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Potential influences of complement factor H in autoimmune inflammatory and thrombotic disorders

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ABSTRACT

Complement system homeostasis is important for host self-protection and anti-microbial immune surveillance, and recent research indicates roles in tissue development and remodelling. Complement also appears to have several points of interaction with the blood coagulation system. Deficiency and altered function due to gene mutations and polymorphisms in complement effectors and regulators, including Factor H, have been associated with familial and sporadic autoimmune inflammatory – thrombotic disorders, in which autoantibodies play a part. These include systemic lupus erythematosus, rheumatoid arthritis, atypical haemolytic uremic syndrome, anti-phospholipid syndrome and age-related macular degeneration. Such diseases are generally complex – multigenic and heterogeneous in their symptoms and predisposition/susceptibility. They usually need to be triggered by vascular trauma, drugs or infection and non-complement genetic factors also play a part. Underlying events seem to include decline in peripheral regulatory T cells, dendritic cell, and B cell tolerance, associated with alterations in lymphoid organ microenvironment. Factor H is an abundant protein, synthesised in many cell types, and its reported binding to many different ligands, even if not of high affinity, may influence a large number of molecular interactions, together with the accepted role of Factor H within the complement system. Factor H is involved in mesenchymal stem cell mediated tolerance and also contributes to self-tolerance by augmenting iC3b production and opsonisation of apoptotic cells for their silent dendritic cell engulfment via complement receptor CR3, which mediates anti-inflammatory-tolerogenic effects in the apoptotic cell context. There may be co-operation with other phagocytic receptors, such as complement C1q receptors, and the Tim glycoprotein family, which specifically bind phosphatidylserine expressed on the apoptotic cell surface. Factor H is able to discriminate between self and nonself surfaces for self-protection and anti-microbe defence. Factor H, particularly as an abundant platelet protein, may also modulate blood coagulation, having an anti-thrombotic role. Here, we review a number of interaction pathways in coagulation and in immunity, together with associated diseases, and indicate where Factor H may be expected to exert an influence, based on reports of the diversity of ligands for Factor H.

Abbreviations: aHUS, atypical haemolytic uremic syndrome; AMD, age-related macular degeneration; aPL, anti-phospholipid antibodies; C3-NeF, C3- nephritic factor; CCP, complement control protein; CEP, Carboxyethylpyrrole; CL, Cardiolipin; CNV, copy number variation; CR, Complement receptor; DAF, Decay accelerating factor, CD55; DDD, dense deposit disease; ECM, extracellular matrix; FH, factor H; FHR, factor H related; GAG, glycosaminoglycan; GSL, glycosphingolipids; IAP, integrin associated protein; LA, lupus anticoagulant; LDL, low density lipoprotein; LXRβ, liver nuclear X receptor β; MAC, complement membrane attack complex; MBL, mannose binding lectin; MCP, membrane cofactor protein, CD46; MDA, malondialdehyde; MPGN2, membranoproliferative glomerulonephritis type2; MSC, mesenchymal stem cell; OSE, oxidation specific neo-epitopes; PMP, platelet α-granules and their micro particles; PNH, paroxysmal nocturnal haemoglobinuria; PS, phosphatidylserine; RA, rheumatoid arthritis; RCA, regulation of complement activation; Siglecs, sialic-acid-binding immunoglobulin-like lectins; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism; TED, thioester containing domain; TF, tissue factor; TLR, toll like receptors; TMA, thrombotic microangiopathy; Tregs, regulatory T cells; TSP-1, thrombospondin-1; TTP, thrombotic thrombocytopenic purpura; vWF, von Willebrand factor.

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1. Introduction

The complement system has a dual innate immune role. It contributes to the maintenance of homeostasis by disposing off cell debris. On the other hand, complement, through its surveillance and recognition of microbes, mounts a defensive action. Recognition of modified self-tissue by complement may lead to injury and disease when the tissue is unprotected by factor H (FH). Both classical and alternative pathways may take part in this discrimination between self and non-self, substantially by negative regulator FH and homologues (Kajander et al., 2011; Ricklin et al., 2010; Zipfel and Lauer, 2013). Besides these complement system related effects, FH can manifest non-canonical properties. Defects and malfunction in complement regulation have been associated with autoimmune, infectious and thrombotic disease susceptibility (Botto et al., 2009; Chen et al., 2010; Zipfel and Skerka, 2009).

Complement and blood coagulation systems are evolutionarily and functionally related. Complement, like the coagulation cascade, is activated by successive limited proteolysis of serine protease zymogens, which are usually associated with non-catalytic cofactor proteins (Reid and Porter, 1981; Tsiftsoglou and Sim, 2004; Sim and Tsiftsoglou, 2004). There is cross-reactivity between complement and coagulation such as the action of complement C1 inhibitor, a serpin, disabling the production of vasoreactive bradykinin by kallikrein, and inhibiting coagulation factors XIa and XIIa (Davis et al., 2010). The Mannan-binding lectin associated serine proteases (MASP) proteases of the complement lectin pathway also activate components of the coagulation pathway (Kozarcanin et al., 2016). A strong common link between diseases such as atypical haemolytic uremic syndrome (aHUS) and systemic lupus erythematosus (SLE) is inflammatory and thrombotic response of vascular endothelial cells, platelets and immune cells. Upon their injury by trauma and subsequent abnormal complement activation on their surface, these cells release pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, as well as pro-coagulant tissue factor (TF). TF is induced by complement anaphylatoxin C5a through its G-protein-coupled receptor on neutrophils, which are also chemo-attracted by C5a to an injury site (Ritis et al., 2006). TNF-α can also induce TF and reduce anti-thrombotic activated protein C and thrombomodulin receptor, whose expression inhibits blood coagulation on endothelial cells and platelets (Esmon, 2004; Markiewski et al., 2007; Oikonomopoulou et al., 2012; Ricklin et al., 2010).

