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Complement and coagulation crosstalk – Factor H in the spotlight

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ABSTRACT

The immune complement and the coagulation systems are blood-based proteolytic cascades that are activated by pathway-specific triggers, based on protein–protein interactions and enzymatic cleavage reactions. Activation of these systems is finely balanced and controlled through specific regulatory mechanisms. The complement and coagulation systems are generally viewed as distinct, but have common evolutionary origins, and several interactions between these homologous systems have been reported. This complement and coagulation crosstalk can affect activation, amplification and regulatory functions in both systems. In this review, we summarize the literature on coagulation factors contributing to complement alternative pathway activation and regulation and highlight molecular interactions of the complement alternative pathway regulator factor H with several coagulation factors. We propose a mechanism where factor H interactions with coagulation factors may contribute to both complement and coagulation activation and regulation within the haemostatic system and fibrin clot microenvironment and introduce the emerging role of factor H as a modulator of coagulation. Finally, we discuss the potential impact of these protein interactions in diseases associated with factor H dysregulation or deficiency as well as evidence of coagulation dysfunction.

1. Introduction

The complement and coagulation pathways (KEGG: hsa04610) are central to host defense against pathogen infection and injury. These blood-based defense systems are composed of proteins that are proteolytically activated, leading to the generation of active molecules essential to immunity and clotting. Complement is involved in the humoral arm of innate immunity, protecting against pathogen invasion and infections of the host (Walport, 2001), and coagulation is involved in haemostasis, preventing fluid loss after vessel injury (Tomaiuolo et al., 2017). These blood-borne systems share evolutionary origins (Dzik, 2019), and exhibit several molecular interactions, elegantly reviewed elsewhere (Conway, 2015, 2018; Foley, 2016; Oncul and Afshar-Kharghan, 2020; Pryzdial et al., 2022; Verschoor and Langer, 2013; Wiegner et al., 2016). In this review, we summarize how coagulation proteases affect complement C3 activation into C3b and conversion into iC3b in conjunction with the role of complement alternative pathway regulator factor H (FH) and highlight the emerging role of factor H as a modulator of coagulation.

2. Complement activation

The complement system is integral to non-cellular innate immunity and comprises about 50 blood and membrane-bound proteins. Complement is activated via three distinct pathways, the classical (CP), lectin (LP) and alternative pathway (AP) (Carroll and Sim, 2011), primarily in response to vascular injury (Kerr and Richards, 2012) and infection (Merle et al., 2015a). The classical pathway is activated via antibody-antigen complexes (Merle et al., 2015b), the lectin pathway by sugar moieties on the surfaces of bacteria (Kozarcanin et al., 2016), and the alternative pathway is constitutively activated by a “tick-over” (Merle et al., 2015b).

All pathways converge on the generation of an enzyme C3 convertase, C4b2a (CP, LP) and C3bBb (AP) (Bajic et al., 2015; Merle et al., 2015b), respectively, which cleaves the central component of the complement system, C3. The cleavage of C3 generates the functional fragments C3b and C3a. The anaphylatoxin C3a is a soluble inflammatory mediator and promotes recruitment of immune cells (Klos et al., 2009) via binding to C3a receptor, C3aR (Klos et al., 2009; Sarma and Ward, 2011). Nascent C3b has the transient ability to attach covalently to a

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nearby surface and can act as an opsonin by tagging a surface for subsequent recognition by complement receptor-bearing phagocytes (Merle et al., 2015b). C3 convertases can bind nearby generated C3b via their C4b or C3b subunits to form the C5 convertases C4b2aC3b (CP, LP) and C3bBbC3b (AP), respectively. This switches their enzymatic specificity from C3 to C5 (Kim et al., 1992), and C5 is cleaved into C5b and C5a (Merle et al., 2015b). The anaphylatoxin C5a promotes inflammation and recruitment of C5a receptor-bearing immune cells to the site of complement activation (Klos et al., 2009; Sarma and Ward, 2011). C5b binds C6, enabling binding to C7 which renders the complex lipophilic (Merle et al., 2015b; Serna et al., 2016). C8 association to the complex is the first membrane insertion event (Hadders et al., 2012), and the C5b-8 complex acts as a receptor for C9 and enables its polymerisation (Bajic et al., 2015; Carroll and Sim, 2011; Serna et al., 2016). Several C9 molecules polymerise to form a pore termed the membrane attack complex (MAC, C5b-9_n) (Morgan, 2016), which forms a lytic pore and causes an osmotic imbalance across a membrane (Bubeck, 2014; Serna et al., 2016).

2.1. Complement amplification by the alternative pathway and its regulation

Complement activation and amplification is maintained by the alternative pathway amplification loop, balancing the generation of C3b - that enhances amplification - with C3b degradation, which down-regulates it (Lachmann, 2009). The alternative pathway is continuously activated at a low level in the blood fluid phase by the "tick-over" mechanism, which is the spontaneous, low level hydrolysis of plasma C3 to C3(H_2O) (Nilsson and Nilsson, 2012). Fluid phase C3(H_2O) can bind factor B (FB), enabling serine protease factor D (FD) to cleave C3(H_2O)-bound factor B, forming the fluid phase C3 convertase complex C3(H_2O)Bb, which is able to cleave C3 (Merle et al., 2015b). This allows constant generation of small amounts of C3b. Complement regulators quickly inactivate C3b into iC3b on host cells and in the fluid phase. Nascent C3b covalently attaches to non-self surfaces, and in the absence of complement regulators (Ferreira et al., 2009; Ramadass et al., 2014); this enables binding of factor B and factor D to form the alternative pathway C3 convertase (C3bBb). This step is quickly amplified as each C3 convertase molecule can cleave many more C3 molecules, thereby generating vast amounts of C3b to opsonise a target surface (Sanchez-Corral et al., 2018; Merle et al., 2015a).

The degree of C3b opsonization and alternative pathway C3 convertase formation is driven by the alternative pathway amplification loop, which is tightly regulated on self-surfaces (Bajic et al., 2015; Carroll and Sim, 2011; Noris and Remuzzi, 2013). Complement regulators are present in both the fluid phase and on self-cells and exhibit overlapping functionality to prevent complement activation and deposition on the self. Regulators act primarily as decay accelerators of the C3 and C5 convertases, as cofactors in the proteolytic inactivation of C3b, or by competitive binding to complement components (Merle et al., 2015a).

2.1.1. Decay accelerating activity

For instance, both membrane-bound complement receptor 1 (CR1, CD35) and DAF (CD55) have decay accelerating activity. Their binding enables the dissociation of the classical and alternative pathway C3 and C5 convertases into their subunits Klickstein et al., 1988; Krych-Goldberg et al., 1999). The alternative pathway C3 convertase C3bBb is primarily dissociated by decay-accelerating factor H (Pouw et al., 2015), releasing the Bb subunit, with C3b available for further degradation by factor I (FI) (Xue et al., 2017).

2.1.2. Cofactor activity

Factor I is a serine protease that, in the presence of a cofactor, cleaves C3b into iC3b. Membrane-bound cofactors include CR1 (CD35), membrane cofactor protein (MCP, CD46), or fluid phase cofactors such as complement C4 binding protein (C4BP) and factor H (FH) (Noris and Remuzzi, 2013). The opsonin iC3b is unable to bind factor B, thus, preventing further alternative pathway C3 convertase formation (Ferreira et al., 2010; Xue et al., 2017). Both iC3b and C3b function as opsonins to promote phagocytosis by binding immune cells expressing complement receptors CR1 and CR3 (also termed CD11b/CD18, or Mac-1) (Lubbers et al., 2017). While MCP, C4BP and factor H act as cofactors in the cleavage of C3b into iC3b, only CR1 enables the further proteolysis of iC3b into C3dg (Davis et al., 1984), which can also function as an opsonin that interacts with cells expressing CR3 and CR2 (CD21) (Bajic et al., 2013).

2.2. Complement regulator factor H

Factor H is the main regulator of the alternative pathway (Merle et al., 2015a) and more generally of complement amplification and can act in the fluid phase as well as on cell surfaces. It regulates the alternative pathway amplification by (1) accelerating the dissociation of the C3 convertase (C3bBb) and C5 convertase (C3bBbC3b) (decay-accelerating activity) (Perkins et al., 2012; Pouw et al., 2015), (2) acting as a cofactor to factor I in the inactivation of C3b into iC3b (cofactor activity) (Jozsi and Zipfel, 2008; Perkins et al., 2012; Pouw et al., 2015), and (3) by competitive binding with factor B to C3b (Blaum et al., 2015; Clark et al., 2010; Dopler et al., 2019; Ferluga et al., 2017; Medjeral-Thomas and Pickering, 2016; Parente et al., 2017; Perkins et al., 2012; Pouw et al., 2015; Wu et al., 2009).

Complement factor H is primarily expressed by the liver, but also by fibroblasts, endothelial cells, mesangial cells, astrocytes, oligodendrocytes and neurons. Factor H is present in human plasma at relatively high concentrations varying between 1 to 2 μM Esparza-Gordillo et al., 2004; de Paula et al., 2003; Hakobyan et al., 2010. It is a 155kDa glycoprotein made up of 20 Short Consensus Repeats (SCR1-20) of approximately 60 amino acids each (Aslam and Perkins, 2001; David et al., 1995; de Cordoba and de Jorge, 2008; Ferreira et al., 2010; Jozsi and Zipfel, 2008; Jozsi et al., 2019). C3b is bound by factor H via three binding sites (Haque et al., 2020; Sharma and Pangburn, 1996). Binding of C3b to factor H SCR1-4 (Sharma and Pangburn, 1996) promotes decay accelerating (C3bBb,C3b) and cofactor activity (C3b inactivation into iC3b) (Ferreira et al., 2009; Morgan et al., 2011). There is further evidence that the domains SCR6-8 and SCR19-20 bind cell surface glycosaminoglycans (GAG) (Herbert et al., 2007) and that SCR19-20 can interact with C3b (Ferreira et al., 2009; Jokiranta et al., 2000; Morgan et al., 2011; Wu et al., 2009), while the observed weak binding of SCR6-8 to C3b (Schmidt et al., 2008) may not be physiologically relevant. While complement activation and regulation of the alternative pathway are the main mechanisms, accumulating evidence suggests alternative activation mechanisms contribute to C3 and C5 activation (Amara et al., 2010; Huber-Lang et al., 2006) and suggest a link of factor H with the coagulation system and haemostasis.

3. Primary haemostasis

In the event of vascular injury, haemostasis is initiated via the activation of coagulation factors and platelets to prevent blood loss. Vascular injury exposes subendothelial collagen, which comes into contact with circulating von Willebrand factor (VWF) and acts as a bridge between platelets and collagen. This enables platelet adhesion and aggregation (Lenting et al., 2015). Platelet activation induces their degranulation, as well as conformational changes, and phospholipid exposure (Broos et al., 2011), causing more platelets to aggregate and adhere to the growing platelet plug (Furie and Furie, 2008), which is strengthened by von Willebrand factor forming multimers (Stockschlaeder et al., 2014).

3.1. Coagulation activation

The coagulation cascade is initiated via the extrinsic or intrinsic pathway. The extrinsic pathway begins with tissue factor (TF) being released from within the vessel wall following injury, coming into contact with plasma (Smith et al., 2015), and binding activated factor VII (FVIIa) (Adams and Bird, 2009; Davie et al., 1991; Mackman et al., 2007; Pilli, 2018). The TF:FVIIa complex activates factor IX (FIXa) (Mackman et al., 2007), that binds to activated factor VIII (FVIIIa). The tenase complex (FIXa:FVIIIa) assembles on a phospholipid surface and activates FX (FXa), which then binds to FVa, forming the prothrombinase (FXa:FVa) complex. The prothrombinase complex converts prothrombin (FII), into active thrombin (FIIa) (Krishnaswamy, 2013). Factor V is activated by the first thrombin in circulation however it can also be activated by FXa on the surface of platelets (Bruce Furie and Furie, 2008; Smith et al., 2015). The intrinsic pathway, or contact activation pathway, is initiated by FXII interacting with negatively charged surfaces (Smith et al., 2015); autoactivation, and via kallikrein. The serine proteases kallikrein is the active form of prekallikrein, itself activated by FXIIa through a positive feedback-loop (Grover and Mackman, 2019). Activated FXIIa activates FXI (FXIa), which activates FIX (FIXa) that binds FVIIIa, forming the tenase complex, where the intrinsic pathway converges with the extrinsic pathway (Colman and Schmaier, 1997).

3.2. Coagulation amplification and maintenance of the fibrin clot

The initial generation of serine protease thrombin (FIIa) quickly progresses into an exponential increase in its localised production, which significantly enhances the haemostatic response. Thrombin generation depends on prothrombin availability (Balendran et al., 2017), and procoagulant factors, which require a negatively charged surface to activate (Campbell et al., 2008). This is facilitated by shear blood flow that influences the availability of procoagulant factors as it delivers or removes new factors (Weisel and Litvinov, 2013). In a positive feedback loop, thrombin further activates factors FV, FXI and FVIII (Adams and Huntington, 2006; Gallwitz et al., 2012). Thrombin is the central serine protease that cleaves fibrinogen into fibrin, which assembles into fibrin fibers, forming a meshwork, or gel, with the platelet plug (Weisel and Litvinov, 2017). Thrombin further activates transglutaminase FXIII (FXIIIa), which crosslinks fibrin fibers and stabilises the clot (Doolittle, 2017; Walton et al., 2015) and also activates protease activated receptors (PARs) on the surface of platelets, contributing to platelet activation (Adams and Bird, 2009; Allen et al., 2004; Cera, 2007; Cera, 2008; Crawley et al., 2007; Ignjatovic et al., 2007; Krishnaswamy, 2013; Licari and Kovacic, 2009; Mann, 2003; Walker and Royston, 2002; Wolberg and Campbell, 2008).

