Hematology-2013

OMICS Group Conferences
Accelerating Scientific Discovery

International Conference on
Hematology & Blood Disorders

September 23-25, 2013 Raleigh, USA

A novel role of protein s in regulating thrombosis, independent of activated Protein c

Rinku Majumder
University of North Carolina at Chapel Hill, USA

Abstract

The plasma glycoprotein Protein S (PS) is a critical, negative regulator of blood coagulation. The importance of PS is demonstrated dramatically by the catastrophic purpura fulminans that develops in rare newborns homozygous for PS mutations; heterozygous individuals have an elevated risk for deep vein thrombosis and other life-threatening thrombotic events. Further, Pros1–/– mice die in utero from a fulminant coagulopathy and associated hemorrhages.

Our research project aims to use the natural anticoagulant Protein S as a preventive agent for X-linked thrombophilia, a disorder of blood coagulation. Blood coagulation, also called hemostasis, normally protects the integrity of blood vessels. Thrombophilia is an abnormality of blood coagulation that increases the risk of thrombosis, a condition that occurs when a platelet (blood cell) aggregate and/or a fibrin clot forms in an intact blood vessel or in a chamber of the heart. This condition can cause a stroke or heart attack. Protein S is a key protein that limits thrombosis, and a deficiency or defect in Protein S is a major cause of thrombosis. Our studies will enable development of anticoagulant therapy for thrombosis.

The interaction between coagulation proteins and platelets is both critical to the maintenance of normal hemostasis and the cause of human cardiovascular disease. In this proposal, we will investigate the biochemical properties of Protein S (PS) and how PS could be used to prevent thrombosis. We recently obtained preliminary data suggesting that PS plays an important role in hemostasis by inhibiting FIXa. We suggest that PS binds to the enzyme FIXa and inhibits FXa generation in the presence and absence of another crucial protein FVIIIa.

As a test case, we will determine whether an increase in FIXa that causes thrombosis could be controlled by using PS. To do so, we will use human and mouse blood plasma and isolated proteins to show that FXa generation by FIXa is regulated by PS. Using plasma and isolated factors, we find that PS binds factor IXa (FIXa) and inhibits factor Xa generation by the FIXa-VIIIa (intrinsic Xase) complex independent of APC. We propose to examine the specificity of PS binding to FIXa and the physiological importance of this novel regulatory role of PS. Our central hypothesis is that PS binds to FIXa specifically in the presence of phosphatidyl serine (PhosSer)-containing membranes and inhibits FXa generation in the presence and absence of FVIIIa.

Paulo Simioni et. al. from Padua, Italy, reported a case of thrombophilia associated with a leucine for arginine substitution at position (R338L) of FIX. The clotting activity of FIX from the proband was approximately eight times the normal level. Our preliminary data showed that the aPTT of proband's plasma reverted back to the normal range with externally added PS, increasing from 25.7 seconds to 33 seconds. This result opens up an excellent opportunity to prevent thrombosis.

The inhibition of FIXa by PS, in part, maintains the haemostatic balance. The results from our proposal will reveal an important, specific role of PS in regulating blood coagulation and answer a major outstanding question, i.e., how does the key anticoagulant PS contribute to down-regulation of the hemostatic response. Finally, our proposal will establish a novel regulatory role of protein S which will enable protein S to be used to treat X-linked thrombophilia.