The complement system encompasses more than 40 secreted and membrane bound proteins, some of which recognise microbial and altered self-molecular patterns. Recognition proteins include C1q of the classical pathway, and mannose binding lectin (MBL), ficolins and other collectins of the lectin pathway (Carroll and Sim, 2011; Kemper et al., 2014; Walport, 2001a). These recognition events trigger activation of C1r, C1s proteases and MASPs, which initiate the catalytic cascade of C2, C4 effector proteins forming the C3 convertase C4bC2a. This enzyme complex cleaves C3 into active C3b moiety and C3a peptide, and C3b initiates formation of the alternative pathway C3 convertase, C3bBb. The alternative pathway is constantly maintained at a low homeostatic level through C3 autocatalysis *via* a hydrolysed intermediate C3(H_2O) molecule which forms a C3 convertase C3(H_2O)Bb, which itself cleaves C3 into reactive C3b and C3a molecules. This process can take place in plasma and on cell and microbe surfaces. The C3 convertases C4bC2a and C3bBb further form C5 convertases C4bC2aC3b and C3bBbC3b, which proteolytically cleave C5 protein into reactive C5b and C5a peptide. C5b propagates the terminal C5b-9 pathway culminating in cytotoxic membrane attack complex (MAC) (Law and Reid, 1995; Walport, 2001a; Walport, 2001b). Cleavage products C3a and C5a are pro-inflammatory and chemo-attractant anaphylatoxins. Thrombin can also directly cleave C5 to produce C5a (Huber-Lang et al., 2006; Meri, 2013). In these events, C3b is a cofactor to the serine protease zymogen factor B. The C3bB complex is activated by serine protease factor D; activated factor D cleaves factor B into the active C3bBb serine protease-complex. The classical pathway is also considered to undergo a constant low activation turnover, required in its dual role in the recognition, surveillance of bacteria and self-tolerance (Ricklin et al., 2010). In addition to cell and bacterial lysis by the MAC, the other immediate complement innate immune defence mechanism is microbe opsonisation through complement fragment deposition on the microbe, enhancing phagocytic cell uptake and microbe destruction, such as by macrophages and dendritic cells (DCs). This mechanism also serves for host apoptotic and necrotic cell clearance (Walport, 2001b).

The complement proteolytic cascade is negatively regulated by complement control protein (CCP) domain containing glycoproteins, such as soluble FH and C4b binding protein (C4bp), and cell membrane bound complement receptor 1 (CR1/CD35), decay accelerating factor (DAF/CD55), and membrane cofactor protein (MCP/CD46). FH competes with factor B for C3b attachment, thereby limiting formation of the C3 convertase C3bBb. FH can also dissociate a formed C3bBb convertase complex, a process known as C3 decay acceleration (Fig. 1) (Hourcade et al., 1989; Weiler et al., 1976). C4bp modulates C4b2a formation similarly to the action of FH on C3bBb. Properdin is a positive regulator of the alternative pathway, which stabilises complement convertases against their decay by regulators (Fearon and Austen, 1975).

C3 is composed of α and β chains, cross-linked by two disulphide bridges. The α chain harbours the N-terminal C3a peptide, various ligand binding sites, and a thioester group. C3 protein is activated by convertases, cleaving C3 into C3a peptide and C3b which undergoes conformational activation changes (Bokisch et al., 1975). C3b and C4b molecules are highly reactive, exposing their internal thioester through which they make ester and amide bonds at random, becoming covalently linked with close-by bacterial and host surfaces. C3b and C4b are short-lived, reacting rapidly with water if no surface is encountered (Dodds et al., 1996; Law and Dodds 1996; Sim et al., 1981a). The serine protease factor I cleaves C3b and C4b, only when they are in complex with FH or other regulators including C4bp, CR1 or MCP. C3b α-chain is cleaved at two sites into 68, 43 and 3 kDa components. The 68 and 43 kDa components are still attached to the C3b β chain, by disulphide links, forming a molecule designated as inactivated C3b (iC3b). The iC3b can be further cleaved by FI or by trypsin-like proteases such as plasmin or thrombin into C3dg or C3d and C3c, which dissociate from each other. If C3b is surface- bound, the iC3b and C3dg or C3d formed from it also remain surface-bound. The surface-bound C3 fragments thus covalently tag or opsonise bacterial and unprotected host cell surfaces for complement receptor binding and engulfment by phagocytic cells. C4b undergoes similar degradation by FI, but since C4 is less abundant than C3, surface-bound C4b or C4d are of much lesser importance than the corresponding C3 fragments (Carroll and Sim, 2011; Davis and Harrison, 1982; Rodriguez de Cordoba et al., 2004; Sim et al., 1981b).

Phagocytic cell complement receptors differ in structure and function. Human CR1 (CD35, C3b/C4b receptor) is composed of 23–37 (length polymorphism) CCP modules, also called SCRs or Sushi domains, and is expressed on a variety of non-immune and immune cells, but largely on red blood cells capturing immune complexes bearing C3b/C4b for clearance by liver macrophages. By having both C3b and C4b binding domains, CR1 is a potent inhibitor of classical as well as alternative pathway through decay-acceleration of their convertases (Fig. 1) (Krych-Goldberg and Atkinson, 2001). CR2 (CD21), made up of 15 or 16 CCPs, is a B cell co-receptor for ligating C3dg-C3d/Ag complexes, for the enhancement of specific B cell receptor signalling (Heyman et al., 1990; Ricklin et al., 2010; van Lookeren Campagne et al., 2007; Walport, 2001b). Macrophage CRIg, a member of the Ig superfamily, which ligates

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