3.3. Coagulation regulation

To prevent excessive fibrin clot growth, regulatory mechanisms are in place to prevent thrombi and control coagulation. Initiation of the coagulation cascade is inhibited by tissue factor pathway inhibitor (TFPI), which downregulates the TF:FVIIa extrinsic pathway (Mast, 2016). Serine protease inhibitors (serpins), such as antithrombin (AT), can rapidly inhibit proteases thrombin and FXa (Rezaie and Giri, 2020), and to a lesser extend FXIa and FXIIa (Danielsson and Bjork, 1983).

Endothelial expressed thrombomodulin (TM) restricts clot formation and coagulation activation to the site of injury (Esmon, 1989; Esmon, 1995). Thrombomodulin is a cofactor for thrombin (Martin et al., 2013); which changes thrombin from its ability to convert fibrinogen into fibrin; to activate protein C (PC) (Fuentes-Prior et al., 2000); and TAFI (thrombin activatable fibrinolysis inhibitor) (Esmon, 1995). Activated protein C (APC) and its cofactor protein S (PS) downregulate the coagulation pathway amplification by inactivating FVa and FVIIIa (Esmon, 1989). On the other hand, activated TAFIa removes lysine residues from C-terminal fibrin, preventing fibrinolysis factors from binding and disintegrating the clot (Bouma and Mosnier, 2006; Laszlo Bajzar and Nesheim, 1996).

3.4. Fibrinolysis

Fibrinolysis is the process of fibrin breakdown by serine protease plasmin. Plasmin is derived from plasminogen, which is activated by tissue plasminogen activator (tPA) released from the endothelium or by circulating urokinase plasminogen activator (uPA) (Ismail et al., 2021). The metalloproteinase ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) is the key regulator of von Willebrand factor multimers in the fibrin clot. As a certain shear is reached in circulation, von Willebrand factor unfolds and exposes an ADAMTS13 cleavage site, leading to degradation of ultra large von Willebrand factor. These regulatory mechanisms prevent thrombi from forming throughout the vessel (DeYoung et al., 2022).

4. Coagulation protease-mediated cleavage of complement C3 and C5

Interestingly, at sites of clot formation, the central processes of coagulation activation that promote thrombin generation and subsequent fibrinolysis, can also facilitate activation of some complement components. For instance, the coagulation protease kallikrein cleaves complement C3 and enables complement activation (Irmscher et al., 2018). Thrombin, factors FIXa, FXa and FXIa, and plasmin can cleave C3 and C5, generating functional anaphylatoxins C3a, C5a (Amara et al., 2010; Foley et al., 2016) and C3b or iC3b-like fragments (Amara et al., 2010; Barthel et al., 2012; Foley et al., 2015). These complement fragments are biologically active in vitro, but not identical to the complement-generated cleavage fragments, due to differing cleavage sites. Furthermore, thrombin cleaving C5 generates C5b, which can form a MAC-like complex (C5b-9T, thrombin-generated C5b-9) with substantial lytic activity (Krisinger et al., 2012). Additionally, anaphylatoxins C3a and C5a are inactivated by carboxypeptidase TAFIa (Leung et al., 2008).

5. Coagulation factors contribute to factor H regulation of C3b

In vitro studies have shown that von Willebrand factor binding with factor H enhances factor I-mediated inactivation of C3b into iC3b (Bettoni et al., 2017; Feng et al., 2015; Noone et al., 2016). Additionally, thrombomodulin (TM) can bind C3b (Heurich et al., 2016) and C3 via its lectin-like domain (DeHelian et al., 2015; Koeppe et al., 2018; Palowitch et al., 2015) and in the presence of factor H is able to moderately enhance the factor I-mediated inactivation of C3b into iC3b and regulate complement activity in serum (Heurich et al., 2016; Mieke Delvaeye et al., 2009). An overview of the functional impact of coagulation serine proteases on the activation of C3 and C5 and inactivation of C3b into iC3b is shown in Fig. 1.

In addition to its central role in complement alternative pathway regulation, there is increasing evidence for numerous interactions of factor H with coagulation components that affect coagulation activity as well as enhancing factor H-mediated inactivation of C3b into iC3b. An overview of the complement and coagulation pathways and factor H central role is summarized in Fig. 2.

6. In vitro evidence of factor H interactions with coagulation factors

Factor H binds coagulation factors relevant for coagulation activation, such as extrinsic pathway coagulation factor FXI (Puy and Pang, 2021), intrinsic FXII (Ferluga et al., 2014; Thangaraj et al., 2020), and thrombin (McCluskey et al., 2021). Factor H also binds to fibrinogen, fibrin and within the fibrin clot (Abbow, 2016; Honda et al., 2017;

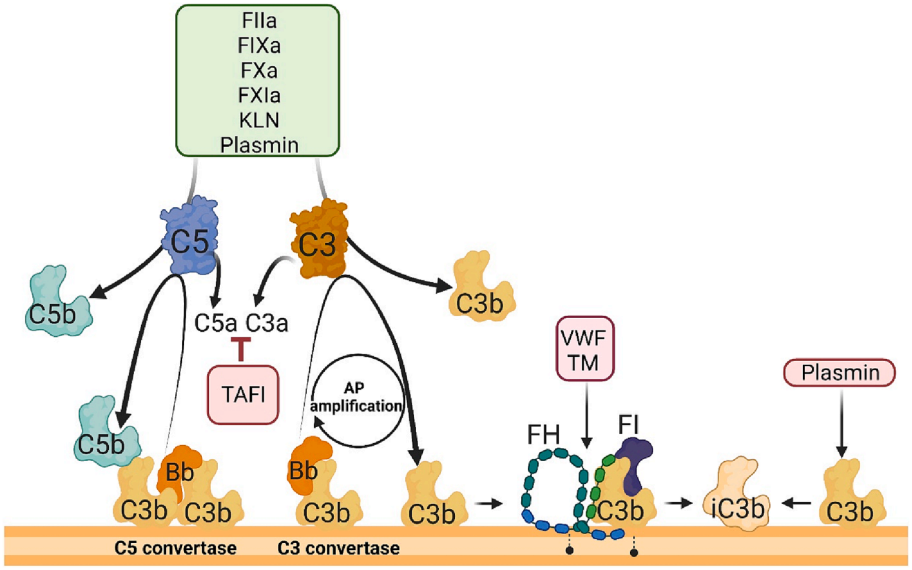

Fig. 1. Overview of the functional consequence of coagulation factors on central mechanisms of complement activation and alternative pathway regulation by factor H. All complement pathways converge at C3 convertase formation and cleavage of C3 (orange), generating anaphylatoxin C3a and opsonin C3b (yellow). Nascent C3b can attach covalently to any nearby cell surface (dashed line with dot indicating binding to membrane bilayer in yellow). C3b on self-surfaces and in the fluid phase is readily inactivated with the help of complement regulators. The main regulator of the alternative pathway (AP) and complement amplification is complement factor H (FH). Factor H is a fluid phase glycoprotein made up of 20 short consensus repeats (SCR), with SCR1-4 (light green) relevant for its decay and cofactor activity, SCR6-8 and SCR19-20 (shown in blue) relevant for its surface binding ability (dashed line with dot indicating surface binding to e.g. glucoseaminoglycans). Factor H is a cofactor for serine protease factor I (FI) cleaving C3b into iC3b (light yellow), which is incapable to form the AP C3 convertase (C3bBb) leading to downregulation of alternative pathway amplification. In vitro studies have shown that coagulation serine proteases thrombin (FIIa), FIXa, FXa, FXIa, kallikrein, and plasmin can also cleave C3 into C3b and that coagulation factors contribute to C3b inactivation into iC3b either by direct enzymatic cleavage (e.g., plasmin) or by enhancing factor H cofactor activity (von Willebrand factor, VWF; thrombomodulin, TM). Both C3b and iC3b can function as opsonins. The alternative pathway C5 convertase (C3bBbC3b) as well as coagulation proteases FIIa, FIXa, FXa, FXIa, and plasmin cleave C5 (blue) into C5a and C5b (light blue). Anaphylatoxins C3a and C5a are inactivated by TAFIa (thrombin activatable fibrinolysis inhibitor). Coagulation factors promoting complement activation through the cleavage of C3 and C5 are shown in green box inserts and those with regulatory functions affecting factor H cofactor activity and inactivation of C3b are shown in red inserts. Blunt arrows (T) indicate inhibition while sharp arrows (→) indicate activation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Stachowicz et al., 2018), as well as FXIII (Akhter et al., 2019; Li et al., 2022; Nikolajsen et al., 2014; Singh et al., 2019). Although contradictory, Feng and Rayes *et al.* demonstrated that the factor H interaction with von Willebrand factor affects ADAMTS13-mediated proteolysis of von Willebrand factor, in addition to its impact on complement regulation (Feng et al., 2013; Rayes et al., 2014). Additionally, platelets bind to factor H (Bhasym et al., 2019; Blatt et al., 2017; Vaziri-Sani et al., 2005). The thrombin-thrombomodulin complex-mediated generation of activated protein C (APC) is significantly enhanced in the presence of factor H (McCluskey et al., 2021). On the endothelium, thrombomodulin has been found to exert non-haemostatic functions (Loghmani and Conway, 2018) including the enhancement of complement regulator factor H-mediated inactivation of C3b and regulation of complement (Mieke Delvaeye et al., 2009). A summary of the factor H interactions with coagulation factors and their functional impact on either complement and/or coagulation activity is shown in Table 1.

7. Binding sites important for factor H interactions with coagulation factors

Important questions remain. Currently, the knowledge of the binding sites involved in factor H interactions with coagulation factors is limited. We know that factor H forms complexes with coagulation FXII and FXI resulting in the inhibition of their catalytic ability (Ferluga et al., 2014) or their ability to become activated (Puy and Pang, 2021), respectively. This would imply a direct binding interaction of factor H with a substrate recognition or secondary binding site influencing catalytic activity. Puy *et al.* reported that factor H is a substrate for FXIa (Puy and Pang, 2021) and cleavage reduces factor H cofactor and decay activity. FXIa cleaves factor H SCR6 at R341/R342. This does not affect factor H regulatory domains (Bhattacharjee et al., 2010; Ferreira et al., 2009; Morgan et al., 2011) located in SCR1-4, as SCR6 is relevant for surface binding (Herbert et al., 2007; Schmidt et al., 2008); however, Puy *et al.* did not test whether this cleavage would impact C3b or surface binding. Factor H interacts with FXIIIa, which in plasma is present as a heterotetramer (FXIII-A2B2) consisting of 2 potentially active A subunits and 2 carrier/inhibitory B subunits (FXIII-B2). Factor H binds with FXIII-B, which has a similar sushi domain structure to factor H (Akhter et al., 2019); possibly suggesting a putative role of FXIII-B in complement regulation. FXIII-B functions primarily as a carrier protein to stabilize FXIII-A in plasma (Katona et al., 2014) and to facilitate the interaction with its primary substrate, fibrinogen, which is another binding partner of factor H, in particular γ-fibrinogen (Honda et al., 2017; Horstmann et al., 1992). Interestingly, Ståhl *et al.* (Ståhl et al., 2008) found that a mutation in factor H SCR20 (E1198Stop) associated with atypical hemolytic uremic syndrome (aHUS) bound less well to normal washed platelets, resulting in complement deposition and platelet activation, impairing the capacity to protect host cells and confirming the importance of the factor H surface binding domain. Additionally, Ueda *et al.* (Ueda et al., 2017) showed in a murine model that a mutation in W1206R (In humans, W1183R is associated with atypical hemolytic uremic syndrome, impairing factor H interaction with host cells, without affecting is complement regulatory ability (Ferreira et al., 2009; Martín Merinero et al., 2021)) resulted in a loss of factor H interaction with cells, without affecting complement regulation, however led to the development of thrombotic microangiopathy (TMA). These mice showed endothelial and vascular smooth muscle cell dysfunction with significantly elevated plasma levels of von Willebrand factor, and a lower ratio of high- to low-molecular-weight von Willebrand factor multimers, which may suggest another factor H link to ADAMTS13-mediated proteolysis and platelet aggregation (Rayes et al., 2014).

