Anticoagulation by a thrombin precursor

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A prothrombin mutant that is activated to yield stable meizothrombin produces dominant inhibition of clot formation in a mouse model of carotid artery injury.

Studies of clot formation in vivo that draw from established details of coagulation biochemistry have the potential for yielding unexpected insights into the regulation of coagulation or suggesting novel strategies for its inhibition. In this vein, Shim and colleagues (page 415) report studies directed at evaluating the potential contribution of meizothrombin to thrombus formation in a mouse carotid artery injury model.

Thrombin catalyzes a spectrum of cleavage reactions relevant to both the procoagulant and anticoagulant pathways of blood coagulation. These features establish thrombin as a key effector and regulator of clot formation. Two cleavages are responsible for the proteolytic conversion of prothrombin to thrombin. As a result of bond cleavage preference, meizothrombin is produced as the principal intermediate when prothrombin activation is catalyzed by the prothrombinase complex. This intermediate is a serine proteinase that is covalently tethered to the fragment 1.2 domain. Meizothrombin therefore represents a transiently produced variant of thrombin that retains membrane binding properties with important functional sites in the proteinase domain modulated by the fragment 1.2 domain. Human or bovine meizothrombin derivatives exhibit greatly reduced activity toward fibrinogen and platelets in comparison to those described for the human and bovine derivatives. They also report the results obtained in a FeCl₃-induced carotid artery injury model using prothrombin⁻/⁻ mice infused with either wild-type II or aII to complement prothrombin levels in these animals. The interesting finding is that infusion of aII leads to a delay instead of shortening in carotid artery occlusion time in an apparently dose-dependent manner. Dominant inhibition of clot formation by aII, which was infused into these animals, implicates a contribution from the anticoagulant properties of meizothrombin produced in this biologically relevant setting. Competitive alternate substrate effects between endogenous prothrombin and aII for cleavage by prothrombinase could also contribute to this effect. Unanswered is whether meizothrombin transiently produced during normal prothrombin activation in vivo significantly participates as a negative effector of clot formation. However, the work suggests that infusion of such zymogen derivatives may yield a novel and potentially viable strategy for triggering the anticoagulant pathway through the selective activation of protein C in the vicinity of sites of prothrombin activation and ongoing thrombus formation.

Arterial occlusion after FeCl₃-induced injury. See the complete figure in the article beginning on page 415.

The WHIMs of leukocytes

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WHIM, a dominant immunodeficiency caused by mutations in the chemokine receptor CXCR4, leads to myeloid and lymphoid retention in tissues producing its cognate ligand, CXCL12 (SDF-1), by virtue of an exaggerated chemotactic and adhesion response to ligand.

Gulino and colleagues (page 444) have put pathophysiologic meaning to the dominant mutations in human CXCR4 leading to the rare combined immunodeficiency, WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome. WHIM is characterized by human papilloma virus (HPV) infections; hypogammaglobulinemia;
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