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Examining coagulation-complement crosstalk: complement activation and thrombosis

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ABSTRACT

The coagulation and complement systems are ancestrally related enzymatic cascades of the blood. Although their primary purposes have diverged over the past few hundred million years, they remain inextricably connected. Both complement and coagulation systems limit infection by pathogens through innate immune mechanisms. Recently, it has been shown that hyperactive complement (in particular, elevated C5a/C5b-9) is involved in the pathogenesis (including thrombosis) of diseases such as paroxysmal nocturnal hemoglobinuria, atypical haemolytic uremic syndrome, antiphospholipid syndrome and bacteremia. Although these diseases together account for many thrombosis cases, there are many more where complement activation is not considered a causative factor leading to thrombosis. To better understand what role complement may play in the pathogenesis of thrombosis a better understanding of the mechanisms that cause over-active complement in thrombotic disease is required.

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Coagulation system activation and regulation

The coagulation system has evolved to limit blood loss at sites of vascular injury. The biological effects of the coagulation system are usually mediated directly by enzymes. For example, thrombin is the agonist that generates a fibrin clot and an agonist for cellular activation via protease activated receptors, or PARs.

Upon vascular injury, tissue factor (TF) is exposed to the blood. TF exposure initiates a series of cleavage events and positive feedback resulting in thrombin generation and fibrin formation (Figure 1A). The enzymes of the coagulation cascade are very efficient when associated with their physiological cofactors (Table 1), meaning that thrombin is generated very rapidly and in relatively large quantities at sites of injury. Consequently, potent inhibitors are required to ensure that excessive coagulation does not occur. The coagulation system is regulated by various classes of inhibitors including the tissue factor pathway inhibitor (TFPI) [1] and protein C, which regulate the initiation phase and propagation phases of thrombin generation, respectively. Additionally, serine protease inhibitors (SERPINs) rapidly and irreversibly inhibit the coagulation enzymes (reviewed in [2]) and in concert with TFPI and the protein C system, ultimately terminate the coagulant response.

Complement system activation and regulation

The complement system's primary role is to seek and destroy pathogens that gain access to the body via vascular injury sites or other routes. In contrast to the coagulation system, the central enzymes of complement (convertases) do not directly activate innate immune mechanisms. This fundamental difference between coagulation and complement can be rationalized by the relatively poor catalytic efficiency and instability of the convertases (Table 1). Instead, complement enzymes liberate "split products" such as C3a and C3b, iC3b and C3d(g), and C5a and C5b that perform the chief functions of complement. These split products are capable of activating a series of receptors (or activating the terminal pathway (TP) in the case of C5b) that collectively induce cellular activation, phagocytosis, chemotaxis, and inflammation via a series of receptors (reviewed in [3]).

The complement system is activated via the classical (CP), lectin (LP) and/or alternative pathways (AP) resulting in the formation of convertases that generate biologically active split products, C3a/C3b and C5a/C5b (Figure 1B). The AP also acts as a major positive feedback pathway generating up to 80% of complement split products C3a and C3b when the CP initiates complement activation [4]. Dissecting which pathway(s) drive complement activation is no small feat in human pathology since the AP is constitutively active, albeit at a very slow rate. In the early 1980s, Pangburn *et al.* demonstrated that C3 constantly and spontaneously "ticks-over" [5], that is, its thioester bond is spontaneously hydrolysed making it a cofactor ($C3(H_2O)$) for AP activity. In recent years, the tick-over mechanism has been challenged by reports that AP C3 activation does not simply "tick-over" but occurs as a result of C3 contact with lipids or biomaterial surfaces [6]. This proposed "contact"

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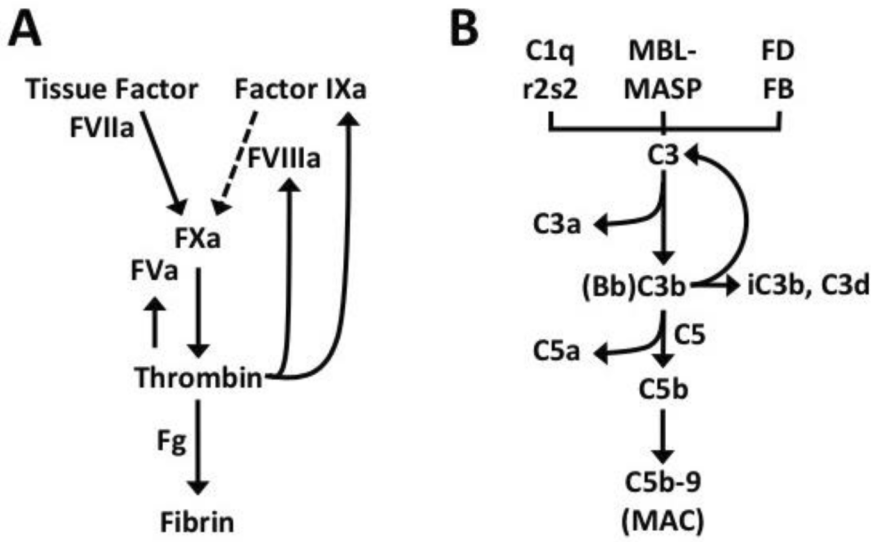

Figure 1. Schemes depicting the major events in the activation of coagulation (A) and complement (B). Key feedback steps are all represented.

mechanism is interesting to consider given that a similar mechanism drives coagulation factor XII activation, however, further studies are required before "tick-over" is displaced as the initiating mechanism of AP activation.