8. Factor H orchestrates multiple complement and coagulation interactions

Factor H binds its natural ligand C3b via three binding sites (Haque et al., 2020; Sharma and Pangburn, 1996); and polyanions via multiple binding sites (Ferreira et al., 2010). Each binding site on factor H interacts with distinct binding affinities, all contributing to stronger

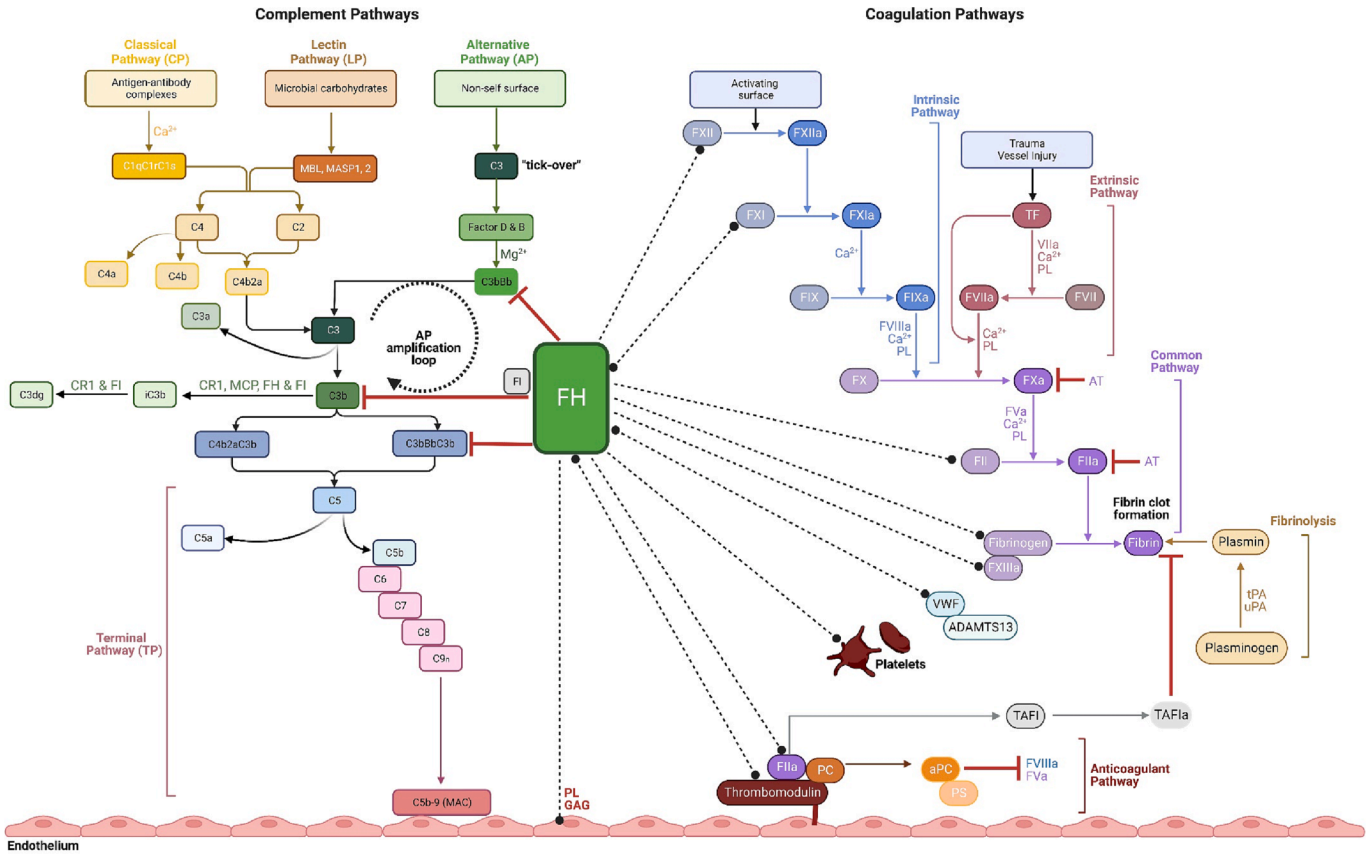

Fig. 2. Overview of the complement and coagulation pathways and complement factor H interactions with coagulation factors. The complement system is activated by three pathways: the classical pathway (CP, yellow), lectin pathway (LP, orange), and alternative pathway (AP, green) via distinct activation mechanisms. Classical and lectin pathway activation leads to the cleavage of C4 and C2, resulting in the formation of the C3 convertase (C4b2a). The alternative pathway is continuously activated by the "tick-over" mechanism of C3 hydrolysis into $C3_{H20}$, which is able to bind factor B (FB) and factor D (FD) to form a C3 convertase ($C3_{H2O}$Bb). This C3 convertase cleaves C3 into anaphylatoxin C3a and opsonin C3b, which can bind FB and FD to form the alternative pathway C3 convertase C3bBb. All pathways converge at the level of C3 convertase formation and cleavage of many C3 molecules, which is amplified by each C3b molecule able to form more C3bBb, known as the alternative pathway amplification loop. The terminal pathway (TP, blue) of complement commences with the formation of the C5 convertases and cleavage of C5 into anaphylatoxin C5a and C5b, and the latter subsequently binds C6, C7, C8, and multiple C9 molecules forming the membrane attack complex (MAC or C5b-9, red). Several complement regulators therefore tightly control complement activation and amplification. Complement regulator factor H (FH, green) is the main regulator found in the fluid phase and also bound to surfaces (dashed line with dot indicating factor H surface binding, to e.g. glucoseaminoglycans, GAG, or phospholipids, PL) that controls the alternative pathway and complement amplification. Factor H has both decay accelerating activity of the alternative pathway C3 and C5 convertases, and is a cofactor for factor I (FI) that cleaves C3b into iC3b, which is unable to form a C3 convertase. Both C3b and iC3b function as opsonins. Factor H has several functions outside of the complement system affecting the coagulation pathways. The coagulation system is activated via the intrinsic (blue) and extrinsic (red) pathway. The common (purple) pathway activation leads to activation of thrombin and subsequent fibrin clot generation, which subsequently undergoes fibrinolysis by plasmin. Surface-expressed thrombomodulin (TM) binds thrombin, leading to the generation of activated protein C (APC) and subsequent downregulation of thrombin activation through inhibition of Va/VIIIa. In vitro studies have shown that factor H binds coagulation factors of the intrinsic coagulation pathway (blue): FXII, FXI, the common pathway (purple): FIIa (thrombin), fibrinogen/ fibrin, FXIIIa, and von Willebrand factor (VWF, light blue) and platelets (brown-red), as well as the anticoagulant pathway (dark red): FIIa (thrombin), thrombomodulin (TM). Factor H affecting coagulation is indicated by a dashed line with dot indicating a functional consequence on the coagulation system or bi-directional dot for functional impact of crosstalk interactions on both complement and coagulation activity. Binding of factor H with coagulation factors primarily affects the activation of the intrinsic and common pathways procoagulant activity, anticoagulant protein C activation, and the conversion of complement C3b into iC3b. Blunt arrows (T) indicate inhibition while sharp arrows (→) indicate activation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

avidity binding of full-length factor H and therefore to its regulatory activity (Haque et al., 2020). Distinct binding affinities and local concentration requirements may modulate the interactions of factor H in the fluid phase, on the cell surface or the localized clot environment. For instance, under physiological conditions, the plasma concentration of prothrombin is about 1.39 μM (Meeks and Abshire, 2008), but only 5-10nM of active thrombin is required at the initiation stage of the clotting process and local fibrin formation (Mann, 2003). Fibrinogen varies between 5.8-11.8 μM in plasma (Göbel et al., 2018), while plasma factor H between 1-2 μM (de Paula et al., 2003; Esparza-Gordillo et al., 2004; Hakobyan et al., 2010). The binding affinities of full-length factor H with coagulation ligands are found to be in the nanomolar (nM) range and are often lower compared with C3b (K_D (nM) low-high: thrombin<fibrinogen<C3b<soluble thrombomodulin (sTM) (Heurich et al., 2016; McCluskey et al., 2021). Consequentially, localized binding interactions in the clot environment may only require nanomolar concentrations for factor H binding with coagulation factors. Additionally, the plasma and surface-bound factor H concentrations may affect clot generation and structure. We found that nM concentrations of factor H enhances fibrin clot generation and forms relatively coarse fibrin clots with lower fiber density (McCluskey et al., 2021), which may impact clot stability and susceptibility to fibrinolysis. This effect is also known for high thrombin concentrations, which produce more dense fibrin networks, which are resistant to fibrinolysis, while low thrombin concentrations produce coarse, more porous networks of relatively unbranched fibrin fibers, susceptible to fibrinolysis (Blombäck et al., 1994; Wolberg

Table 1
Factor H binding with coagulation factors and platelets and the functional impact on complement or coagulation function. Overview of in vitro evidence of factor H binding with coagulation factors FXIIa, FXIa, thrombin, fibrinogen, FXIIIa, von Willebrand factor (VWF), and platelets, and thrombomodulin and a summary of complement or coagulation functions.

Reference	Factor H binding coagulation factor	Complement function	Coagulation function
Thangaraj et al. (2020), Ferluga et al. (2014)	**FXII/XIIa**	None reported	• Factor H binding inhibits FXIIa activation of kallikrein amidolytic activity. • Direct interaction between factor XII (FXII) and factor H in pure protein systems: i. Enzyme-linked immunosorbent assay (ELISA) analysis of FXII: factor H interaction. ii. Surface plasmon resonance (SPR) analysis of the binding of FXII to immobilized factor H. • Presence of α-FXIIa: factor H complex in contact-activated normal human plasma. • Significantly elevated α-FXIIa: factor H complex levels in contact-activated plasma from hereditary angioedema (HAE) patients.
Puy and Pang (2021)	**FXI/XIa**	• FXIa cleavage of factor H reduces factor H-mediated decay of C3bBb and binding to human endothelial cells. • FXIa reduces factor H and factor I-mediated cleavage of C3b.	• Factor H inhibits FXIa activation by thrombin.
McCluskey et al. (2021)	**Thrombin (FIIa)**	• Factor H binds thrombin with nM affinity. • Physiological thrombin does not affect factor H-dependent regulation of complement–mediated haemolysis.	• Absence of factor H prolongs tail bleeding time in factor H knockout *CFH*$^{-/-}$ mice. • Activated partial thromboplastin time (aPTT) is elevated in human factor H-depleted citrate plasma. • Factor H acts a cofactor for thrombin by enhancing fibrin generation and altering fibrin clot structure. • Factor H enhances the thrombin and thrombin-thrombomodulin-mediated activation of protein C.
Horstmann et al. (1992) McCluskey et al. (2021)	**Fibrinogen**	• Factor H binds fibrinogen with nM affinity. • Fibrinogen binding with factor H does not affect factor H decay accelerating activity of the complement alternative pathway C3 convertase (C3bBb).	• In the presence of factor H, pure protein fibrin clots have larger fibers separated by more numerous and larger pores and reduced fiber density.
Nikolais et al. (2014), Ferluga et al. (2014), Singh et al. (2019), Akhter et al. (2019), Li et al. (2022)	**FXIII/XIIIa**	• FXIII-B binding with factor H has no effect on factor H cofactor activity in the inactivation of C3b. • FXIII-B subunit has no effect on the rate of complement activation.	• Factor H binds and is a substrate for FXIIIa. • Sequence homology between FXIII-B and factor H.
Rayes et al. (2014), Feng et al. (2013) Feng et al. (2015), Noone et al. (2016), Peyvandi et al. (2011)	**Von Willebrand factor (VWF)**	• Factor H binds to von Willebrand factor. • Von Willebrand factor enhances factor H/factor I-mediated inactivation of C3b	• Factor H binds to von Willebrand factor and may affect cleavage of von Willebrand factor by ADAMTS-13. • Factor H inhibited ADAMTS13-mediated proteolysis of von Willebrand factor and promoted platelet aggregation. • Factor H increases cleavage of recombinant VWF-A2 by ADAMTS13
Walter et al. (2008), Blatt et al. (2017)Vaziri-Sani et al. (2005), Blatt et al. (2016), Saggu et al. (2013)	**Platelets**	• Factor H binds to platelets in a dose-dependent manner. • A C- terminal factor H mutation associated with atypical hemolytic uremic syndrome (aHUS) reduces factor H binding to platelets, and enables complement activation on the surface of platelets and their activation.	• Factor H regulates platelet activation and aggregation by properdin-mediated complement activation. • Platelets secrete factor H. Uptake of factor H by platelets. • Factor H binds platelets in a dose dependent manner via its C-terminal region.
Delvayae et al. (2009), Heurich et al. (2016)	**Thrombomodulin (TM)**	• Thrombomodulin binds C3b and factor H. • Thrombomodulin enhances the inactivation of C3b into iC3b by factor H and factor I • Atypical hemolytic syndrome – associated thrombomodulin mutants showed reduced C3b conversion to iC3b • Soluble thrombomodulin moderately inhibits complement activity in serum.	• Factor H enhances the thrombin-thrombomodulin mediated activation of protein C several fold stronger than factor H and thrombin alone.

Abbreviations: aHUS = atypical hemolytic uremic syndrome, FH = Complement factor H, FI = Complement factor I, AP = alternative pathway, VWF = von Willebrand factor, aPTT = activated partial thromboplastin time, TM = Thrombomodulin, FIIa = thrombin, FXI = factor XI, FXII = factor XII, FXIII = factor XIII.

and Campbell, 2008). Thus, circulating concentrations of complement and coagulation components, and in particular factor H, would not only affect the ability to form complexes with coagulation factors but may also affect the clot structure and potentially fibrinolysis.

Factor H binds other proteins and cells outside of the complement or coagulation system via specific SCR domains (Kopp et al., 2012), which either affecting regulation of C3, factor H activity or its binding to cell surfaces or polyanions. This suggests that factor H may exhibit location-specific recognition of surfaces like the fibrin clot via distinct binding sites independent of its complement regulatory domains.

