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Natural mechanisms that combat thrombosis, especially the protein C system

Mary J. Heeb
The Scripps Research Institute, USA

Abstract

Both procoagulant and anticoagulant mechanisms are needed to maintain hemostatic balance, but procoagulant mechanisms often tip the balance; consequently, half of us will die of unwanted blood clots (thrombosis). Procoagulant mechanisms include exposure of tissue factor from underlying blood vessel layers, and generation of activated coagulation factors such as factor (F) Xa. Anticoagulant mechanisms include clot lysis, and the action of anticoagulant proteins, especially activated protein C (APC) and its cofactor, protein S (PS). Heterozygous deficiencies of these proteins are associated with 20X increased risk of thrombosis; homozygous deficiencies are potentially fatal at birth.

Activated platelets are major sites of procoagulant reactions, but those reactions must be balanced by anticoagulant mechanisms. We examined the direct, APC-independent activity of PS on activated platelets, which is unaffected by cleavage by a platelet membrane protease. Plasma-derived Zn^{++}-containing PS at sub-physiologic concentrations inhibited generation of thrombin and FXa on activated platelets. In the presence of neutralizing anti-PS antibodies, thrombin generation on activated platelets was 2.6X increased, and platelet PS at low concentration inhibited thrombin generation ~5X more efficiently than plasma-derived PS. Platelet PS had a higher apparent MW than plasma PS. It was phosphorylated by kinases released from platelets, but other differences were evident.

Platelet kinases that phosphorylate PS were characterized as casein kinase-1/2-like. Purified casein kinase-2 enhanced PS' APC cofactor activity, and a casein kinase-2 site was identified at Thr37 in PS. Thr37 was in turn found to be part of a FVa binding site on PS that affected both APC cofactor activity and direct anticoagulant activities. We aim to identify other differences in platelet PS, other phosphorylation sites that affect its activities, and other sites of protein-protein interaction that affect PS anticoagulant activities. We will extend studies showing that PS is antithrombotic in a baboon thrombosis model, and thus has therapeutic potential

Biography

Dr. Heeb received her Ph.D. in biochemistry from Georgetown University and has conducted research at The Scripps Research Institute for 30 years. She is presently an Associate Professor focused on mechanisms of action of anticoagulant proteins such as activated protein C and protein S. Other studies included protein Z-dependent protease inhibitor, protein Z, FVa, FIXa, clinical studies, platelet studies, prostate specific antigen, hK2 and lectins of oral bacteria. She has published 76 papers. She has 4 children and 6 grandchildren.