The clotting cascade plays an essential role in hemostasis but also contributes to many pathological processes, such as thrombosis. The cascade can be divided into 2 major phases: initiation and amplification (Figure). The initiation phase is triggered by the tissue factor/factor VIIa complex (known as the extrinsic pathway) and generates small amounts of thrombin that activates cofactors (FVIIia and FVa) and proteases (FXIa). The tissue factor/factor VIIa complex is rapidly inactivated by tissue factor pathway inhibitor. The amplification phase is driven by components of the intrinsic pathway (FXIa, FXIa, FIXa, and FVIIIa) and generates large amounts of thrombin. Importantly, individuals with deficiencies in either FVIII (hemophilia A) or FIX (hemophilia B) are prone to spontaneous hemorrhages. In contrast, individuals lacking FXI rarely exhibit any spontaneous hemorrhages. These observations suggest that FVIII and FIX form a primary amplification loop in thrombin generation, whereas FXI could be considered as a secondary amplification loop (Figure).

Several studies have shown that either genetic reduction or pharmacological inhibition of different proteins in the coagulation cascade reduces atherosclerosis in mouse models. For instance, apolipoprotein E (ApoE−/−) mice lacking FVIII have reduced atherosclerosis compared with ApoE−/− mice with normal levels of FVIII. This result was confirmed in an independent study. Interestingly, a deficiency of FVIII did not reduce atherosclerosis in the LDLR−/− mouse model. The development of atherosclerosis in ApoE−/− was also reduced by the pharmacological inhibition of thrombin with melagtran or by either a 50% genetic reduction of prothrombin.

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Ganor et al. show that a deficiency of FXI reduces atherosclerosis in ApoE−/− mice. So why is this observation noteworthy? Previous studies have shown that FVIII plays a role in atherosclerosis in ApoE−/− mice. What is surprising is that a coagulation protease in a secondary amplification loop of the clotting cascade impacts atherosclerosis in a similar manner to FVIII deficiency, which is in the primary amplification loop. Indeed, at 42 weeks, atherosclerosis was reduced by 25% in the aortic sinus and by 49% in the aortic arch in apoe/FXI double knockout mice compared with ApoE−/− controls. However, it would be interesting to directly compare the reduction of atherosclerosis in ApoE−/− mice lacking either FVIII or FXI.

How does FXI affect the progression of atherosclerosis in ApoE−/− mice? The most likely explanation is that FXI deficiency reduces thrombin levels in the atherosclerotic plaque (Figure). There are multiple mechanisms by which thrombin could increase atherosclerosis that include increasing fibrin, increasing platelet activation, and increasing inflammation via activation of protease-activated receptors. Further studies are needed to determine the relative contributions of these different pathways to atherosclerosis in mouse models.

Atherothrombosis is a term used to describe rupture of atherosclerotic plaques. Not surprisingly, the clotting cascade plays a central role in the formation of occlusive thrombi that lead to myocardial infarction and stroke. A model of atherothrombosis has been developed in the mouse that consists of rupturing atherosclerotic plaques using ultrasound and then visualizing the formation of the thrombus. Two recent studies showed roles of the tissue factor/FVIIa complex in the initiation of thrombus formation and components of the intrinsic pathway (FXII and FXI) in the amplification of the thrombus. In particular, a reduction of FXI levels with an antisense oligonucleotide limited the amplification of the thrombus.

What are the clinical implications of the study by Ganor et al? Importantly, Mega et al. showed that addition of low doses of the FXa inhibitor rivaroxaban to patients with recent acute coronary syndrome reduced the rates of death from cardiovascular causes without increasing fatal bleeding. However, there was a significant increase in intracranial hemorrhage in the rivaroxaban group compared with the placebo group. Can we target the clotting cascade more safely? The answer is maybe. In a recent study, an FXI antisense oligonucleotide was used to reduce FXI levels in patients before total knee replacement surgery to ~17% of normal levels. Strikingly, the rate of symptomatic and asymptomatic venous thromboembolism in the patients was reduced from 30% in the group treated with the low molecular weight heparin enoxaparin to 4% in the group with reduced FXI levels; there were similar rates of bleeding in the 2 groups. Given this result, one wonders if reducing FXI levels or inhibition of FXI in patients with a recent acute coronary syndrome would also reduce death rates in a similar manner to treatment with rivaroxaban but without an increase in intracranial hemorrhage.

The clotting cascade has been studied for many years, but there are still mysteries to be solved. The fact that a deficiency of FXI reduces atherosclerosis in a mouse model is surprising and suggests that targeting FXI may not only reduce atherothrombosis but also atherosclerosis itself.
**Disclosures**

N. Mackman is a consultant for Bayer.

**References**

The Clot Thickens in Atherosclerosis
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doi: 10.1161/ATVBAHA.116.307094
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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