9. A potential role of factor H in the fibrin clot microenvironment

The current evidence of factor H interactions with coagulation factors points to common mechanisms in the defense against (endothelial) injury resulting in clot formation. Here we propose a joint mechanism, primarily localized at the fibrin clot microenvironment in response to injury, where coagulation proteases also support local complement activation and proteolysis, with a central role for factor H as both a cell surface and a fluid phase regulator (Fig. 3). Surface binding of factor H to the endothelium (Jokiranta et al., 2005) is integral to complement regulation through binding interactions with glycosaminoglycans, (Schmidt et al., 2008) phospholipids (Perkins et al., 2012; Tan et al., 2010) and opsonin C3b (Jokiranta et al., 2000; Morgan et al., 2011), but is also facilitated by binding to endothelial thrombomodulin (Mieke Delvaeye et al., 2009), the surface of platelets (Ståhl et al., 2008; Vaziri-Sani et al., 2005) or to collagen-bound von Willebrand factor (Feng et al., 2013; Noone et al., 2016; Rayes et al., 2014). Factor H surface binding ability allows the regulation of C3b deposition and complement amplification on self-surfaces by promoting the conversion of C3b into iC3b, which is enhanced in the presence of endothelial thrombomodulin (Mieke Delvaeye et al., 2009). In the event of vascular injury, thrombomodulin helps localize the clot to the site of injury (Esmon, 1995), which is enhanced in the presence of factor H by promoting thrombomodulin-thrombin mediated protein C activation (McCluskey et al., 2021). At the site of injury, exposed subendothelial collagen (Stockschlaeder et al., 2014) binds von Willebrand factor, the latter promoting factor H-mediated C3b conversion into iC3b (Rayes et al., 2014). Von Willebrand factor supports the adhesion of platelets (Stockschlaeder et al., 2014), which store and carry surface-bound factor H to control complement activation on the platelet surface (Blatt et al., 2017; Kahr and FGP, Christoph Licht. , 2008; Ståhl et al., 2008; Vaziri-Sani et al., 2005). During primary haemostasis, clot formation progresses through the activation of the coagulation cascade, leading to activation of FXIa, while FXIIa does not appear to be required for haemostasis. Nevertheless, both FXII (McCarty et al., 2020) and FXI (Puy and Pang, 2021) bind and form complexes with factor H, with FXIa possibly affecting factor H regulatory function. Downstream generation of thrombin leads to fibrin clot generation, and while factor H binds both fibrinogen/fibrin (Abbow, 2016) and thrombin, the thrombin-factor H interaction enhances thrombin's procoagulant function, affecting lag time and velocity of fibrin clot generation. This results in a more porous clot structure with less dense fibers (McCluskey et al., 2021). The clot is strengthened via the action of thrombin-activated FXIIIa, which binds factor H, but does not affect factor H cofactor activity (Singh et al., 2019), possibly facilitating the attachment of factor H to fibrinogen. Factor H orchestrates these binding interactions with coagulation components relevant to primary haemostasis via its multiple binding interactions with the endothelium, platelets and components of the fibrin clot microenvironment. Complement deposition on the fibrin clot is further facilitated via locally activated coagulation proteases FIIa, FIXa, FXa, FXIa and plasmin, which are able to cleave C3 into C3b and then iC3b (Amara et al., 2010; Foley et al., 2015). Locally, generation of anaphylatoxins and opsonins may facilitate the recruitment and attachment of immune cells to the site of injury (Foley and Conway, 2016). Platelets may also play a role in the recruitment of immune cells such as monocytes and leukocytes via adhesion molecules and release of chemokines (Budnik and Brill, 2018; Engelmann and Massberg, 2013). In the fluid phase, factor H is able to support the inactivation of circulating C3b, which is enhanced in the presence of soluble thrombomodulin (Heurich et al., 2016), released from damaged endothelial cells (Ohlin et al., 2005). Factor H also enhances the fluid phased activation of protein C by thrombin and thrombomdulin-thrombin complexes (McCluskey et al., 2021), allowing for downregulation of coagulation activation (Esmon, 1989). Thus, factor H plays multiple roles by regulating complement deposition on self-surfaces and the fluid phase, which is enhanced in the presence of a number of coagulation factors. Factor H interaction with coagulation proteins further affects fibrin clot generation, clot structure, and clot localization (Fig. 3).

10. C3 and its proteolytic fragments C3b and iC3b in the fibrin clot microenvironment

Altogether, we propose that factor H and its interaction with coagulation components facilitates the generation of C3b and iC3b and their deposition at sites of injury, which promotes recruitment of immune cells to that region (Delvaeye and Conway, 2009). Several factor H interactions with coagulation ligands have shown to enhance factor H cofactor activity and cleavage of C3b into iC3b (Table 1), or coagulation protease-mediated activation of C3 into C3a and C3b, and the latter further into iC3b (Fig. 1). This may suggest that C3b and iC3b are present in the clot environment. Indeed several complement components (Stachowicz et al., 2018), including C3, C5 and factor H have been found present in the fibrin clot and at relatively high concentrations (Howes et al., 2012; Ząbczyk et al., 2019). While C3 can directly bind fibrinogen and fibrin and affect fibrinolysis (King et al., 2021), little is known about the function of its cleavage fragments C3b and iC3b in relation to the clot environment. Interestingly, complement receptor 3 (CR3; CD11b/CD18, Mac-1, αMβ2) is a multi-ligand receptor with various roles in immunity and the main receptor for iC3b (Lamers et al., 2021). CR3 is also a receptor for fibrinogen, aiding the proinflammatory function of fibrinogen and fibrin on blood macrophages and monocytes (Schoenmakers et al., 2005). These shared receptor interactions further highlight the potential impact of immune components and cells on hemostasis (Luo et al., 2020), as well as thrombosis (Rawish et al., 2021), with the latter also able to initiate the innate immune response (Engelmann and Massberg, 2013).

The mechanism proposed in Fig. 3 focuses on factor H and is largely derived from in vitro evidence and the systemic relevance of these interactions remains elusive. Interestingly, several complement animal models do suggest a physiological role of complement in coagulation dysfunction, hemostasis and clot formation.

11. In vivo evidence of complement and coagulation interactions in animal models

Few animal models have investigated complement and coagulation interactions and little is known of the impact of factor H deficiency or dysfunction on coagulation activity in vivo. Several in vitro studies suggests that various coagulation serine proteases are able to activate complement, and that coagulation factors are able to mediate the proteolytic breakdown of complement activation fragments. However, the in vivo relevance of coagulation proteases bypassing complement-mediated activation mechanisms has been debated. For instance, Keshari *et al.* (Keshari et al., 2017) reported on the absence of complement system activation in a model of generalized experimental coagulation and fibrinolysis in baboons. By excluding tissue damage or inflammation as confounding factors, a significant increase in thrombin and plasmin generation had no significant effect on complement C3b, C5a, and sC5b-9 generation (Keshari et al., 2017). Considering that fibrinogen was almost consumed within a short period of time, this model may have overlooked more subtle effects. Furthermore, the requirements of robust complement and coagulation activation on endogenous surfaces such as on platelets or the endothelium was not addressed as activation of complement was monitored in the fluid phase only. It is surprising that excessive concentration of coagulation proteases did not affect fluid phase activation of complement. This may be explained by their swift inactivation by serine protease inhibitors. This study also raises questions concerning the extent of complement deposition on endothelial surfaces, the presence of complement deposition on the fibrin mesh formed as a result of fibrinogen consumption, and local complement component concentration in the clot environment. It needs

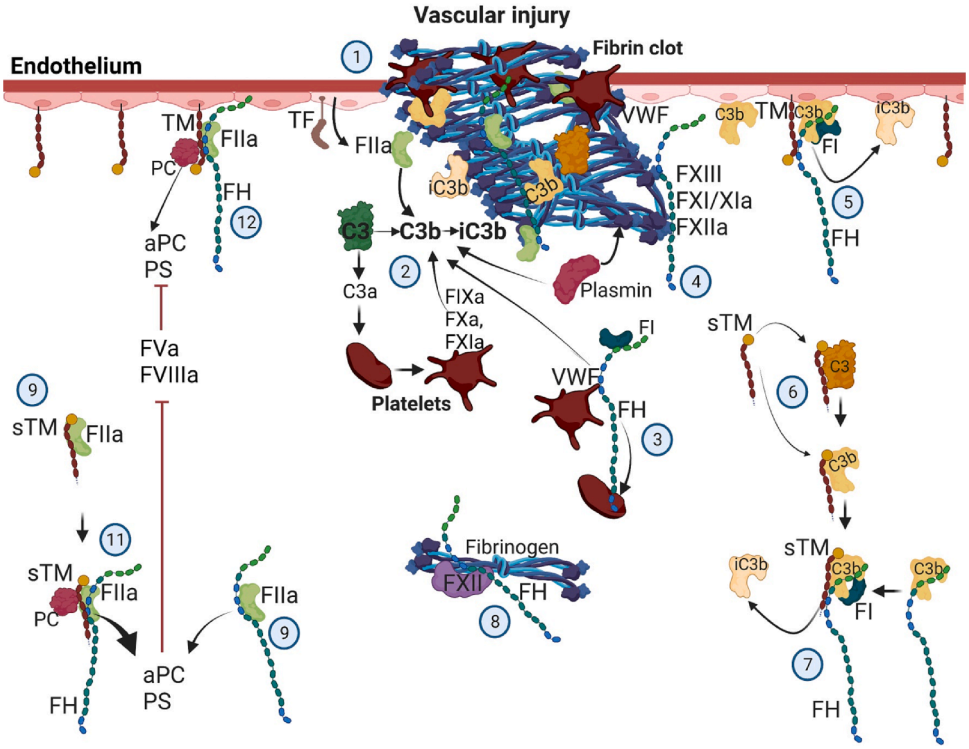

Fig. 3. Overview of the proposed mechanism of the role of factor H on clot formation and coagulation activity in response to vascular injury. 1. Vascular injury of the endothelium leads to activation of complement and coagulation pathways. Disruption of vessel walls exposes tissue factor (TF) and the TF-FVIIa complex activates the coagulation cascade. This leads to thrombin (FIIa, green) generation, subsequent fibrin clot (blue) formation and activation of platelets (red) at the site of tissue injury. Factor H (FH) binds to fibrinogen and fibrin (dark blue) and affects fibrin clot structure resulting in larger more numerous pores (central clot structure). Plasmin (purple) promotes fibrinolysis of the fibrin clot. 2. Activated coagulation proteases thrombin (green), FXa, FXIa and plasmin (purple) contribute to the cleavage of circulating complement C3 into C3a and C3b (light yellow) and subsequently iC3b (taupe). Anaphylatoxin C3a can bind to platelets expressing C3a-receptor (C3aR) and leading to platelet activation. Complement components C3, C3b and iC3b are deposited on the fibrin mesh of the fibrin clot. 3. Factor H (FH) can bind to platelets via its C-terminal domain (blue) and controls complement activation on the surface of platelets and platelet activation. Factor H binding von Willebrand factor (VWF) enhances ADAMTS13-mediated cleavage of VWF, and VWF in complex with factor H enhances its cofactor activity in the factor I (FI)-mediated inactivation of C3b, inhibits ADAMTS13-mediated proteolysis of VWF and promotes platelet aggregation. 4. Factor H also binds to FXIIa, FXIa, and is a substrate for FXIIIa. FXIa affects FH/FI-mediated cleavage of C3b into iC3b. 5. Complement activation (and coagulation proteases) result in C3 cleavage into C3b and C3b deposition on nearby cell surfaces. C3b is cleaved into iC3b by FH/FI. On normal endothelium, thrombomodulin (red) is expressed, which can interact with deposited C3b and surface-bound factor H, enhancing the inactivation of C3b into iC3b. 6. In the event of vessel injury, thrombomodulin is released from the cell surface into the fluid phase as soluble thrombomodulin (sTM). 7. Thrombomodulin can bind complement C3 and C3b and enhances inactivation of circulating C3b into iC3b by FH/FI. 8. In the fluid phase, factor H forms complexes with FXII/XIIa, which is having an inhibitory effect on FXII contact plasma activation, and factor H also binds soluble fibrinogen. 9. In the presence of factor H, thrombin-mediated protein C (PC) activation is enhanced. 10. The soluble thrombomodulin-thrombin complex activates protein C into activated protein C (APC), which is enhanced in the presence of factor H 11. in the fluid phase, and 12. on the cell surface. Blunt arrows (T) indicate inhibition while sharp arrows (→) indicate activation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to be pointed out that the 'pure coagulation' approach may mask subtle effects that occur over time. Thus, a sensitive model showing the potential of coagulation-mediated complement activation remains outstanding. We do however have some evidence supporting the relevance of complement and coagulation interactions in vivo, mostly from complement deficient mouse models. Complement knockout mice have shown coagulation or haemostatic complications. For instance, C3 knockout mice (*C3*$^{-/-}$) show increased bleeding times, lower platelet aggregation, decreased thrombus weight and size, without evidence of thrombosis (Borkowska et al., 2013; Gushiken et al., 2009; Huber-Lang et al., 2006; Muller-Calleja et al., 2018; Subramaniam et al., 2017). This is supported by further evidence of C3 affecting haemostasis in vitro, including activating tissue factor (Muller-Calleja et al., 2018), and stimulating platelet activation (Saggu et al., 2013). In addition, C3 binds fibrinogen and renders fibrin fibers thinner with smaller pores within the clot, increasing clot lysis time (King et al., 2021). C3 has also been reported to enhance neutrophil and monocyte adhesion with platelets (Swystun and Liaw, 2016), possibly via the action of C3 derived opsonins C3b and iC3b. C3 derived anaphylatoxin C3a stimulates platelet aggregation (Sauter et al., 2018) and the importance of C3a and its receptor was show in C3aR knockout mice (*C3aR*$^{-/-}$), impacting bleeding cessation and thrombus formation (Sauter et al., 2018). Abnormal haemostatic profiles have also been observed in C5 knockout mice (*C5*$^{-/-}$) (Mizuno et al., 2017). Specifically the thrombus size and weight was reduced in *C5*$^{-/-}$ mice, as well as decreased fibrin clot fibers and pores (Subramaniam et al., 2017). Together, the C3 and C5 knock out mouse models demonstrate the significant involvement of complement C3 and C5 in haemostasis and clot formation. Additionally, complement C6 knockout mice (*C6*$^{-/-}$) (Bhole and Stahl, 2004) show increased bleeding times, and lower platelet aggregation, indicating that the complement terminal pathway also has a role in haemostasis. In complement regulator factor H deficient mice (*CFH*$^{-/-}$), we reported increased bleeding time, with increased plasma haemoglobin (Hb) and soluble thrombomodulin (sTM) indicating vascular damage, but no increase in thrombin-antithrombin (TAT) levels as a measure of coagulation activation was observed (McCluskey et al., 2021).

