Editorial

Factor VII–Activating Protease
Coagulation, Fibrinolysis, and Atherothrombosis?

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The mechanistic description of a biological process first involves the development of an inventory of constituents that are presumed essential for the expression of the function. Although initially based on pathology, more frequently this inventory is developed by in vitro tests on the biochemistry, cell biology, or molecular genetics of a process. Elaborate schemes describing physiological reaction systems are frequently developed on the basis of these in vitro–developed inventories; however, it is becoming commonplace knowledge that the ultimate test of biological relevance, ie, a clinical phenotype, does not exist. In the coagulation system, this is evident in descriptions of the “intrinsic pathway” of coagulation, which take the view that surface contact activation of factor XII is the initial process. However, defects in the contact pathway produce no hemorrhagic phenotype. The protein contains domain structures that are presumed essential for the expression of recognition.

In the present issue of Circulation, the article titled “Marburg I Polymorphism of Factor VII–Activating Protease: A Prominent Risk Predictor of Carotid Stenosis” by Willeit and colleagues provides important observations that appear to require the inclusion of a novel serine protease, the factor VII–activated protease (FSAP), into the inventory of molecules associated with the coagulation/fibrinolytic process. FSAP was identified by a number of investigators and isolated either because of its affinity for immobilized hyaluronic acid or its presence in commercial prothrombin complex concentrates. The protein contains domain structures frequently associated with coagulation and fibrinolytic enzymes, including three “EGF”- like domains, a “kringle,” and a serine protease domain. Additional studies indicated that FSAP is a potent activator of the coagulation zymogen factor VII (hence its name) and was also an activator of single-chain pro-urokinase-type plasminogen activator.

Genetic studies observed relatively common polymorphisms in this protein, one of which (Marburg 1) showed diminished activity in pro-urokinase activation. The present study by Willeit et al presents an epidemiological analysis of 810 subjects with regard to the association of the Marburg polymorphisms with progressive stages of stenotic vessel disease originating from atherothrombosis. These data demonstrate an association between the Marburg 1 polymorphism and the risk for the evolution and progression of carotid stenosis. The observation of a phenotype associated with this FSAP mutation appears to require its inclusion into the inventory of reactants in coagulation/fibrinolytic mechanisms.

Because the Marburg 1 polymorphism is associated with reduced activity in the fibrinolytic system, one might jump to the conclusion that the pathological phenotype is associated with a diminished capacity for clot dissolution; however, it is also appealing to consider that the function potential for this protein is coincident with its title. Plasma factor VIIa is an essential contributor to the initiation of a coagulation response. Approximately 1% of total plasma factor VII protein is present as the cleaved enzymatic form of the protein, factor VIIa. However, the activity of this erstwhile serine protease is virtually nonexistent until it binds to tissue factor. As a consequence, plasma factor VIIa is impervious to the numerous serpin inhibitors present in blood. Factor VII is feedback activated by many of the proteases produced during the blood coagulation response, but the extent of the thrombin production reaction is largely dependent on the preexistent concentration of factor VIIa in plasma and the concentration of tissue factor presented by the vascular lesion. At present, no adequate description exists for the mechanism by which resident plasma factor VIIa is produced and circulates. Studies linking plasma factor VII/VIIa activity with cardiovascular risk have been reported but remain controversial. It is difficult to say at this juncture whether the discrepancies in the various studies are a consequence of differences in study design or of the difficulty in measuring factor VII zymogen and factor VIIa activity with functional assays. The FSAP is a leading candidate for the maintenance of plasma factor VIIa, and its evaluation may prove useful. The FSAP also provides an additional linkage between the initiation of the coagulation system and fibrinolysis; thus, the association of the protein with an atherothrombotic phenotype is most intriguing.

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References


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