The finding that humans with hereditary factor XI deficiency have relatively mild bleeding tendencies—yet are significantly protected against certain thrombotic diseases—has sparked considerable interest in factor XI/XIa as a target for novel antithrombotic treatments.

In the classic waterfall description of blood coagulation, there are 2 ways to trigger the plasma clotting system: the tissue factor (or extrinsic) pathway and the contact (or intrinsic) pathway.1 Extensive studies in knockout mice have demonstrated that the triggering of blood clotting via the tissue factor/factor VIIa complex (TF:VIIa) is essential for normal hemostasis.2 In contrast, humans and mice that completely lack the proteins that trigger the contact pathway (factor XII, prekallikrein, or high molecular weight kininogen) exhibit no bleeding tendencies, indicating that the triggers of the classical contact/intrinsic pathway are dispensable for normal hemostasis.3

See accompanying article on page 1670

Although factor XI is activated by factor XIIa in the classic waterfall description of blood clotting, in stark contrast to the phenotype with factor XII deficiency, humans with severe factor XI deficiencies do exhibit bleeding diatheses.4 Patients with factor XI deficiency tend to have relatively mild bleeding tendencies and generally do not bleed spontaneously (other than menorrhagia). Rather, when these patients bleed, it is typically after injury or surgery, especially in tissues with a high thrombolytic potential, such as the oral cavity or urinary tract. Heterozygous humans with factor XI deficiency bleed less frequently than do homozygous patients.5 Knockout mice lacking factor XI have no detectable deficiency in hemostasis, although bleeding has not specifically been tested in tissues with high thrombolytic capacity in these animals.3

The very different bleeding phenotypes between severe factor XI and factor XII deficiencies in man suggested that, in normal hemostasis, factor XI must be activated by a protease other than factor XIIa. In 1991, 2 groups reported that thrombin can feed back to activate factor XI,6,7, which could allow sustained thrombin generation and possibly also inhibition of fibrinolysis via thrombin-activatable fibrinolysis inhibitor.8 These reports were initially criticized on the basis that the kinetics of factor XI activation by thrombin are very slow, and that plasma contains such a high concentration of competing thrombin substrates that physiological levels of factor XI activation by thrombin were unlikely (reviewed by Löwenberg et al). However, subsequent studies directly demonstrated factor XI activation in plasma that was independent of factor XII.9,10 Our laboratory recently showed that polyphosphate secreted from activated human platelets profoundly accelerates factor XI activation by thrombin, suggesting that platelet polyphosphate may be the important physiological cofactor for this reaction.11 The Figure summarizes current thinking for the role of factor XI in normal hemostasis (and thrombotic disease), in the context of a revised clotting cascade.

Hereditary factor XI deficiency is relatively common in Jews of Ashkenazi origin, and epidemiological studies of this population have revealed that severe factor XI deficiency confers protection against both ischemic stroke and deep-vein thrombosis (although not from acute myocardial infarction).6,12 Other epidemiological studies have reported that elevated plasma factor XI levels in the general population correlate with risk of venous thromboembolism and ischemic stroke, although with more mixed results regarding risk of myocardial infarction (reviewed by He et al13). Thus, extensive findings in both humans and experimental animals13 indicate that targeting factor XI/XIa may reduce the risk of certain thrombotic diseases in humans, although potentially having much lower rates of bleeding side effects compared with currently used anticoagulants, which target the common pathway of blood clotting (ie, inhibit factor Xa, thrombin, or both).

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Crosby et al14 report that reducing plasma factor XI levels in baboons was associated with a significant decrease in thrombogenicity without increasing experimental bleeding. In particular, this study used second-generation antisense oligonucleotides (ASOs) to knock down factor XI biosynthesis in vivo in these animals, reporting a dose- and time-dependent lowering of factor XI levels in their plasma. This parallels previous studies from this team using ASOs to reduce factor XI expression in experimental mice and cynomolgus monkeys, which likewise reduced thrombosis without inducing significant bleeding.15,16 In the present study, the authors used collagen-coated grafts in arteriovenous shunts in baboons to induce thrombosis. The platelet-rich thrombi within the grafts themselves were not decreased in severity by targeting factor XI by ASOs (or by administering blocking antifactor XI antibodies), which was not surprising given the results of previous studies indicating that extremely potent anticoagulants (with high bleeding risk) are required to block this process. However, propagation of a fibrin-rich thrombus (or tail) downstream of the collagen-coated surface is known to be highly sensitive to anticoagulant treatment in this model.17 Intriguingly, in the present study, reducing the plasma levels of factor XI in baboons by as little as 50% was sufficient to cause measurable reductions in thrombus propagation. This suggests that even relatively modest reductions in plasma factor XI activity may be sufficient to protect against at least some types of thrombosis. Furthermore, previous studies using ASOs to knock down factor XI levels in mice reported

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1454
that factor XI ASO treatment in combination with low molecular weight heparin or clopidogrel (an antiplatelet agent) exhibited increased antithrombotic efficacy, whereas not increasing the bleeding risk relative to administering heparin or clopidogrel alone. Knocking down factor XI levels also has the advantage that reversing this type of therapy is as simple as adding back the missing factor XI, which could be important given the relatively long tissue half-life of ASOs. Potential disadvantages of this approach include the relatively slow onset of ASO-mediated knockdown factor XI levels, as well as possibly lower antithrombotic efficacy compared with anticoagulants that target the common pathway of blood clotting. Taken together, however, these findings point toward targeting factor XI as a promising treatment modality for decreasing thrombotic risk, however, these findings point toward targeting factor XI as a potential antithrombotic strategy with lowered bleeding risk.

Figure. The revised plasma clotting cascade. In normal hemostasis, clotting is triggered at 2 points by the tissue factor/factor VIIa (TF:VIIa) pathway, leading first to activation of factors IX and X and, ultimately, thrombin generation and the formation of a fibrin clot. Thrombin also activates factor XI in a feedback reaction that is greatly stimulated by platelet polyphosphate, which may be the physiological cofactor for this reaction. Although factor Xla is dispensable for normal hemostasis, it is a potent factor XI activator, and a number of animal studies have shown that factor XII contributes to thrombosis. An open question, therefore, is what is the major pathway for factor XI activation in thrombotic diseases—activation by thrombin, factor Xla, or perhaps both? (Not shown: factor XI can undergo autoactivation, which is also stimulated by polyphosphate.)

Disclosures
None.

References


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