This finding in *CFH*$^{-/-}$ mice is supported by an ex vivo study in human factor H-depleted plasma, where absence of factor H resulted in prolonged clotting time, as indicated by elevated activated partial thromboplastin time (aPTT). Addition of anti-factor H antibody, blocking SCR19-20 to normal human plasma also resulted in elevated aPTT (McCluskey et al., 2021); which suggests a direct role of factor H, and its C-terminal domain, in fibrin clot generation.

12. Factor H deficiency or dysfunction in human disease

In human plasma, normal levels of factor H range between 1-2 μM (Esparza-Gordillo et al., 2004) and there is little known about whether

factor H plasma levels correlate with clotting time. While we observed a prolonged clotting time in human factor H-depleted citrated plasma, in the absence of alternative pathway activation or consumption (McCluskey et al., 2021); human factor H deficiency or dysregultion results in uncontrolled alternative pathway activation (Pangburn, 2002). Complement deficiencies and dysfunction are associated with various infectious, inflammatory and (auto)immune diseases. They are often associated with factor H gene mutations and polymorphisms, resulting in factor H deficiency or dysfunctional factor H, as well as anti-factor H autoantibodies. Factor H deficiency in patients is characterized by low or absent factor H concentration in plasma as well as low concentration of C3, due to secondary consumption. These patients are characterized by complement dysregulation and C3 activation in plasma, resulting in continuous activation of the alternative complement pathway (Kopp et al., 2012). The generation of downstream molecules C5a and C5b-9 (MAC) affect endothelial tissue factor expression (Ritis et al., 2006) and C5b-9 deposition stimulates endothelial cells to secrete von Willebrand factor (Hattori et al., 1989), induces secretion of platelet storage granules (Ando et al., 1988) and increases platelet prothrombinase activity (Wiedmer et al., 1986). Uncontrolled complement activation is leading to hypocomplementemia and activation of complement on susceptible tissue surfaces, such as the kidney glomerular basement membrane. This membrane does not express intrinsic complement regulators (Thurman, 2020) and therefore may depend especially on the surface binding ability of factor H (Le Quintrec et al., 2010). This most commonly results in the renal pathology C3 glomerulopathy (C3G) (Wong and Kavanagh, 2018), also described as membranoproliferative glomerulonephritis type II (MPGN II) or dense deposit disease (DDD) (Chen et al., 2014; Master Sankar Raj et al., 2016; Meri, 2013; Sethi and Fervenza, 2014; Smith et al., 2011; Smith et al., 2019; Vernon et al., 2016) and factor H loss-of-function is the most common genetic complement defect in atypical hemolytic uremic syndrome (aHUS) (Bu et al., 2018; de Cordoba and de Jorge, 2008; Goicoechea de Jorge et al., 2018; Goodship, 2006; Jokiranta et al., 2006; Maga et al., 2010; Pickering and Cook, 2008; Pouw et al., 2019; Sanchez-Corral et al., 2002; Ståhl et al., 2008; Vernon et al., 2016).

12.1. Factor H deficiency is associated with thrombotic microangiopathy

Atypical HUS is characterized by thrombotic microangiopathy (TMA) (Jokiranta, 2017; Kavanagh et al., 2013; Meri, 2013; Zhang et al., 2017), with evidence of endothelial and red blood cell damage and thrombotic vascular occlusions (Kurosawa and Stearns-Kurosawa, 2014; Meri, 2013; Palma et al., 2021). Thrombotic microangiopathy is a result of heterogeneous pathological mechanisms described as thrombocytopenia as a result of platelet aggregation and thrombi formation, microangiopathic haemolytic anaemia (MAHA), and end organ damage (George and Nester, 2014; Scully et al., 2017; Thompson and Kavanagh, 2022). AHUS is a complement-mediated TMA as a result of a hereditary or acquired deficiency of complement regulatory proteins (e.g., factor H, CD46 or factor I) leading to dysregulation of the alternative pathway (Goodship et al., 2017). This diminishes host endothelial cell and platelet protection from complement damage. Furthermore, factor H dysfunction affects predominately the factor H C-terminus, also preventing cell surface regulation (Ferreira et al., 2009). However, a direct link of factor H interactions with coagulation function has not been shown yet in that context. Interestingly, a recent study determined coagulation and fibrinolysis profiles in aHUS and secondary TMA patients and observed elevated activated partial thromboplastin time (aPTT) (Sakurai et al., 2020). APTT measures the activity of the intrinsic and common pathways of coagulation, indicating that clotting time is elevated in aHUS patients. These findings support our own observations of elevated aPTT in factor H-depleted human plasma (McCluskey et al., 2021). Hence this could point towards a clotting dysfunction potentially influencing those coagulation factors that are functionally linked to factor H, such as fibrinogen, factors FXIIa, FXIa, or thrombin.

While hereditary or acquired deficiency of complement regulatory proteins, such as factor H, is predominantly linked to rare renal disorders, more moderate changes in circulating factor H plasma levels has been linked to infectious, vascular, or eye disease (Chen et al., 2015; Shimizu et al., 2021). Other diseases, where thrombosis (or bleeding) presents together with dysfunction of complement activation and regulation, include (paroxysmal nocturnal hemoglobinuria) PNH (Hill et al., 2013), ischemia-reperfusion injury (Gorsuch et al., 2012), disseminated intravascular coagulation (Popescu and Lupu, 2022) and sepsis (Lupu et al., 2014). Interestingly, a recent sepsis study showed a correlation between plasma factor H levels with clotting time aPTT and fibrinogen levels (Shimizu et al., 2021). Thus, factor H plasma levels, but possibly also mutations, polymorphisms or anti-factor H antibodies affecting its interactions with coagulation factors, may have a direct impact on haemostatic functions in diseases, where the alternative pathway is involved in pathology (Lasne et al., 2006).

13. Conclusions

This review highlights the central role of complement regulator factor H as a modulator of, not only complement regulation, but also coagulation. In vitro studies have shown that factor H binds coagulation factors FXII, FXI, FIIa (thrombin), fibrinogen and fibrin, FXIIIa, von Willebrand factor and platelets, as well as the anticoagulant pathway modulator thrombomodulin. Factor H plays multiple roles regulating complement deposition on self-surfaces and complement regulation in the fluid phase. This is enhanced in the presence of coagulation von Willebrand factor and thrombomodulin. Factor H binding with thrombin affects fibrin clot generation, clot structure, and its interaction with thrombomodulin enhances anticoagulant protein C activation.

Further, in vitro findings suggests that various coagulation serine proteases are able to directly activate complement, for instance C3 into C3b and iC3b, and that coagulation factors are able to affect the proteolytic breakdown of complement activation fragments. However, the in vivo relevance of coagulation proteases bypassing complement-mediated activation mechanisms is limited. Some in vivo evidence, which is largely derived from complement knockout mouse models, generally point towards a role of complement proteins in haemostasis or thrombosis, including factor H affecting clotting time.

Overall, complement factor H interactions with coagulation factors have potentially significant roles in diseases where both complement alternative pathway and factor H dysfunction or deficiency contributes to pathology.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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References

Abbow, H., 2016. Studies on Ligand Interactions of Human Complement Factor H. University of Leicester.

Adams, R.L., Bird, R.J., 2009. Review article: Coagulation cascade and therapeutics update: relevance to nephrology. Part 1: Overview of coagulation, thrombophilias and history of anticoagulants. Nephrology (Carlton) 14 (5), 462–470.

Adams, T.E., Huntington, J.A., 2006. Thrombin-cofactor interactions: structural insights into regulatory mechanisms. Arterioscler Thromb. Vasc. Biol. 26 (8), 1738–1745.

Akhter, M.S., Singh, S., Yadegari, H., Ivaskevicius, V., Oldenburg, J., Biswas, A., 2019. Exploring the structural similarity yet functional distinction between coagulation factor XIII-B and complement factor H sushi domains. J. Thromb. Thrombolysis. 48 (1), 95–102.

Allen, G.A., Oliver, J.A., Hoffman, M., Roberts, H.R., Monroe, D.M., 2004. Impact of procoagulant concentration on rate, peak and total thrombin generation in a model system. J. Thromb. Haemost. 2, 402–413.

Amara, U., Flierl, M.A., Rittirsch, D., Klos, A., Chen, H., Acker, B., et al., 2010. Molecular intercommunication between the complement and coagulation systems. J Immunol. 185 (9), 5628–5636.

Ando, B., Wiedmer, T., Hamilton, K.K., Sims, P.J., 1988. Complement proteins C5b–9 initiate secretion of platelet storage granules without increased binding of fibrinogen or von Willebrand factor to newly expressed cell surface GPIIb-IIIa. J. Biol. Chem. 263 (24), 11907–11914.

Aslam, M., Perkins, S.J., 2001. Folded-back solution structure of monomeric factor H of human complement by synchrotron X-ray and neutron scattering, analytical ultracentrifugation and constrained molecular modelling. J. Mol. Biol. 309 (5), 1117–1138.

Bajic, G., Yatime, L., Sim, R.B., Vorup-Jensen, T., Andersen, G.R., 2013. Structural insight on the recognition of surface-bound opsonins by the integrin I domain of complement receptor 3. Proc. Natl. Acad. Sci. U.S.A. 110 (41), 16426–16431.

Bajic, G., Degn, S.E., Thiel, S., Andersen, G.R., 2015. Complement activation, regulation, and molecular basis for complement-related diseases. EMBO J. 34 (22), 2735–2757.

Balendran, C.A., Lovgren, A., Hansson, K.M., Nelander, K., Olsson, M., Johansson, K.J., et al., 2017. Prothrombin time is predictive of low plasma prothrombin concentration and clinical outcome in patients with trauma hemorrhage: analyses of prospective observational cohort studies. Scand. J. Trauma Resusc. Emerg. Med. 25 (1), 30.

Barthel, D., Schindler, S., Zipfel, P.F., 2012. Plasminogen is a complement inhibitor. J. Biol. Chem. 287 (22), 18831–18842.

Bettoni, S., Galbusera, M., Gastoldi, S., Donadelli, R., Tentori, C., Sparta, G., et al., 2017. Interaction between multimeric von willebrand factor and complement: a fresh look to the pathophysiology of microvascular thrombosis. J. Immunol. 199 (3), 1021–1040.

Bhasym, A., Bhakuni, T., Guchhait, P., 2019. Elevated surface-bound complement FH alters the function of platelets and monocytes in FHR1/3 null healthy individuals. Blood Cell Mol. Dis. 79, 102349.

Bhattacharjee, A., Lehtinen, M.J., Kajander, T., Goldman, A., Jokiranta, T.S., 2010. Both domain 19 and domain 20 of factor H are involved in binding to complement C3b and C3d. Mol. Immunol. 47 (9), 1686–1691.

Bhole, D., Stahl, G.L., 2004. Molecular basis for complement component 6 (C6) deficiency in rats and mice. Immunobiology 209 (7), 559–568.

Blatt, A.Z., Saggu, G., Kulkarni, K.V., Cortes, C., Thurman, J.M., Ricklin, D., et al., 2016. Properdin-mediated C5a production enhances stable binding of platelets to granulocytes in human whole blood. J. Immunol. 196 (11), 4671–4680.

Blatt, A.Z., Saggu, G., Cortes, C., Herbert, A.P., Kavanagh, D., Ricklin, D., et al., 2017. Factor H C-terminal domains are critical for regulation of platelet/granulocyte aggregate formation. Front Immunol. 8, 1586.

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

Blombäck, B., Carlsson, K., Fatah, K., Hessel, B., Procyk, R., 1994. Fibrin in human plasma: gel architectures governed by rate and nature of fibrinogen activation. Thromb Res. 75 (5), 521–538.

Borkowska, S., Suszynska, M., Wysoczynski, M., Ratajczak, M.Z., 2013. Mobilization studies in C3-deficient mice unravel the involvement of a novel crosstalk between the coagulation and complement cascades in mobilization of hematopoietic stem/progenitor cells. Leukemia 27 (9), 1928–1930.

Bouma, B.N., Mosnier, L.O., 2006. Thrombin activatable fibrinolysis inhibitor (TAFI)–how does thrombin regulate fibrinolysis? Ann. Med. 38 (6), 378–388.

Broos, K., Feys, H.B., De Meyer, S.F., Vanhoorelbeke, K., Deckmyn, H., 2011. Platelets at work in primary hemostasis. Blood Rev. 25 (4), 155–167.

Bruce Furie, M.D., Furie, B.C., 2008. Ph.D. Mechanisms of thrombus formation. New England J. Med. 359, 938–949.

Bu, F., Zhang, Y., Wang, K., Borsa, N.G., Jones, M.B., Taylor, A.O., et al., 2018. Genetic analysis of 400 patients refines understanding and implicates a new gene in atypical hemolytic uremic syndrome. J. Am. Soc. Nephrol. 29 (12), 2809–2819.

Bubeck, D., 2014. The making of a macromolecular machine: assembly of the membrane attack complex. Biochemistry 53 (12), 1908–1915.

Budnik, I., Brill, A., 2018. Immune factors in deep vein thrombosis initiation. Trends Immunol. 39 (8), 610–623.

Campbell, R.A., Overmyer, K.A., Bagnell, C.R., Wolberg, A.S., 2008. Cellular procoagulant activity dictates clot structure and stability as a function of distance from the cell surface. Arterioscler. Thromb. Vasc. Biol. 28 (12), 2247–2254.

