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Commentary

Plasmin as a complement C5 convertase

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Both the complement and coagulation/fibrinolytic systems are essential components of the host defense system that evolved early in the evolution of vertebrates (Krem and Di Cera, 2002). While the coagulation and fibrinolytic systems are necessary for maintenance of the integrity of the vasculature, these systems also respond to infections, and together with the complement system, play an important role in innate and adaptive immunity.

There are two pathways in mammals that initiate coagulation and three that initiate complement while fibrinolysis commences in response to the presence of a fibrin clot (Bajic et al., 2015; Smith et al., 2015). The intrinsic or contact pathway for initiation of coagulation and the alternative (properdin) and lectin pathways that initiate complement activation are activated by specific properties of some surfaces such as bacterial or yeast cell walls.

Cross talk between the various systems is apparent with several well-described interactions such as that between C4-binding protein (C4BP) that regulates complement by inhibiting the classical initiation pathway and protein S, the latter being a cofactor for activated protein C, a regulator of coagulation and inflammation. There are *in vitro* and *in vivo* data that suggest coagulation cascade enzymes such as thrombin could cleave C5, carrying out the same reactions as the C5 convertase (Huber-Lang et al., 2006). The cleavage products, however, did not directly generate C5a (Krisinger et al., 2012).

A new study (Foley et al., 2016) shows in a venous stasis model that C5a correlates strongly with clot weight implying that pathways initiated during clot formation lead to C5 cleavage. In contrast, there is a very weak correlation with thrombin–antithrombin complexes, suggesting that thrombin is not directly cleaving C5. They then investigated the ability of thrombin, factor Xa and plasmin to cleave C5 by measuring formation of C5a by ELISA. Plasmin, the effector enzyme in the fibrinolytic cascade, was the only enzyme that was able to cleave complement C5 at a similar rate as the canonical C5 convertase formed from complement components. The resultant C5b can assemble into the next stage of the terminal pathway, C5b,6, showing that the C5b generated by plasmin cleavage is functional in assembling the membrane attack complex.

The hypothesis that plasmin can act as a C5 convertase was tested in an arterial model in which plasminogen was activated by tissue plasminogen activator (tPA). They found that the levels of C5a were increased, consistent with plasmin activating C5.

C5 activation with consequent generation of C5a and the membrane attack complex is a feature of many diseases such as arthritis, sepsis and acute lung injury. Defining the extent of plasmin's role in C5 cleavage outside of its role in thrombotic diseases would clarify if this reaction is important in other contexts. The possibility of exploiting this mechanism as a therapeutic target would need to be approached carefully because of the critical role plasmin plays not just in fibrinolysis but also in tissue repair and inflammatory cell migration (Syrovets et al., 2012).

The idea that plasmin is a *bona fide* C5 convertase has several implications for the links between complement and coagulation. Fibrinolysis occurs after coagulation and therefore, the C5 cleavage products will be present during clot resolution as well as clot formation and progression. However, C5a is a major chemoattractant and activator for neutrophils, leading to elaboration of procoagulant neutrophil extracellular traps (NETs) (Yousefi et al., 2009). Leukocytes attracted to the thrombus can contribute to lysis by secretion of plasminogen activators, thus the precise balance between the prothrombotic and fibrinolytic factors may depend on the disease setting.

This study focused on the role of plasmin in C5 cleavage in thrombotic scenarios, but complement plays a key role in eliminating infections. In some infectious diseases such as Yersinia, fibrinogen deficiency leads to decreased survival while plasminogen deficiency increases survival (Degen et al., 2007). The survival advantage conferred by plasminogen deficiency is effectively eliminated in fibrinogen/plasminogen double deficient mice. Thus formation of fibrin prevents the spread of the disease and fibrinolysis promotes it. The Yersinia virulence factor, Pla, can activate plasminogen and many other bacteria express plasminogen activators. It will be important to investigate the role of plasmin in activating the terminal pathway of complement under these circumstances.

Foley et al. (Foley et al., 2016) only consider the forward reactions, but these cascades are tightly regulated. The rate of plasminogen activation is closely controlled by the availability of tPA as well as by plasminogen activator inhibitor-1 while plasmin activity is regulated by alpha-2 antiplasmin. Interestingly, carboxypeptidase B2 (TAFI), which can be activated from its zymogen by either thrombin bound on thrombomodulin

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or by plasmin (Morser et al., 2010), both reduces activation of plasminogen as well as inactivating C3a and C5a, thereby functioning as a regulator of both the enzyme cleaving C5 and one of the products, C5a.

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