretion of SIBLING (small integrin-binding ligand, N-linked glycoproteins) proteins with the ability to bind to soluble factor H and cell surface integrins, serving as a bridge for factor H cell surface protection, and; c) interaction with adrenomedullin, a vasoactive peptide hormone that is present in many tissues and biological fluids and is expressed in a variety of tumors, thus aggravating malignancy (Ajona et al., 2007; Fedarko et al., 2001; Jain et al., 2002; Junnikkala et al., 2000; Junnikkala et al., 2002; Martinez et al., 2003; Wilczek et al., 2008; Zudaire et al., 2003). Interestingly, the interaction between factor H (also known as andrenomedullin-binding protein 1; AMBP-1) and adrenomedullin, which can be detrimental in cancer, has been shown to have possible therapeutic application in various inflammatory diseases. This therapeutic potential is due, at least in part, to a factor H chaperone-like role whereby it protects against degradation of adrenomedullin, allowing suppression of the immune response and regulation of cytokine expression (Wang and Yang, 2009; Yang et al., 2009; Zudaire et al., 2006).

Numerous pathogens have the capacity to interact with factor H, and are summarized in figure 3. Some of the interactions have been shown to confer resistance to the alternative pathway and, in the case of *N. meningitidis*, the factor H-binding protein (fHbp) is a current vaccine candidate for group B meningococcal disease (Granoff, 2010). Various microbes recruit factor H by interacting with the same regions in factor H that have been described to bind host cell markers, specifically regions CCP 19–20 and CCP 6–7, suggesting a common mechanism used by pathogens to evade complement activation. Interestingly, it has been shown recently that factor H bound to *Candida albicans*, contrary to the unwanted complement regulatory effects, actually mediates phagocytosis and killing of these pathogens via additional interaction with CR3 on neutrophils (Losse et al., 2010).

4. Conclusions

Factor H is a versatile and essential molecule for control of the alternative pathway of complement. Figure 4 summarizes the main points discussed in this review and emphasizes the extraordinary ability of factor H to recognize, bind to and protect cells undergoing physiological processes, cells and tissues undergoing complement-mediated damage, and even pathogenic cells that have learned to use this protection as an immune evasion strategy. Thus, further studies aimed at deciphering the fine molecular mechanisms of cell recognition by factor H are warranted. In this regard, the study of disease-associated mutations and

polymorphisms in factor H will continue to be essential. Therapies aimed at targeting the protective effects of factor H to inflammatory sites in disease as well as vaccines aimed at targeting unwanted factor H binding and protection of pathogenic cells should prove to be greatly beneficial. A large number of research groups have made seminal contributions over the past four decades to factor H research, only a portion of which have been cited here due to space constraints. Some excellent reviews have been cited in an attempt to compensate for omissions.

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Abbreviations

aHUS	atypical hemolytic uremic syndrome
ARMD	age-related macular degeneration
DDD	dense deposit disease/membranoproliferative glomerulonephritis type II
fH-CR2	factor H-complement receptor 2 chimeric protein
AMBP-1	adrenomedullin binding protein-1/factor H
FHL-1	factor H-like 1 protein
FHR	factor H related protein
CCP	complement control protein unit
SCR	short consensus repeat
RCA	regulators of complement activation

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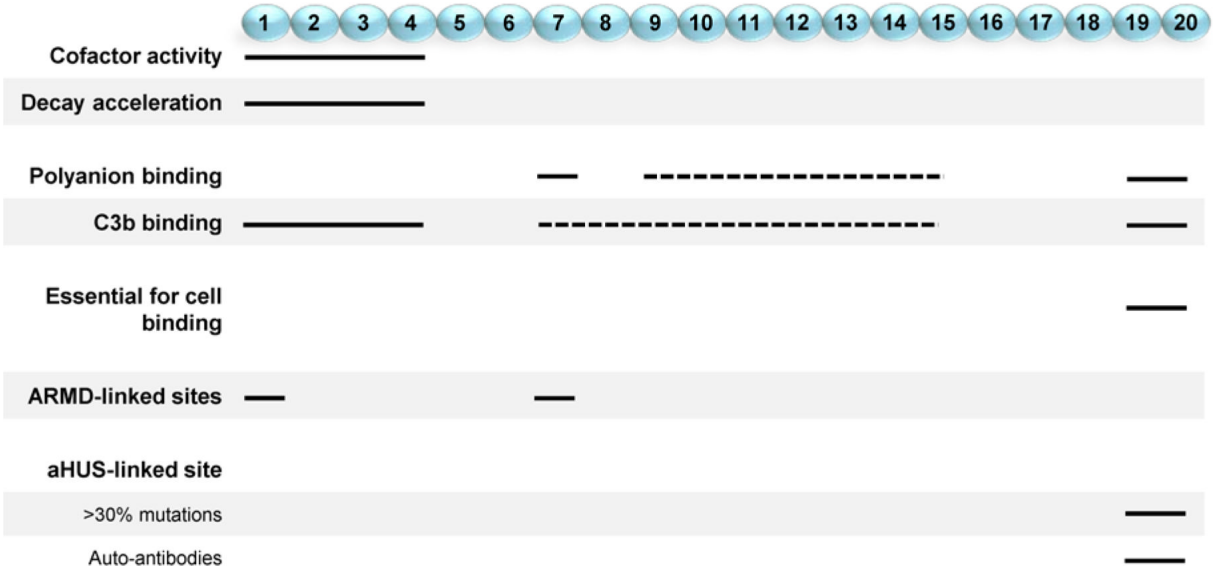