Carroll, M.V., Sim, R.B., 2011. Complement in health and disease. Adv. Drug Deliv. Rev. 63 (12), 965–975.

Cera, E.D., 2007. Thrombin as procoagulant and anticoagulant. J. Thromb. Haemost. 5.

Cera, E.D., 2008. Thrombin. Mol. Aspects Med. 29.

Chen, S.-F., Wang, F.-M., Li, Z.-Y., Yu, F., Zhao, M.-H., Chen, M., 2015. Plasma complement factor H is associated with disease activity of patients with ANCA-associated vasculitis. Arthritis Res. Ther. 17 (1), 129.

Chen, Q., Wiesener, M., Eberhardt, H.U., Hartmann, A., Uzonyi, B., Kirschfink, M., et al., 2014. Complement factor H-related hybrid protein deregulates complement in dense deposit disease. J. Clin. Invest. 124 (1), 145–155.

Clark, S.J., Bishop, P.N., Day, A.J., 2010. Complement factor H and age-related macular degeneration: the role of glycosaminoglycan recognition in disease pathology. Biochem. Soc. Trans. 38 (5), 1342–1348.

Colman, R.W., Schmaier, A.H., 1997. Contact system: a vascular biology modulator with anticoagulant, profibrinolytic, antiadhesive, and proinflammatory attributes. Blood 90 (10), 3819–3843.

Conway, E.M., 2015. Reincarnation of ancient links between coagulation and complement. J. Thromb. Haemost. 13 (Suppl 1), S121–S132.

Conway, E.M., 2018. Complement-coagulation connections. J. Thromb. Haemost. 29 (3), 243–251.

Crawley, J.T.B., Chion, C.K.N.K., Lane, D.A., 2007. The central role of thrombin in hemostasis. J. Thromb. Haemost. 5.

Danielsson, A., Bjork, I., 1983. Properties of antithrombin-thrombin complex formed in the presence and in the absence of heparin. Biochem. J. 213, 345–353.

David, Gordon, R.M.K., Blackmore, Timothy K., Kwong, Jeffrey, Lublin, Douglas M., 1995. Identification of complement regulatory domains in human factor H. J. Immunol. 155, 348–356.

Davie, E.W., Kazuo Fujikawa, W.K., 1991. The coagulation cascade: initiation, maintenance, and regulation. Biochemistry 30 (43), 10363–10370.

Davis 3rd, A.E., Harrison, R.A., Lachmann, P.J., 1984. Physiologic inactivation of fluid phase C3b: isolation and structural analysis of C3c, C3d, g (alpha 2D), and C3g. J. Immunol. 132 (4), 1960–1966.

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

de Paula, P.F., Barbosa, J.E., Junior, P.R., Ferriani, V.P., Latorre, M.R., Nudelman, V., et al., 2003. Ontogeny of complement regulatory proteins - concentrations of factor h, factor I, c4b-binding protein, properdin and vitronectin in healthy children of different ages and in adults. Scand. J. Immunol. 58 (5), 572–577.

DeHelian, D., Holt, T., Fritzinger, N., Koeppe, J.R., 2015. Investigating interactions between the lectin-like domain of thrombomodulin and complement component 3. Biophys. J. 108 (2), 513a–a514.

Delvaeye, M., Conway, E.M., 2009. Coagulation and innate immune responses: can we view them separately? Blood 114 (12), 2367–2374.

DeYoung, V., Singh, K., Kretz, C.A., 2022. Mechanisms of ADAMTS13 regulation. J. Thromb. Haemost. 20 (12), 2722–2732.

Doolittle, R.F., 2017. The conversion of fibrinogen to fibrin: A brief history of some key events. Matrix Biol. 60–61, 5–7.

Dopler, A., Guntau, L., Harder, M.J., Palmer, A., Hochsmann, B., Schrezenmeier, H., et al., 2019. Self versus nonself discrimination by the soluble complement regulators factor H and FHL-1. J Immunol. 202 (7), 2082–2094.

Dzik, S., 2019. Complement and coagulation: cross talk through time. Transfus Med. Rev. 33 (4), 199–206.

Engelmann, B., Massberg, S., 2013. Thrombosis as an intravascular effector of innate immunity. Nat. Rev. Immunol. 13 (1), 34–45.

Esmon, C.T., 1989. The roles of protein C and thrombomodulin in the regulation of blood coagulation. J. Biol. Chem. 264 (9), 4743–4746.

Esmon, C.T., 1995. Thrombomodulin as a model of molecular mechanisms that modulate protease specificity and function at the vessel surface. FASEB J. 9 (10), 946–955.

Esparza-Gordillo, J., Soria, J., Buil, A., Almasy, L., Blangero, J., Fontcuberta, J., et al., 2004. Genetic and environmental factors influencing the human factor H plasma levels. Immunogenetics. 56 (2), 77–82.

Esparza-Gordillo, J., Soria, J., Buil, A., Almasy, L., Blangero, J., Fontcuberta, J., et al., 2004. Genetic and environmental factors influencing the human factor H plasma levels. Immunogenetics. 56 (2), 77–82.

Feng, S., Liang, X., Cruz, M.A., Vu, H., Zhou, Z., Pemmaraju, N., et al., 2013. The interaction between factor H and Von Willebrand factor. PLoS One 8 (8), e73715.

Feng, S., Liang, X., Kroll, M.H., Chung, D.W., Afshar-Kharghan, V., 2015. von Willebrand factor is a cofactor in complement regulation. Blood 125 (6), 1034–1037.

Ferluga, J., Kishore, U., Sim, R.B., 2014. A potential anti-coagulant role of complement factor H. Mol. Immunol. 59 (2), 188–193.

Ferluga, J., Kouser, L., Murugaiah, V., Sim, R.B., Kishore, U., 2017. Potential influences of complement factor H in autoimmune inflammatory and thrombotic disorders. Mol. Immunol. 84, 84–106.

Ferreira, V.P., Herbert, A.P., Cortes, C., McKee, K.A., Blaum, B.S., Esswein, S.T., et al., 2009. The binding of factor H to a complex of physiological polyanions and C3b on cells is impaired in atypical hemolytic uremic syndrome. J. Immunol. 182 (11), 7009–7018.

Ferreira, V.P., Pangburn, M.K., Cortes, C., 2010. Complement control protein factor H: the good, the bad, and the inadequate. Mol. Immunol. 47 (13), 2187–2197.

Foley, J.H., 2016. Examining coagulation-complement crosstalk: complement activation and thrombosis. Thromb. Res. 141, S50–S54.

Foley, J.H., Conway, E.M., 2016. Cross talk pathways between coagulation and inflammation. Circ Res. 118 (9), 1392–1408.

Foley, J.H., Peterson, E.A., Lei, V., Wan, L.W., Krisinger, M.J., Conway, E.M., 2015. Interplay between fibrinolysis and complement: plasmin cleavage of iC3b modulates immune responses. J Thromb Haemost. 13 (4), 610–618.

