Feedback controversy stops here

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In this issue of Blood, Kravtsov and colleagues provide conclusive evidence for factor XII-independent activation of factor XI in plasma.

Even though nearly 20 years have passed since thrombin-mediated factor (f)XI activation was first described,1,2 the relevance of this feedback activation for coagulation remains controversial. In the activated partial thromboplastin time, fXI becomes activated by fXIIa due to contact activation-initiated coagulation. However, the relevance of fXIIa-mediated fXI activation in hemostasis is questionable because individuals with fXII deficiency do not show signs of a bleeding tendency. In contrast, fXI deficiency is associated with a mild to moderate bleeding tendency, especially in tissues with a high local fibrinolytic activity. Alternative pathways for activation of fXI should therefore exist. Besides fXIIa, thrombin, meizothrombin, and fXII (auto-activation) were shown to activate fXI. Upon initiation of coagulation with low concentrations of tissue factor and thrombin, fXI contributes to (further) thrombin generation. The extra generation of thrombin via this pathway resulted in clot resistance to fibrinolysis, providing an explanation for the bleeding tendency of fXI-deficient individuals.3

Although feedback activation in coagulation has been described by many laboratories using different techniques, skepticism about its relevance remained. The most recent study that tried to disprove feedback activation of fXI was a study by Pedicord and colleagues in the Proceedings of the National Academy of Sciences.4 This study could not demonstrate fXIIa generation when thrombin or tissue factor was added to plasma. As with all scientific findings, it is much more difficult to prove the absence of an effect than the presence thereof. Also, the technology that was used in this study was clearly inferior compared with earlier publications. However, the authors justifiably concluded that the reagents used in (some of) the previous studies may have contained traces of fXIIa that could have led to the erroneous conclusion that fXI activation occurred independent of fXII. Instead of ignoring the conclusions of this paper, Kravtsov et al decide to do one better and demonstrate feedback activation of fXI in plasma. With their report in this issue of Blood, they convincingly succeed.5

Using a state-of-the-art thrombin generation assay, the authors confirm that fXI contributed to thrombin generation in plasma at low concentrations of tissue factor and thrombin. As had already been shown before,1 any influencing effect of contaminating fXIIa could be excluded, thereby taking away one of the strongest arguments of Pedicord et al.4 The beauty of the current study is the elegant tools that have been generated. With a fXI mutant (fXI-Ala83-84) that is activated normally by fXIIa but poorly by thrombin, it was proven that thrombin-mediated fXI activation occurs in plasma. Furthermore, an antibody (14E11) directed against fXI was described that blocks fXI activation in the activated partial thromboplastin time, but does not interfere with fXIIa activity. In the thrombin generation assay, this antibody significantly reduced fXIIa-mediated thrombin generation without affecting thrombin generation triggered by tissue factor or thrombin, thereby discriminating between fXIIa- and thrombin-mediated activation of fXI.

The study by Kravtsov et al convincingly demonstrates feedback activation of fXI as a contributing factor in thrombin generation. However, several issues remain. First, it is not apparent which of the 2 thrombin forms, α-thrombin or meizothrombin, is the most relevant activator of fXI. Second, it cannot be excluded that there is a plasma cofactor for thrombin-mediated fXI activation. Third, since all studies so far have been performed under static conditions, the relevance of feedback activation should be investigated under flow conditions or even better in vivo.

Is there a role for fXII-mediated activation of fXI? Since fXII-deficient patients do not bleed, a role of fXII as “initiator” of coagulation appears to be minimal. Also, there is evolutionary evidence that fXII is not involved in activation of fXI: both cetaceans (whales, porpoises, and dolphins) and birds have lost the function of the fXII gene. However, this does not exclude that fXIIa-mediated fXI activation (and subsequent coagulation reactions) can occur during certain pathologic processes. In different experimental mouse models, fXII deficiency protected against thrombus formation in a similar fashion to fXI- and fIX deficiency, suggesting a contributory role for the classic intrinsic pathway of coagulation in pathologic thrombus growth.6 If this is also true for humans remains to be established.

The study by Kravtsov et al provides interesting options for therapeutic interventions. With the 14E11 antibody, proof-of-principle was obtained for the possibility to target fXIIa-mediated activation of fXI, which is important for enhanced thrombus growth, without interfering with thrombin-mediated activation of factor XI that is important for hemostasis. To prove that this concept is a novel “magic bullet” for thrombosis treatment and prevention will be the challenge for the near future.

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REFERENCES


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