blood® Editorial

Introduction to a review series on factor XI

Factor XI is located near the "top" of the contact phase pathway, activated by factor XIIa to factor XIa, which then goes on to activate factor IX to factor IXa. Thrombin is also able to activate factor XI, thereby providing a feedback loop resulting in the amplification of thrombin generation. Deficiency of factor XI is associated with bleeding manifestations, but the clinical phenotype is variable and differs from the bleeding observed with deficiency of factor IX or factor VIII, also part of the contact phase pathway. Recently, it has been noted that inhibiting factor XIa provides an antithrombotic effect with a low risk of bleeding. This observation has led to an increase in interest in targeting factor XI and factor XIa as an alternative to the direct oral anticoagulants, targeting factor Xa and thrombin.

This review series begins with an overview into the biology of factor XI, addresses our current understanding and approaches to the management of factor XI deficiency, and culminates with a discussion of current strategies targeting factor XI and factor XIa for anticoagulant therapy. The series includes the following 3 articles.

- Samantha A. Moellmer, Cristina Puy, and Owen J. T. McCarty, "Biology of factor XI"
- Assaf Arie Barg, Tami Livnat, and Gili Kenet, "Factor XI deficiency: phenotypic age-related considerations and clinical approach towards bleeding risk assessment"
- David Gailani and Andras Gruber, "Targeting factor XI and factor XIa to prevent thrombosis"

Factor XI is a homodimeric molecule, consisting of 2 identical subunits, each having 4 apple domains and 1 serine protease domain. It differs from the vitamin K–dependent zymogens, factors II, VII, IX, and X, by the absence of the characteristic γ-carboxyglutamate domain of these clotting factors. Moellmer et al review the biology of factor XI by systematically describing key structural and functional characteristics of the individual domains and addressing how these different properties contribute to the multifunctional properties of factor XI. They also weave into their discussion the different mutations that have been described in patients with factor XI deficiency and note which ones have been associated with a bleeding phenotype and which ones have not. By using this approach, the authors set the stage for the 2 articles that follow.

Factor XI deficiency is a rare bleeding disorder with an estimated prevalence of 1 per million in the general population, but it occurs much more frequently in certain ethnic populations because of specific founder mutations. Barg et al review the clinical manifestations associated with factor XI deficiency and describe how the bleeding risk can change during the lifespan of the individual patient. Bleeding is generally uncommon in infancy and early childhood but becomes more problematic for females during their reproductive years. For elderly individuals, clinical situations requiring treatment with antithrombotic therapies are encountered and need to be addressed. When assessing the bleeding risk for the individual patient, the personal bleeding history is 1 of the more important variables to be considered. Laboratory assays, including the factor XI level itself, are less useful for predicting bleeding risk. Fresh frozen plasma is most commonly used for replacement therapy, as factor XI concentrates have been associated with thrombotic complications, and antifibrinolytic agents are important adjunctive therapies for the prevention and management of bleeding complications.

In contrast to bleeding symptoms associated with factor XI deficiency, strategies targeting the activation of factor XI, or the activity of factor XIa, have been attracting considerable attention for the prevention and treatment of thromboembolism. Gailani and Gruber review the current status of this therapeutic approach, highlighting the antithrombotic efficacy as well as the decreased frequency of hemorrhagic complications associated with inhibition of factor XI. Mechanistic interventions include the use of antisense oligonucleotides that result in a decrease in factor XI in the circulation, antibodies that block zymogen activation and/or enzyme activity, and small molecules that bind to the active site and inhibit protease function. Several studies have shown that inhibition of factor XI/factor XIa can reduce venous thrombosis following total knee arthroplasty compared with enoxaparin, without increasing the incidence of bleeding. Initial studies designed to investigate secondary prevention of ischemic stroke and in patients with heart disease have underscored the safety of these agents, even in patients receiving concomitant antiplatelet therapy. Multiple large phase 3 studies are ongoing to determine the efficacy of inhibiting factor XI for these clinical indications.

These reviews highlight what we know about factor XI, the scientific and clinical directions we are headed in, and where more research and development are needed. Exciting times are on the horizon!

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