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ANALYSIS OF THROMBUS FORMATION DYNAMICS IN ADAMTS13-/- MICE AFTER ENDOTHELIAL INJURY

Abstract

The peculiar occurrence of what is known as post-flight cardiovascular dysfunction (often described within the context of "Apollo 15 space syndrome") is of interest to many hematologists. Our lab is interested in the increase in thrombocytopenia (low platelet counts) and abnormalities in blood clotting observed in patients, thought to be a result of the development of thrombi at sites of vascular injury in microgravity conditions. Thrombotic thrombocytopenic purpura (TTP) is a potentially fatal syndrome caused by deficiency of ADAMTS13, which cleaves plasma glycoprotein von Willebrand Factor (VWF). The clinical manifestations of this disease are surprisingly similar to the hematologic complications associated with post-flight cardiovascular dysfunction. Proteolytic cleavage of VWF on endothelial cells by ADAMTS13 is critical to maintaining normal hemostasis by generating VWF multimers in sizes that are hemostatically adequate, but not thrombogenic. We hypothesize that Adamts13-/- mice, who exhibit hyper-thrombotic phenotypes, can be restored to normal clotting states by infusion of ADAMTS13. Using the FeCl3 injury model in the mesentery artery of C57BL/6 mice, we have found that thrombus formation is accelerated in injured arteries of Adamts13-/- mice, and that Infusion of ADAMTS13 in Adamts13-/- mice prolongs the occlusion time in FeCl3 induced mesentery artery injury. Both the time required for formation of a thrombus and the occlusion time of the vessel are restored to within 80% of the normal value. To determine the composition and morphology Adamts13-/- mice thrombi, we developed a method to examine thrombi after FeCl3 injury before and after injection of ADAMTS13 and variants using electron microscopy. Preliminary analysis indicates that normal thrombi appear to be well-formed and fibrin-rich, whereas Adamts13-/- mice exhibit thrombi with multiple malformations and areas enriched with platelets and erythrocytes (less apparent fibrin). ADAMTS13 appears to be sufficient for proteolytic cleavage of VWF, offering systemic protection of mice against FeCl3-induced arterial thrombosis. An apparent difference in composition of thrombi necessitates study on the formation dynamics as a function of time and with infusion of ADAMTS13 and truncations to determine whether normal thrombus formation can be restored. This analysis of thrombi–along with subsequent studies–will allow us to understand the mechanisms of normal thrombosis, which may then be applied to microgravity studies using a rotating wall vessel bioreactor system to simulate microgravity environments. The results of this subsequent work should help establish potential susceptibilities and determine the mechanistic basis of thrombotic disorders observed in post-flight cardiovascular dysfunction.