Fig. 1.

Functional domains of factor H and main regions in which mutations, polymorphisms or autoantibodies are associated with disease. Factor H is composed of 20 CCP units. Solid lines indicate the regions of factor H that exhibit critical functions such as controlling complement activation, binding to C3b, recognizing host cells, or that have disease-linked polymorphisms (ARMD), mutations (aHUS), or that are recognized by autoantibodies (aHUS) associated with disease. Dotted lines indicate regions where reported binding sites or functions remain uncertain.

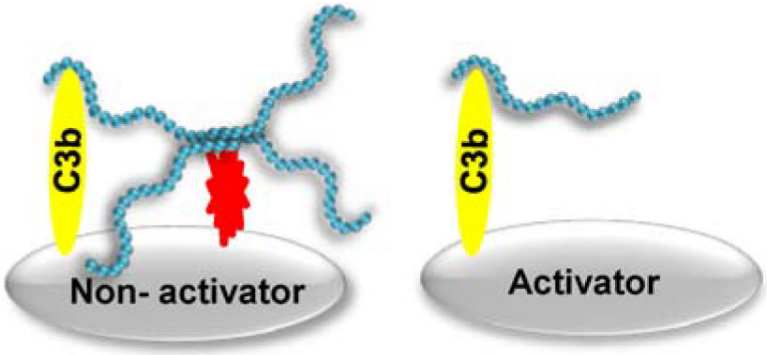

Fig. 2.

Model illustrating host cell-specific tetramer assembly. Human cells and tissues possess surface-bound polyanionic structures (*red structure*) including heparan, other glycosaminoglycans and sialic acids many of which are known to interact with factor H (*blue*). The interactions may induce self assembly (*left panel*) at the C-terminus region of factor H and result in a higher density of factor H on the surface of host cells that inactivates C3b (*yellow structure*), through the N-terminal region of factor H. Microbes and other particles generally lack such polyanions (*right panel*) and these surfaces would not tetramerize factor H resulting in reduced control of the alternative pathway of complement. As a result, alternative pathway activation and C3b amplification would be expected to occur with minimal control on microbes (*right panel*) while amplification would be inhibited on the host (*left panel*). The multimeric interactions between the C-terminal region of factor H and C3b/C3d, which may also facilitate dimer/tetramer assembly, are not shown in this model.

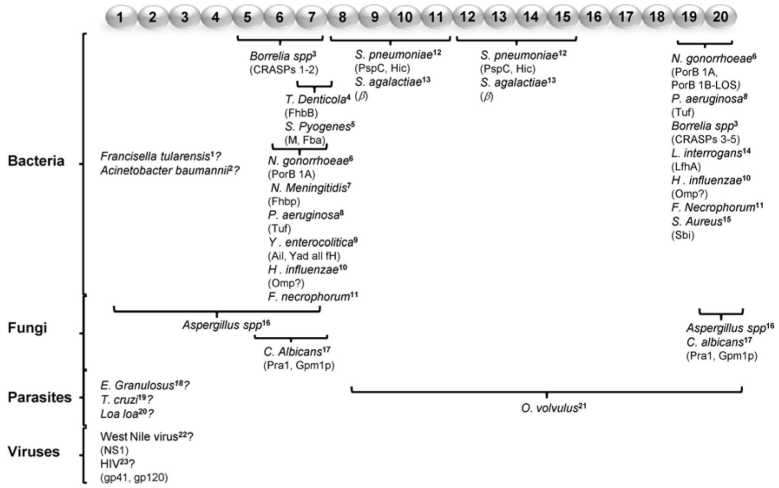

Fig. 3.

