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Protein S, a new agent in adjunct therapy of hemophilia-B

Background: Current treatment of hemophilia-B consists of infusion of factor IX (FIX) concentrates to substitute for deficient FIX, i.e., replacement therapy. Yet, replacement is only temporary, as infused FIX is cleared rapidly from a patient's plasma. We found that Protein S (PS) inhibits FIX and importantly, anti-PS antibody increased FIX activity in hemophilia-B plasma, implying that blocking PS activity may achieve longer lasting replacement therapy.

Aims: To assess the effectiveness of anti-PS antibody in reducing clotting time.

Method & Results: We used a modified aPTT assay (clotting initiated with FIX) with FIX-deficient plasma and varied the concentrations of added FIX and anti-PS antibody. The aPTT clotting times in the presence and absence of anti-PS antibody were measured for 2.5 (51 sec+Ab; 69 sec+Ab), 5 (43 sec+Ab; 59 seconds+Ab), 10 (38 sec+Ab; 51 sec+Ab), and 20 nM FIXa (33 sec+Ab; 40 sec+Ab). Results showed that in FIX-deficient plasma, an anti-PS antibody would make added FIXa ~3 fold more active. We also performed a thrombin generation assay with the same FIX-deficient plasma in the presence of 1, 2.5 and 5 nM FIXa and measured peak thrombin formation in the presence of anti-PS antibody. Both the thrombin generation assay and the clotting assay gave similar results, i.e., addition of neutralizing anti-PS antibody made FIX ~3 fold more active. In wild type mice we have found that PS inhibited thrombin generation. Work is underway to assess hemostasis in hemophilia-B mice receiving a low dose of FIX and PS antibodies. Improved hemostasis in this mouse model would move anti-PS antibody to the forefront as a possible adjunct in hemophilia therapy.

Conclusion: Our findings suggest that administration of anti-PS antibodies to hemophilia-B patients may achieve the goal of longer lasting replacement therapy. Antibody blocking PS activity towards FIXa is the most straightforward approach and one most likely to succeed.

Biography

Rinku Majumder has completed her PhD in 1999 from Bose Institute, India and Postdoctoral studies from UNC Chapel Hill, School of Medicine in 2003. She is currently an Associate Professor in the Department of Biochemistry & Molecular Biology at LSU Health Science Center, School of Medicine. She has published more than 22 papers in reputed journals and has been serving as a standing study section Member for NIH, AHA grants. She is the Reviewer for reputed journals like *Blood, JTH, JBC, Plos One, Biochemistry and Thrombosis Hemostasis.*

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