Targeting factor XI to prevent thrombosis

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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 two ways to trigger the plasma clotting system: the tissue factor (or extrinsic) pathway and the contact (or intrinsic) pathway. Extensive studies in knockout mice have demonstrated that triggering of blood clotting via the tissue factor/factor VIIa complex (TF:VIIa) is essential for normal hemostasis. 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.

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. Factor XI deficient patients tend to have relatively mild bleeding tendencies and generally do not bleed spontaneously (other than menorrhagia). Rather, when these patients bleed it is typically following injury or surgery, especially in tissues with a high thrombolytic potential such as the oral cavity or urinary tract. Heterozygous factor XI deficient humans bleed less frequently than homozygous patients. 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.

The very different bleeding phenotypes between severe factor XI versus factor XII deficiencies in man suggested that, in normal hemostasis, factor XI must be activated by a protease other than factor XIIa. In 1991, two groups reported that thrombin can feed back to activate factor XI, which could allow sustained thrombin generation and possibly also inhibition of fibrinolysis via thrombin-activatable fibrinolysis inhibitor (TAFI). 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 physiologic levels of factor XI activation by thrombin were unlikely (reviewed by Löwenberg et al\textsuperscript{5}). However, subsequent studies directly demonstrated factor XI activation in plasma that was independent of factor XII.\textsuperscript{9, 10} Our lab recently showed that polyphosphate secreted from activated human platelets profoundly accelerates factor XI activation by thrombin, suggesting that platelet polyphosphate may be the important physiologic cofactor for this reaction.\textsuperscript{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 epidemiologic 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).\textsuperscript{4, 12} Other epidemiologic 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 al\textsuperscript{8}). Thus, extensive findings in both humans and experimental animals\textsuperscript{13} indicate that targeting factor XI/XIa may reduce the risk of certain thrombotic diseases in humans while potentially having much lower rates of bleeding side effects compared with current used anticoagulants, which target the common pathway of blood clotting (i.e., inhibit factor Xa and/or thrombin).

In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Crosby et al\textsuperscript{14} 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.\textsuperscript{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 anti-factor 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.\textsuperscript{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 that factor XI ASO treatment in combination with low MW heparin or clopidogrel (an antiplatelet agent) exhibited increased antithrombotic efficacy while not increasing the bleeding risk relative to administering heparin or clopidogrel alone.\textsuperscript{16} 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,\textsuperscript{16} 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 to 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, with perhaps much lower bleeding side effects compared to the anticoagulants that are currently used clinically.

References

The revised plasma clotting cascade. In normal hemostasis, clotting is triggered at two points by the 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\textsuperscript{6,7} that is greatly stimulated by platelet polyphosphate,\textsuperscript{11} which may be the physiologic cofactor for this reaction. Although factor XIIa is dispensable for normal hemostasis,\textsuperscript{3} it is a potent factor XI activator and a number of animal studies have shown that factor XII contributes to thrombosis.\textsuperscript{3} An open question, therefore, is what is the major
pathway for factor XI activation in thrombotic diseases—activation by thrombin, factor XIIa, or perhaps both? (Not shown: factor XI can undergo autoactivation, which is also stimulated by polyphosphate.\textsuperscript{11})