Foley, J.H., Walton, B.L., Aleman, M.M., O'Byrne, A.M., Lei, V., Harrasser, M., et al., 2016. Complement activation in arterial and venous thrombosis is mediated by plasmin. EBioMedicine 5, 175–182.
Fuentes-Prior, P., Iwanaga, Y., Huber, R., Pagila, R., Rumennik, G., Seto, M., et al., 2000. Structural basis for the anticoagulant activity of the thrombin–thrombomodulin complex. Nature 404 (6777), 518–525.
Furie, B., Furie, B.C., 2008. Mechanisms of thrombus formation. N. Engl. J. Med. 359 (9), 938–949.
Gallwitz, M., Enoksson, M., Thorpe, M., Hellman, L., 2012. The extended cleavage specificity of human thrombin. PLoS One 7 (2), e31756.
George, J.N., Nester, C.M., 2014. Syndromes of thrombotic microangiopathy. N. Engl. J. Med. 371 (7), 654–666.
Göbel, K., Eichler, S., Wiendl, H., Chavakis, T., Kleinschnitz, C., Meuth, S.G., 2018. The coagulation factors fibrinogen, thrombin, and factor XII in inflammatory disorders—a systematic review. Front. Immunol. 9.
Goicoechea de Jorge, E., Tortajada, A., Garcia, S.P., Gastoldi, S., Merinero, H.M., Garcia-Fernandez, J., et al., 2018. Factor H Competitor generated by gene conversion events associates with atypical hemolytic uremic syndrome. J Am Soc Nephrol. 29 (1), 240–249.
Goodship, T.H., 2006. Factor H genotype-phenotype correlations: lessons from aHUS, MPGN II, and AMD. Kidney Int. 70 (1), 12–13.
Goodship, T.H., Cook, H.T., Fakhouri, F., Fervenza, F.C., Frémeaux-Bacchi, V., Kavanagh, D., et al., 2017. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int. 91 (3), 539–551.
Gorsuch, W.B., Chrysanthou, E., Schwaeble, W.J., Stahl, G.L., 2012. The complement system in ischemia-reperfusion injuries. Immunobiology 217 (11), 1026–1033.
Grover, S.P., Mackman, N., 2019. Intrinsic pathway of coagulation and thrombosis. Arterioscler. Thromb. Vasc. Biol. 39 (3), 331–338.
Gushiken, F.C., Han, H., Li, J., Rumbaut, R.E., Afshar-Kharghan, V., 2009. Abnormal platelet function in C3-deficient mice. J. Thromb. Haemost. 7 (5), 865–870.
Hadders, M.A., Bubeck, D., Roversi, P., Hakobyan, S., Forneris, F., Morgan, B.P., et al., 2012. Assembly and regulation of the membrane attack complex based on structures of C5b6 and sC5b9. Cell Rep. 1 (3), 200–207.
Hakobyan, S., Tortajada, A., Harris, C.L., de Córdoba, S.R., Morgan, B.P., 2010. Variant-specific quantification of factor H in plasma identifies null alleles associated with atypical hemolytic uremic syndrome. Kidney Int. 78 (8), 782–788.
Haque, A., Cortes, C., Alam, M.N., Sreedhar, M., Ferreira, V.P., Pangburn, M.K., 2020. Characterization of binding properties of individual functional sites of human complement factor H. Front, Immunol. 11, 1728.
Hattori, R., Hamilton, K.K., McEver, R.P., Sims, P.J., 1989. Complement proteins C5b–9 induce secretion of high molecular weight multimers of endothelial von Willebrand factor and translocation of granule membrane protein GMP-140 to the cell surface. J. Biol. Chem. 264 (15), 9053–9060.
Herbert, A.P., Deakin, J.A., Schmidt, C.Q., Blaum, B.S., Egan, C., Ferreira, V.P., et al., 2007. Structure shows that a glycosaminoglycan and protein recognition site in factor H is perturbed by age-related macular degeneration-linked single nucleotide polymorphism. J. Biol. Chem. 282 (26), 18960–18968.
Heurich, M., Preston, R.J., O'Donnell, V.B., Morgan, B.P., Collins, P.W., 2016. Thrombomodulin enhances complement regulation through strong affinity interactions with factor H and C3b-Factor H complex. Thromb. Res. 145, 84–92.
Hill, A., Kelly, R.J., Hillmen, P. Thrombosis in paroxysmal nocturnal hemoglobinuria. Blood. 2013;121(25):4985-96; quiz 5105.
Honda, K.I., Asada, R., Kageyama, K., Fukuda, T., Terada, H., Yasui, T., et al., 2017. Protein complex of fibrinogen gamma chain and complement factor H in ovarian cancer patient plasma. Anticancer Res. 37 (6), 2861–2866.
Horstmann, R.D., Sievertsen, H.J., Leippe, M., Fischetti, V.A., 1992. Role of fibrinogen in complement inhibition by streptococcal M protein. Infect. Immun. 60 (12), 5036–5041.
Howes, J.M., Richardson, V.R., Smith, K.A., Schroeder, V., Somani, R., Shore, A., et al., 2012. Complement C3 is a novel plasma clot component with anti-fibrinolytic properties. Diab. Vasc. Dis. Res. 9 (3), 216–225.
Huber-Lang, M., Sarma, J.V., Zetoune, F.S., Rittirsch, D., Neff, T.A., McGuire, S.R., et al., 2006. Generation of C5a in the absence of C3: a new complement activation pathway. Nat. Med. 12 (6), 682–687.
Ignjatovic, V., Greenway, A., Summerhayes, R., Monagle, P., 2007. Thrombin generation: the functional role of alpha-2-macroglobulin and influence of developmental haemostasis. Br. J. Haematol. 138 (3), 366–368.
Irmscher, S., Doring, N., Halder, L.D., Jo, E.A.H., Kopka, I., Dunker, C., et al., 2018. Kallikrein cleaves C3 and activates complement. J. Innate Immun. 10 (2), 94–105.
Ismail, A.A., Shaker, B.T., Bajou, K., 2021. The plasminogen-activator plasmin system in physiological and pathophysiological angiogenesis. Int. J. Mol. Sci. 23 (1).
Jokiranta, T.S., 2017. HUS and atypical HUS. Blood. 129 (21), 2847–2856.
Jokiranta, T.S., Hellwage, J., Koistinen, V., Zipfel, P.F., Meri, S., 2000. Each of the three binding sites on complement factor H interacts with a distinct site on C3b. J. Biol. Chem. 275 (36), 27657–27662.
Jokiranta, T.S., Cheng, Z.Z., Seeberger, H., Jòzsi, M., Heinen, S., Noris, M., et al., 2005. Binding of complement factor H to endothelial cells is mediated by the carboxy-terminal glycosaminoglycan binding site. Am. J. Pathol. 167 (4), 1173–1181.
Jokiranta, T.S., Jaakola, V.P., Lehtinen, M.J., Parepalo, M., Meri, S., Goldman, A., 2006. Structure of complement factor H carboxyl-terminus reveals molecular basis of atypical haemolytic uremic syndrome. EMBO J. 25 (8), 1784–1794.
Jozsi, M., Schneider, A.E., Karpati, E., Sandor, N., 2019. Complement factor H family proteins in their non-canonical role as modulators of cellular functions. Semin. Cell Dev. Biol. 85, 122–131.
Jozsi, M., Zipfel, P.F., 2008. Factor H family proteins and human diseases. Trends Immunol. 29 (8), 380–387.
Kahr, W.H.A., Licht, Christoph, 2008. Complement factor H in human platelets: implications for atypical HUS. Blood 112 (11).
Katona, É., Pénzes, K., Csapó, A., Fazakas, F., Udvardy, M.L., Bagoly, Z., et al., 2014. Interaction of factor XIII subunits. Blood 123 (11), 1757–1763.
Kavanagh, D., Goodship, T.H., Richards, A., 2013. Atypical hemolytic uremic syndrome. Semin. Nephrol. 33 (6), 508–530.
Kerr, H., Richards, A., 2012. Complement-mediated injury and protection of endothelium: lessons from atypical haemolytic uraemic syndrome. Immunobiology 217 (2), 195–203.
Keshari, R.S., Silasi, R., Lupu, C., Taylor Jr., F.B., Lupu, F., 2017. In vivo-generated thrombin and plasmin do not activate the complement system in baboons. Blood 130 (24), 2678–2681.
Kim, Y.U., Carroll, M., Isenman, D., Nonaka, M., Pramoonjago, P., Takeda, J., et al., 1992. Covalent binding of C3b to C4b within the classical complement pathway C5 convertase. determination of amino acid residues involved in ester linkage formation. J. Biol. Chem. 267 (6), 4171–4176.
King, R.J., Schuett, K., Tiede, C., Jankowski, V., John, V., Trehan, A., et al., 2021. Fibrinogen interaction with complement C3: a potential therapeutic target to reduce thrombosis risk. Haematologica.
Klickstein, L.B., Bartow, T.J., Miletic, V., Rabson, L.D., Smith, J.A., Fearon, D.T., 1988. Identification of distinct C3b and C4b recognition sites in the human C3b/C4b receptor (CR1, CD35) by deletion mutagenesis. J. Exp. Med. 168 (5), 1699–1717.
Klos, A., Tenner, A.J., Johswich, K.O., Ager, R.R., Reis, E.S., Kohl, J., 2009. The role of the anaphylatoxins in health and disease. Mol Immunol. 46 (14), 2753–2766.
Koeppe, J.R., Ellis, G., Joannides, N., Wiltsie, V., 2018. Investigating the role of thrombomodulin in the activation of complement. Biophys. J. 114 (3).
Kopp, A., Hebecker, M., Svobodová, E., Józsi, M., 2012. Factor h: a complement regulator in health and disease, and a mediator of cellular interactions. Biomolecules 2 (1), 46–75.
Kozarcanin, H., Lood, C., Munthe-Fog, L., Sandholm, K., Hamad, O.A., Bengtsson, A.A., et al., 2016. The lectin complement pathway serine proteases (MASPs) represent a possible crossroad between the coagulation and complement systems in thromboinflammation. J. Thromb. Haemost. 14 (3), 531–545.
Krishnaswamy, S., 2013. The transition of prothrombin to thrombin. J. Thromb. Haemost. 11 (Suppl 1), 265–276.
Krisinger, M.J., Goebeler, V., Lu, Z., Meixner, S.C., Myles, T., Pryzdial, E.L., et al., 2012. Thrombin generates previously unidentified C5 products that support the terminal complement activation pathway. Blood 120 (8), 1717–1725.
Krych-Goldberg, M., Hauhart, R.E., Subramanian, V.B., Yurcisin 2nd, B.M., Crimmins, D. L., Hourcade, D.E., et al., 1999. Decay accelerating activity of complement receptor type 1 (CD35). Two active sites are required for dissociating C5 convertases. J. Biol. Chem. 274 (44), 31160–31168.
Kurosawa, S., Stearns-Kurosawa, D.J., 2014. Complement, thrombotic microangiopathy and disseminated intravascular coagulation. J. Intensive Care. 2 (1), 65.
Lachmann, P.J. Chapter 4 - The Amplification Loop of the Complement Pathways. In: Alt FW, editor. Advances in Immunology. 104: Academic Press; 2009. p. 115-49.
Lamers, C., Plüss, C.J., Ricklin, D., 2021. The promiscuous profile of complement receptor 3 in ligand binding, immune modulation, and pathophysiology. Front. Immunol. 12, 662164.
Lasne, D., Jude, B., Susen, S., 2006. From normal to pathological hemostasis. Canad. J. Anaesthesia = J. Canadien D'anesthesie 53 (6 Suppl), S2–S.
Laszlo Bajzar, J.M., Nesheim, M., 1996. TAFI, or plasma procarboxypeptidase B, couples the coagulation and fibrinolytic cascades through the thrombin-thrombomodulin complex. J. Biol. Chem. 271 (28), 16603–16608.
Le Quintrec, M., Roumenina, L., Noris, M., Frémeaux-Bacchi, V., 2010. Atypical hemolytic uremic syndrome associated with mutations in complement regulator genes. Semin. Thromb. Hemost. 36 (6), 641–652.
Lenting, P.J., Christophe, O.D., Denis, C.V., 2015. von Willebrand factor biosynthesis, secretion, and clearance: connecting the far ends. Blood 125 (13), 2019–2028.
Leung, L.L., Myles, T., Nishimura, T., Song, J.J., Robinson, W.H., 2008. Regulation of tissue inflammation by thrombin-activatable carboxypeptidase B (or TAFI). Mol. Immunol. 45 (16), 4080–4083.
Li, B., Bechtler, C., Jenny, L., Ricklin, D., Schroeder, V. Exploring the function of factor XIII free B subunit: Interactions with complement factors and a novel approach to identify potential binding partners. 2022;6(5):e12766.
Licari, L.G., Kovacic, J.P., 2009. Thrombin physiology and pathophysiology. J. Vet. Emerg. Crit. Care (San Antonio). 19 (1), 11–22.
Loghmani, H., Conway, E., 2018. Exploring traditional and nontraditional roles for thrombomodulin. Blood 132 (2), 148–158.
Longstaff, C., 2018. Measuring fibrinolysis: from research to routine diagnostic assays. J. Thromb. Haemost. 16 (4), 652–662.
Lubbers R, van Essen MF, van Kooten C, Trouw LA. Production of complement components by cells of the immune system. 2017;188(2):183–94.
Luo, S., Hu, D., Wang, M., Zipfel, P.F., Hu, Y., 2020. Complement in hemolysis- and thrombosis- related diseases. Front. Immunol. 11.
Lupu, F., Keshari, R.S., Lambris, J.D., Coggeshall, K.M., 2014. Crosstalk between the coagulation and complement systems in sepsis. Thromb. Res. 133 (Suppl 1), S28–S31.
Mackman, N., Tilley, R.E., Key, N.S., 2007. Role of the extrinsic pathway of blood coagulation in hemostasis and thrombosis. Arterioscler Thromb. Vasc. Biol. 27 (8), 1687–1693.
Maga, T.K., Nishimura, C.J., Weaver, A.E., Frees, K.L., Smith, R.J., 2010. Mutations in alternative pathway complement proteins in American patients with atypical hemolytic uremic syndrome. Hum. Mutat. 31 (6), E1445–E1460.

