Protein C

Protein C is an anticoagulant serine protease activated by the blood coagulation pathway.

It is a vitamin K-dependent plasma protein zymogen whose genetic mild or severe deficiencies are linked with risk for venous thrombosis or neonatal purpura fulminans, respectively. Studies over past decades showed that activated protein C (APC) inactivates factors (F) Va and VIIIa to down-regulate thrombin generation. More recent basic and preclinical research on APC has characterized the direct cytoprotective effects of APC that involve gene expression profile alterations, anti-inflammatory and anti-apoptotic activities and endothelial barrier stabilization. These actions generally require endothelial cell protein C receptor (EPCR) and protease activated receptor-1. Because of these direct cytoprotective actions, APC reduces mortality in murine endotoxemia and severe sepsis models and provides neuroprotective benefits in murine ischemic stroke models. Furthermore, APC reduces mortality in patients with severe sepsis (PROWESS clinical trial). Although much remains to be clarified about mechanisms for APC's direct effects on various cell types, it is clear that APC's molecular features that determine its antithrombotic action are partially distinct from those providing cytoprotective actions because we have engineered recombinant APC variants with selective reduction or retention of either anticoagulant or cytoprotective activities. Such APC variants can provide relatively enhanced levels of either cytoprotective or anticoagulant activities for various therapeutic applications. We speculate that APC variants with reduced anticoagulant action but normal cytoprotective actions hold the promise of reducing bleeding risk because of attenuated anticoagulant activity while reducing mortality based on direct cytoprotective effects on cells [1)].

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Griffin JH, Fernández JA, Gale AJ, Mosnier LO. Activated protein C. J Thromb Haemost. 2007 Jul;5 Suppl 1:73-80. Review. PubMed PMID: 17635713.