The Intrinsic Pathway of Coagulation as a Target for Antithrombotic Therapy

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KEYWORDS

• Intrinsic pathway • Contact activation • Thrombosis • Factor XI • Factor XII

KEY POINTS

- The term intrinsic pathway refers to a series of sequential reactions involving the plasma proteins factors VIII, IX, XI, and XII; prekallikrein; and high-molecular-weight kininogen, which are required for initiation of coagulation in the activated partial thromboplastin time assay.
- Certain components of the intrinsic pathway that serve a limited role in hemostasis (factor XI), or are not required for hemostasis (factor XII, prekallikrein, and high-molecular-weight kininogen), are required for clot formation in animal models of thrombosis.
- Epidemiologic data indicate that factor XI contributes to venous thromboembolism and ischemic stroke, and may contribute to myocardial infarction in humans, whereas factor XII likely contributes to thrombus formation when blood is exposed to artificial surfaces, such as during cardiopulmonary bypass and extracorporeal membrane oxygenation.
- Reducing factor XI level to 20% of normal by antisense oligonucleotide technology was more effective than standard-dose low-molecular-weight heparin in preventing venous thrombosis during knee replacement surgery, without comprising intraoperative or postoperative hemostasis.
- By targeting components of the intrinsic pathway of coagulation with therapeutic inhibitors, it may be possible to uncouple antithrombotic effects from anticoagulant (antihemostatic) effects, improving the safety of antithrombotic therapy.

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INTRODUCTION

The protease thrombin makes essential contributions to hemostasis through its capacity to catalyze conversion of fibrinogen to fibrin, to stimulate platelet and vascular endothelial cells, and to activate plasma coagulation factors.[1] Thrombin also plays a central role in thrombosis, and several approaches have been developed to manipulate this enzyme to achieve an antithrombotic effect. The activity of thrombin or factor (f) Xa (the enzyme responsible for converting prothrombin to thrombin) can be inhibited directly with drugs targeting the enzyme active sites (argatroban, dabigatran, and bivalirudin for thrombin; rivaroxaban, apixaban, and edoxaban for fXa),[2] or indirectly with heparin-related compounds (unfractionated or low-molecular-weight heparin or fondaparinux) that enhance the activity of the plasma inhibitor antithrombin.[3] Alternatively, synthesis of prothrombin and fX, the precursors of thrombin and fXa, can be reduced with vitamin K antagonists such as warfarin.[4] Use of these effective antithrombotic strategies comes with a well-recognized cost. Thrombin and fXa serve vital roles in hemostasis, and therapies directed at them increase bleeding. Use of heparin is associated with major bleeding rates of up to 3%, and 2% to 13% with warfarin.[3–5] Newer oral thrombin and fXa inhibitors seem to cause less bleeding than the older drugs, and are easier to use.[2,6] However, because of their mechanisms of action, there are limits on the types of patients who are eligible to receive them, the clinical settings in which they can be used, and the intensity of anticoagulation that can be applied.

The strategy of targeting thrombin and/or fXa to achieve an antithrombotic effect is based on the intuitive notion that formation of an intravascular thrombus is largely the result of dysregulation of processes normally involved in hemostasis. This premise is currently being reconsidered. There is substantial interest in developing and testing novel therapies that target the proteases of the plasma intrinsic pathway of coagulation (fIX, fXI, fXII, and prekallikrein [PK]) for treating or preventing thromboembolic disorders.[7–9] The physiologic importance of the intrinsic pathway has been questioned since the original descriptions of the cascade-waterfall model of coagulation[10,11] because, although some components of the pathway are clearly required for hemostasis, others are not.[12] This article reviews preclinical and clinical data supporting the hypothesis that components of the intrinsic pathway, and perhaps the intrinsic pathway itself, contribute to thrombosis, and that a useful antithrombotic effect can be achieved by targeting plasma factors that serve minor roles in hemostasis. To understand how the intrinsic pathway might contribute to thrombosis, we first need to review how understanding of this pathway has evolved over the past 50 years.

THE INTRINSIC PATHWAY IN MODELS OF BLOOD COAGULATION

The Cascade-Waterfall Model of Thrombin Generation

The cascade-waterfall hypotheses of intrinsic coagulation was first proposed in 2 landmark articles in 1964 by Macfarlane,[10] and by Davie and Ratnoff.[11] In subsequent models based on this scheme, the process of thrombin generation is the result of amplification of a procoagulant signal initiated by conversion of fXII to fXIIa, followed sequentially by activation of the enzyme precursors fXI, fIX, fX, and prothrombin (**Fig. 1**A). At the time this model was proposed, it was recognized that much of the cascade could be bypassed through a process involving fVIIa (see **Fig. 1**A),[10,11] but the importance of this was not clear. The scheme in **Fig. 1**A depicts the major enzyme reactions that contribute to plasma clotting in the activated partial thromboplastin time (aPTT) and prothrombin time (PT) assays used in clinical practice. There are 2 triggering mechanisms that converge at the level of fX activation. Activation through