Mann, K.G., 2003. What is all that thrombin for? J. Thromb. Haemost. 1, 1504–1514.
Martín Merinero, H., Zhang, Y., Arjona, E., del Angel, G., Goodfellow, R., Gomez-Rubio, E., et al., 2021. Functional characterization of 105 factor H variants associated with aHUS: lessons for variant classification. Blood. 138 (22), 2185–2201.
Martin, F.A., Murphy, R.P., Cummins, P.M., 2013. Thrombomodulin and the vascular endothelium: insights into functional, regulatory, and therapeutic aspects. Am. J. Phys. Heart Circ. Phys. 304 (12), H1585–H1597.
Mast, A.E., 2016. Tissue Factor Pathway Inhibitor. Arterioscler. Thromb. Vasc. Biol. 36 (1), 9–14.
Master Sankar Raj, V., Gordillo, R., Chand, D.H., 2016. Overview of C3 Glomerulopathy. Front. Pediatr. 4, 45.
McCarty, O.J.T., Thangaraj, S.S., Christiansen, S.H., Graversen, J.H., Sidelmann, J.J., Hansen, S.W.K., et al., 2020. Contact activation-induced complex formation between complement factor H and coagulation factor XIIa. J. Immunol. 18 (4), 876–884.
McCluskey, G., Davies, G.E., Velounias, R.L., Hughes, T.R., Morgan, B.P., Preston, R.J.S., Collins, P.W., Jenkines, P.V, Heurich, M., 2021. Complement Regulator Factor H is a Cofactor for Thrombin in both Pro- and Anticoagulant Roles. bioRxiv 2021, https://doi.org/10.1101/2021.07.22.452893.
Medjeral-Thomas, N., Pickering, M.C., 2016. The complement factor H-related proteins. Immunol. Rev. 274 (1), 191–201.
Meeks, S.L., Abshire, T.C., 2008. Abnormalities of prothrombin: a review of the pathophysiology, diagnosis, and treatment. Haemophilia 14 (6), 1159–1163.
Meri, S., 2013. Complement activation in diseases presenting with thrombotic microangiopathy. Eur. J. Intern. Med. 24 (6), 496–502.
Merle, N.S., Church, S.E., Fremeaux-Bacchi, V., Roumenina, L.T., 2015a. Complement system part I - molecular mechanisms of activation and regulation. Front. Immunol. 6, 262.
Merle, N.S., Noe, R., Halbwachs-Mecarelli, L., Fremeaux-Bacchi, V., Roumenina, L.T. 2015b. Complement system part II: role in immunity. Front. Immunol. 6. https://doi.org/10.3389/fimmu.2015.00257.
Mieke Delvaeye PD, Marina Noris, Ph.D., Astrid De Vriese, M.Sc., Charles T. Esmon, Ph. D., Naomi L. Esmon, Ph.D., Gary Ferrell, M.Sc., Jurgen Del-Favero, Ph.D., Stephane Plaisance, Ph.D., Bart Claes, M.Sc., Diether Lambrechts, Ph.D., Carla Zoja, Ph.D., Giuseppe Remuzzi, M.D., and Edward M. Conway, M.D., Ph.D. 2009. Thrombomodulin mutations in atypical hemolytic–uremic syndrome. New England J. Med. 361, 345–357. https://doi.org/10.1056/NEJMoa0810739.
Mizuno, T., Yoshioka, K., Mizuno, M., Shimizu, M., Nagano, F., Okuda, T., et al., 2017. Complement component 5 promotes lethal thrombosis. Sci. Rep. 7, 42714.
Morgan, B.P., 2016. The membrane attack complex as an inflammatory trigger. Immunobiology. 221 (6), 747–751.
Morgan, H.P., Schmidt, C.Q., Guariento, M., Blaum, B.S., Gillespie, D., Herbert, A.P., et al., 2011. Structural basis for engagement by complement factor H of C3b on a self surface. Nat. Struct. Mol. Biol. 18 (4), 463–470.
Muller-Calleja, N., Ritter, S., Hollerbach, A., Falter, T., Lackner, K.J., Ruf, W., 2018. Complement C5 but not C3 is expendable for tissue factor activation by cofactor-independent antiphospholipid antibodies. Blood Adv. 2 (9), 979–986.
Nikolajsen, C.L., Dyrlund, T.F., Poulsen, E.T., Enghild, J.J., Scavenius, C., 2014. Coagulation factor XIIIa substrates in human plasma: identification and incorporation into the clot. J. Biol. Chem. 289 (10), 6526–6534.
Nilsson, B., Nilsson, E.K., 2012. The tick-over theory revisited: is C3 a contact-activated protein? Immunobiology 217 (11), 1106–1110.
Noone, D.G., Riedl, M., Pluthero, F.G., Bowman, M.L., Liszewski, M.K., Lu, L., et al., 2016. Von Willebrand factor regulates complement on endothelial cells. Kidney Int. 90 (1), 123–134.
Noris, M., Remuzzi, G., 2013. Overview of complement activation and regulation. Semin Nephrol. 33 (6), 479–492.
Ohlin, A.K., Larsson, K., Hansson, M., 2005. Soluble thrombomodulin activity and soluble thrombomodulin antigen in plasma. J. Thromb. Haemost. 3 (5), 976–982.
Oncul, S., Afshar-Kharghan, V., 2020. The interaction between the complement system and hemostatic factors. Curr. Opin. Hematol. 27 (5), 341–352.
Palma, L.M.P., Sridharan, M., Sethi, S., 2021. Complement in secondary thrombotic microangiopathy. Kidney Int. Rep. 6 (1), 11–23.
Palowitch, G., Gambone, C., Koeppe, J.R., 2015. Interactions between thrombomodulin and complement component C3 studied by fluorescence resonance energy transfer. Biophys. J. 108 (2).
Pangburn, M.K., 2002. Cutting edge: localization of the host recognition functions of complement factor H at the carboxyl-terminal: implications for hemolytic uremic syndrome. J Immunol. 169 (9), 4702–4706.
Parente, R., Clark, S.J., Inforzato, A., Day, A.J., 2017. Complement factor H in host defense and immune evasion. Cell Mol. Life Sci. 74 (9), 1605–1624.
Perkins, S.J., Nan, R., Li, K., Khan, S., Miller, A., 2012. Complement factor H-ligand interactions: self-association, multivalency and dissociation constants. Immunobiology 217 (2), 281–297.
Peyvandi, F., Garagiola, I., Baronciani, L., 2011. Role of von Willebrand factor in the haemostasis. Blood Transfus. 9 (Suppl 2), s3–s8.
Pickering, M.C., Cook, H.T., 2008. Translational mini-review series on complement factor H: renal diseases associated with complement factor H: novel insights from humans and animals. Clin. Exp. Immunol. 151 (2), 210–230.
Pilli, V.S., 2018. Understanding the Clotting cascade, regulators, and clinical modulators of coagulation. Hematol. - Latest Res. Clin. Adv.
Popescu, N.I., Lupu, C. Disseminated intravascular coagulation and its immune mechanisms. 2022;139(13):1973–86.
Pouw, R.B., Vredevoogd, D.W., Kuijpers, T.W., Wouters, D., 2015. Of mice and men: The factor H protein family and complement regulation. Mol. Immunol. 67 (1), 12–20.
Pouw, R.B., Brouwer, M.C., de Gast, M., van Beek, A.E., van den Heuvel, L.P., Schmidt, C. Q., et al., 2019. Potentiation of complement regulator factor H protects human endothelial cells from complement attack in aHUS sera. Blood Adv. 3 (4), 621–632.
Pryzdial, E.L.G., Leatherdale, A., Conway, E.M., 2022. Coagulation and complement: Key innate defense participants in a seamless web. Front. Immunol. 13, 918775.
Puy, C., Pang, J. Cross-talk between the complement pathway and the contact activation system of coagulation: activated factor XI neutralizes complement Factor H. 2021; 206(8):1784-1792.
Ramadass, M., Ghebrehiwet, B., Smith, R.J., Kew, R.R., 2014. Generation of multiple fluid-phase C3b:plasma protein complexes during complement activation: possible implications in C3 glomerulopathies. J. Immunol. 192 (3), 1220–1230.
Rawish, E., Sauter, M., Sauter, R., Nording, H., Langer, H.F., 2021. Complement, inflammation and thrombosis. Br. J. Pharmacol. 178 (14), 2892–2904.
Rayes, J., Roumenina, L.T., Dimitrov, J.D., Repessé, Y., Ing, M., Christophe, O., et al., 2014. The interaction between factor H and VWF increases factor H cofactor activity and regulates VWF prothrombotic status. Blood 123 (1), 121–125.
Rezaie, A.R., Giri, H., 2020. Anticoagulant and signaling functions of antithrombin. J. Thromb. Haemost. 18 (12), 3142–3153.
Ritis, K., Doumas, M., Mastellos, D., Micheli, A., Giaglis, S., Magotti, P., et al., 2006. A novel C5a receptor-tissue factor cross-talk in neutrophils links innate immunity to coagulation pathways. J. Immunol. 177 (7), 4794–4802.
Saggu, G., Cortes, C., Emch, H.N., Ramirez, G., Worth, R.G., Ferreira, V.P., 2013. Identification of a novel mode of complement activation on stimulated platelets mediated by properdin and C3(H2O). J. Immunol. 190 (12), 6457–6467.
Sakurai, S., Kato, H., Yoshida, Y., Sugawara, Y., Fujisawa, M., Yasumoto, A., et al., 2020. Profiles of coagulation and fibrinolysis activation-associated molecular markers of atypical hemolytic uremic syndrome in the acute phase. J. Atheroscler. Thromb. 27 (4), 353–362.
Sanchez-Corral, P., Perez-Caballero, D., Huarte, O., Simckes, A.M., Goicoechea, E., Lopez-Trascasa, M., et al., 2002. Structural and functional characterization of factor H mutations associated with atypical hemolytic uremic syndrome. Am. J. Hum. Genet. 71 (6), 1285–1295.
Sanchez-Corral, P., Pouw, R.B., Lopez-Trascasa, M., Jozsi, M., 2018. Self-damage caused by dysregulation of the complement alternative pathway: relevance of the factor H protein family. Front. Immunol. 9, 1607.
Sarma, J.V., Ward, P.A., 2011. The complement system. Cell Tissue Res. 343 (1), 227–235.
Sauter, R.J., Sauter, M., Reis, E.S., Emschermann, F.N., Nording, H., Ebenhöch, S., et al., 2018. Functional relevance of the anaphylatoxin receptor C3aR for platelet function and arterial thrombus formation marks an intersection point between innate immunity and thrombosis. Circulation 138 (16), 1720–1735.
Schmidt, C.Q., Herbert, A.P., Kavanagh, D., Gandy, C., Fenton, C.J., Blaum, B.S., et al., 2008. A new map of glycosaminoglycan and C3b binding sites on factor H. J. Immunol. 181 (4), 2610–2619.
Schoenmakers, S.H.H.F., Reitsma, P.H., Spek, C.A., 2005. Blood coagulation factors as inflammatory mediators. Blood Cell Mol. Dis. 34 (1), 30–37.
Scully, M., Cataland, S., Coppo, P., de la Rubia, J., Friedman, K.D., Kremer Hovinga, J., et al., 2017. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. J. Thromb. Haemost. 15 (2), 312–322.
Serna, M., Giles, J.L., Morgan, B.P., Bubeck, D., 2016. Structural basis of complement membrane attack complex formation. Nat. Commun. 7, 10587.
Sethi, S., Fervenza, F.C., 2014. Pathology of renal diseases associated with dysfunction of the alternative pathway of complement: C3 glomerulopathy and atypical hemolytic uremic syndrome (aHUS). Semin. Thromb. Hemost. 40 (4), 416–421.
Sharma, A.K., Pangburn, M.K. Identification of three physically and functionally distinct binding sites for C3b in human complement factor H by deletion mutagenesis. Proc. Natl. Acad. Sci. U.S.A. 1996;93(20):10996.
Shimizu, J., Fujino, K., Sawai, T., Tsujita, Y., Tabata, T., Eguchi, Y., 2021. Association between plasma complement factor H concentration and clinical outcomes in patients with sepsis. Acute Med. Surgery 8 (1), e625.
Singh, S., Akhter, M.S., Dodt, J., Volkers, P., Reuter, A., Reinhart, C., et al., 2019. Identification of potential novel interacting partners for coagulation factor XIII B (FXIII-B) subunit, a protein associated with a rare bleeding disorder. Int. J. Mol. Sci. 20 (11).
Smith, R.J.H., Appel, G.B., Blom, A.M., Cook, H.T., D'Agati, V.D., Fakhouri, F., et al., 2019. C3 glomerulopathy - understanding a rare complement-driven renal disease. Nat. Rev. Nephrol. 15 (3), 129–143.
Smith, R.J., Harris, C.L., Pickering, M.C., 2011. Dense deposit disease. Mol. Immunol. 48 (14), 1604–1610.
Smith, S.A., Travers, R.J., Morrissey, J.H., 2015. How it all starts: initiation of the clotting cascade. Crit. Rev. Biochem. Mol. Biol. 50 (4), 326–336.
Stachowicz, A., Zabczyk, M., Natorska, J., Suski, M., Olszanecki, R., Korbut, R., et al., 2018. Differences in plasma fibrin clot composition in patients with thrombotic antiphospholipid syndrome compared with venous thromboembolism. Sci. Rep. 8 (1), 17301.
Ståhl, A.L., Vaziri-Sani, F., Heinen, S., Kristoffersson, A.C., Gydell, K.H., Raafat, R., et al., 2008. Factor H dysfunction in patients with atypical hemolytic uremic syndrome contributes to complement deposition on platelets and their activation. Blood 111 (11), 5307–5315.
Stockschlaeder, M., Schneppenheim, R., Budde, U., 2014. Update on von Willebrand factor multimers: focus on high-molecular-weight multimers and their role in hemostasis. Blood Coagulat. Fibrinolysis 25 (3), 206–216.
Subramaniam, S., Jurk, K., Hobohm, L., Jackel, S., Saffarzadeh, M., Schwierczek, K., et al., 2017. Distinct contributions of complement factors to platelet activation and fibrin formation in venous thrombus development. Blood 129 (16), 2291–2302.

Swystun, L.L., Liaw, P.C., 2016. The role of leukocytes in thrombosis. Blood 128 (6), 753–762.
Tan, L.A., Yu, B., Sim, F.C.J., Kishore, U., Sim, R.B., 2010. Complement activation by phospholipids: the interplay of factor H and C1q. Protein Cell 1 (11), 1033–1049.
Thangaraj, S.S., Christiansen, S.H., Graversen, J.H., Sidelmann, J.J., Hansen, S.W.K., Bygum, A., et al., 2020. Contact activation-induced complex formation between complement factor H and coagulation factor XIIa. J. Thromb. Haemost. 18 (4), 876–884.
Thompson, G.L., Kavanagh, D., 2022. Diagnosis and treatment of thrombotic microangiopathy. Int. J. Lab. Hematol. 44 (S1), 101–113.
Thurman, J.M., 2020. Complement and the kidney: an overview. Adv. Chronic Kidney Dis. 27 (2), 86–94.
Tomaiuolo, M., Brass, L.F., Stalker, T.J., 2017. Regulation of Platelet activation and coagulation and its role in vascular injury and arterial thrombosis. Interv. Cardiol Clin. 6 (1), 1–12.
Ueda, Y., Mohammed, I., Song, D., Gullipalli, D., Zhou, L., Sato, S., et al., 2017. Murine systemic thrombophilia and hemolytic uremic syndrome from a factor H point mutation. Blood 129 (9), 1184–1196. https://doi.org/10.1182/blood-2016-07-728253.
Vaziri-Sani, F., Hellwage, J., Zipfel, P.F., Sjöholm, A.G., Iancu, R., Karpman, D., 2005. Factor H binds to washed human platelets. J. Thromb. Haemostasis. 3.
Vaziri-Sani, F., Hellwage, J., Zipfel, P.F., Sjöholm, A.G., Iancu, R., Karpman, D., 2005. Factor H binds to washed human platelets. J. Thromb. Haemost. 3 (1), 154–162.
Vernon, K.A., Ruseva, M.M., Cook, H.T., Botto, M., Malik, T.H., Pickering, M.C., 2016. Partial Complement Factor H Deficiency Associates with C3 Glomerulopathy and Thrombotic Microangiopathy. J. Am. Soc. Nephrol. 27 (5), 1334–1342.
Verschoor, A., Langer, H.F., 2013. Crosstalk between platelets and the complement system in immune protection and disease. Thromb. Haemost. 110 (5), 910–919.
Walker, C.P., Royston, D., 2002. Thrombin generation and its inhibition: a review of the scientific basis and mechanism of action of anticoagulant therapies. Br. J. Anaesth. 88 (6), 848–863.
Walport, M.J., 2001. Complement First of Two Parts. New England Journal of Medicine 344 (14), 1058–1066.
Walton, B.L., Byrnes, J.R., Wolberg, A.S., 2015. Fibrinogen, red blood cells, and factor XIII in venous thrombosis. J. Thromb. Haemost. 13 (Suppl 1), S208–S215.
Weisel, J.W., Litvinov, R.I., 2013. Mechanisms of fibrin polymerization and clinical implications. Blood 121 (10), 1712–1719.
Weisel, J.W., Litvinov, R.I., 2017. Fibrin formation, structure and properties. Subcell Biochem. 82, 405–456.
Wiedmer, T., Esmon, C.T., Sims, P.J., 1986. On the mechanism by which complement proteins C5b–9 increase platelet prothrombinase activity. J. Biol. Chem. 261 (31), 14587–14592.
Wiegner, R., Chakraborty, S., Huber-Lang, M., 2016. Complement-coagulation crosstalk on cellular and artificial surfaces. Immunobiology 221 (10), 1073–1079.
Wolberg, A.S., Campbell, R.A., 2008. Thrombin generation, fibrin clot formation and hemostasis. Transfus Apher Sci. 38 (1), 15–23.
Wong, E.K.S., Kavanagh, D., 2018. Diseases of complement dysregulation—an overview. Semin. Immunopathol. 40 (1), 49–64.
Wu, J., Wu, Y.Q., Ricklin, D., Janssen, B.J., Lambris, J.D., Gros, P., 2009. Structure of complement fragment C3b-factor H and implications for host protection by complement regulators. Nat. Immunol. 10 (7), 728–733.
Xiao, J., Melvin, R.L., Salsbury, F.R., 2017. Mechanistic insights into thrombin's switch between "slow" and "fast" forms. Phys. Chem. Chem. Phys. 19 (36), 24522–24533.
Xue, X., Wu, J., Ricklin, D., Forneris, F., Di Crescenzio, P., Schmidt, C.Q., et al., 2017. Regulator-dependent mechanisms of C3b processing by factor I allow differentiation of immune responses. Nat. Struct. Mol. Biol. 24 (8), 643–651.
Xue, X., Wu, J., Ricklin, D., Forneris, F., Di Crescenzio, P., Schmidt, C.Q., et al., 2017. Regulator-dependent mechanisms of C3b processing by factor I allow differentiation of immune responses. Nat. Struct. Mol. Biol. 24 (8), 643–651.
Ząbczyk, M., Stachowicz, A., Natorska, J., Olszanecki, R., Wiśniewski, J.R., Undas, A., 2019. Plasma fibrin clot proteomics in healthy subjects: Relation to clot permeability and lysis time. J. Proteomics 208, 103487.
Zhang, K., Lu, Y., Harley, K.T., Tran, M.H., 2017. Atypical hemolytic uremic syndrome: a brief review. Hematol. Rep. 9 (2), 7053.