

Bloodless Coup at the Endothelial Surface: New APC Variants & Sepsis

By Margaret Ragni, MD

Activated protein C (APC) is not only a potent anticoagulant — it is also a potent anti-inflammatory and cytoprotective agent. The benefit APC provides in severe sepsis is through these latter effects, but the major risk associated with APC is through its anticoagulant effects, which lead to bleeding complications in some. The interesting papers presented in the blood coagulation and fibrinolysis simultaneous sessions show APC is protective in several pre-clinical sepsis models, including the rodent ischemic stroke model, lipopolysaccharide endotoxemia model, and in the rodent sepsis model, suggesting potential new therapeutic applications.

Jong-Sup Bae, St. Louis University, is presenting innovative work (abstract #62) on the development of APC variants with no anticoagulant activity, but which retain anti-inflammatory and cytoprotective properties. By adding a disulfide bond between β -sheets of the APC molecule, an APC variant was developed that no longer binds to the functional Ca^{2+} binding site, the so-called “70-80 loop” of the molecule, rendering it resistant to thrombin activation. The elimination of the anticoagulant action of APC was confirmed by factor Va degradation and plasma-based clotting assays. Importantly, the capacity for anti-inflammatory and cytoprotective effects by this APC variant appeared normal based on intact endothelial protein C receptor (EPCR) and protease activated receptor-1 (PAR-1) signaling. These signaling pathways were previously presented by Dr. Hartmut Weiler in the Sunday Plenary Session as the pathways conferring survival advantage in severe sepsis. Whether this APC variant will be a safer drug in patients with severe sepsis must await the results of clinical trials.

Another exciting paper (abstract #895) will be presented by Andras Gruber, MD, Oregon Health and Science University, who evaluated whether short-term thrombomodulin-dependent protein C activator (PCA) reduces bleeding in an experimental mouse ischemic stroke model. In this model, APC has been shown to be neuroprotective during transient intraluminal middle cerebral artery occlusion. As compared with rtPA, PCA significantly reduced local hemorrhage and neurological scores, suggesting the possibility of benefit in patients with acute ischemic stroke.

A third paper (abstract #61) evaluates the role of platelets in sepsis survival. Anna Kowalska, PhD, Children’s Hospital of Philadelphia, will present data investigating the role of platelet factor 4 (PF4) released from platelets activated during sepsis in APC generation and survival in sepsis. Using a lethal lipopolysaccharide (LPS) endotoxemia model, platelets decreased by 70 percent within two hours of LPS injection, accompanied by only a moderate 20 percent increase in PF4 levels, consistent with previously observed PF4 binding to endothelium. APC levels also increased, but less so in PF4^{-/-} mice, presumably due to the protective effect of APC generation. Mortality in the PF4^{-/-} mouse did not improve with mouse PF4^{-/-} platelets, but did improve after hPF4⁺ platelets were infused, suggesting that platelets with high PF4 levels may be a potential therapeutic strategy.

In abstract #65, Xia Yang, PhD, and colleagues at Scripps Research Institute developed mutants of the two APC receptors, endothelial protein C receptor (EPCR), and protease activated receptor-1 (PAR-1), responsible for cytoprotective and anti-inflammatory APC activity. Despite eradication of the anti-inflammatory activity and the cytoprotective activity of these mutants, APC maintained its anticoagulant activity independent of these functions. The authors suggest that the APC variants might be useful in assessing new APC variant molecules for treating sepsis, specifically to help determine the relative anticoagulant vs. cytoprotective activities.