Interaction of factor H with multiple pathogens. The proteins involved in binding are indicated in parentheses. Pathogens that bind factor H but where the interacting domain is unknown are indicated with question marks. Superscripts in bold refer to cited works as follows: **Bacteria**: **1** (Ben and Klimpel, 2008), **2** (Kim et al., 2009), **3** (Wallich et al., 2005; Rossmann et al., 2007; Kraiczy et al., 2006; Kraiczy et al., 2004; Kraiczy et al., 2001b; Kraiczy et al., 2001a; Hovis et al., 2004; Hartmann et al., 2006; Kraiczy et al., 2003; McDowell et al., 2003), **4** (McDowell et al., 2009; McDowell et al., 2007; McDowell et al., 2005), **5** (Blackmore et al., 1998a; Horstmann et al., 1988; Kotarsky et al., 1998; Sharma and Pangburn, 1997), **6** (Ngampasutadol et al., 2008; Ram et al., 1998a; Shaughnessy et al., 2009), **7** (Shaughnessy et al., 2009; Schneider et al., 2009; Schneider et al., 2006; Madico et al., 2007), **8** (Kunert et al., 2007), **9** (Biedzka-Sarek et al., 2008b; Biedzka-Sarek et al., 2008a; China et al., 1993), **10** (Hallstrom et al., 2008), **11** (Friberg et al., 2008), **12** (Dave et al., 2001; Dave et al., 2004; Duthy et al., 2002; Hammerschmidt et al., 2007; Janulczyk et al., 2000; Neeleman et al., 1999), **13** (Areschoug et al., 2002; Jarva et al., 2004), **14** (Meri et al., 2005; Stevenson et al., 2007; Verma et al., 2006), and **15** (Haupt et al., 2008); **Fungi**: **16** (Vogl et al., 2008; Behnsen et al., 2008) and **17** (Luo et al., 2009; Meri et al., 2002a; Poltermann et al., 2007); **Parasites**: **18** (Diaz et al., 1997), **19** (Joiner et al., 1986), **20** (Haapasalo et al., 2009) and **21** (Meri et al., 2002b); **Viruses**: **22** (Chung et al., 2006) and **23** (Pinter et al., 1995b; Pinter et al., 1995a; Stoiber et al., 1995b; Stoiber et al., 1995a).

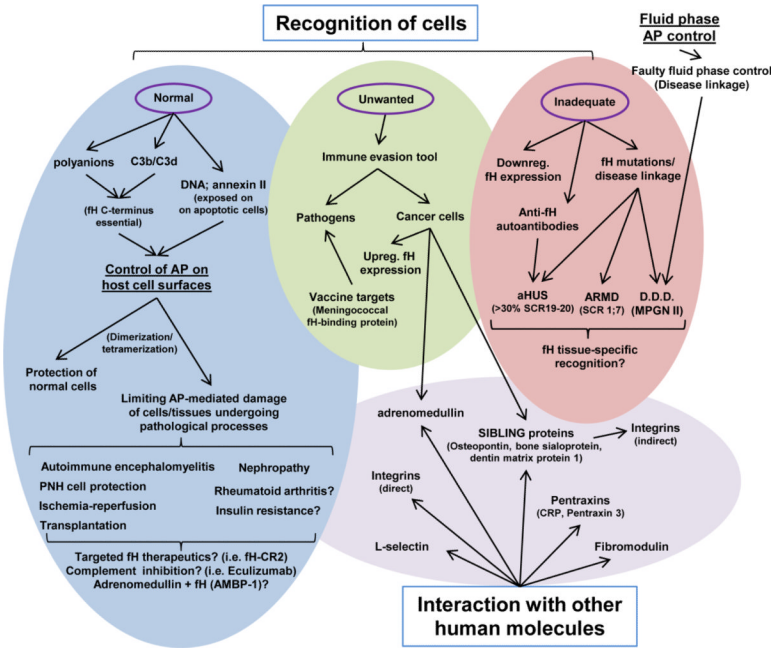

Fig. 4.

Summary of factor H recognition functions and interactions. Briefly, factor H is essential for fluid phase alternative pathway complement control, as well as for protection of host cells. Normal recognition of cell surfaces is required for effective protection. Thus, mutations and polymorphisms in factor H can result in inadequate protection and disease. Unwanted protection from factor H can result from efficient binding to certain pathogens and cancer cells. Interaction of factor H with other molecules is also shown. Abbreviations: AP, alternative pathway; fH, factor H; MPGN II/DDD, dense deposit disease; ARMD, age-related macular degeneration; aHUS, atypical hemolytic uremic syndrome.