As complement activation is amplified, the substrate specificity of the convertases changes from C3 to C5 [7] resulting in release of the potent anaphylatoxin C5a and C5b, the initiator of the TP of complement. The TP culminates in the formation of the membrane attack complex (MAC or C5b-9), which disrupts the osmotic balance of cells causing cell lysis or cellular activation in the case of sub-lytic concentrations.

The initiation phase of CP- and LP-mediated complement activation is tightly regulated by SERPINs such as C1-inhibitor that rapidly and irreversibly inhibit the activity of C1r enzyme, C1s enzyme and MASPs (reviewed in [8]). This level of control ensures that complement activation is localized to sites of damage or pathogen invasion. Since the convertases are relatively inefficient enzymes (Table 1) potent irreversible inhibitors are not required to regulate their function. Instead, the convertases are regulated by a series of decay factors (including CD55 (decay-accelerating factor) and factor H) that cause dissociation of enzyme-cofactor complexes [8].

Complement C5 and Consequences of Complement-Coagulation Crosstalk

Cleavage of complement C5 liberates split products C5a and C5b (leading to MAC formation), which collectively activate platelets [9], induce tissue factor expression [10-14] and activate endothelial cells causing the secretion of von Willebrand factor [15] and exposure of prothrombinase assembly sites [16] and P-selectin [17]. This coupled with the clear association between complement dyregulation, C5 cleavage and thrombosis in diseases such as paroxysmal nocturnal hemoglobinuria (reviewed in [18]) and atypical haemolytic uremic syndrome make C5 an interesting, but unconventional procoagulant molecule. Clinical trials demonstrating that complement C5 inhibition prevents thrombosis in patients with PNH and aHUS [19-21] provides further support for the notion that C5 is critically important in the development of thrombosis in these patients. The link between C5 and coagulation/thrombosis is further supported by bacteremia and antiphophoslipid syndrome studies. When *Neisseria meningitidis* or *E. coli* are exposed to the blood, complement is potently activated and tissue factor expression is upregulated. Recent studies have shown that these events are linked. Inhibition of complement C3 with compstatin [13] or C5 with eculizumab [14] in combination with CD14 inhibitors reduces tissue factor expression, which would presumably decrease coagulation system activation in bacteremia and sepsis. Similarly, the antiphospholipid antibody β2GPI has been shown to potently activate complement and has been hypothesized to contribute to thrombosis in antiphospholipid syndrome (APS) through complement-mediated mechanisms. This hypothesis is supported by a study where $C3^{-/-}$ or $C5^{-/-}$ mice were injected with β2GPI but were protected against thrombosis compared to wild type mice demonstrating a clear role for both C3 and C5 in thrombosis in these animal studies. Further work is required before these findings in bacteremia and APS studies can be extrapolated into humans; however, the persistence and consistency of a link between C5 and thrombosis in various models suggests that C5 and/or C5a receptors may be a therapeutically targeted to limit thrombosis in diseases of hyper-active complement activation. These connections between complement and thrombosis are compelling, but a major question remains: Does complement activation cause or promote prevalent types of thrombosis? When an identifiable risk factor is present, the risk factor (e.g. factor V-Leiden, atherosclerosis, cancer, etc) and not complement is the most likely determinant of thrombosis. Therefore, in the absence of a defective complement regulatory protein or potent complement agonist, it is unlikely that complement system activation precipitates thrombosis. As a nascent thrombus is forming, however, complement will become activated and may play a critical role in thrombus propagation and subsequent complications such as post-thrombotic syndrome. The number of potential complement activators at sites of thrombosis is vast, with thrombin, plasmin, damaged endothelium, DNA and elastase among the leading candidates. Thrombin has garnered much attention recently as a complement activator since it reportedly cleaves C5, generating biologically active C5a independently of C5 convertases (i.e. in $C3^{-/-}$ mice) [22]. This report and others suggest that thrombin-mediated C5a generation is deleterious in models of acute lung injury [22] pulmonary contusion [23], treachea transplant [24], arthritis [25] and transfusion [26] and increases G-CSF-mediated hematopoietic stem/progenitor cell mobilization [27]. The claim that thrombin directly activates complement C5 in a physiologically meaningful way [22,28,29] has been questioned [30] since the kinetics of C5 cleavage by thrombin appear to be very poor [22,30-32] as compared to the efficiency of thrombin cleaving its coagulation-based

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