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“Protein S signaling: a potential target to prevent cardiac arrest induced pulmonary and atrial emboli.”

Abstract

Objective: Clot retraction is vital for hemostasis. Aberrant clot retraction increases the risk of pulmonary embolism, stroke, heart attack, and even cardiac arrest. Our data suggest that Protein S (PS), an anticoagulant, is required for clot retraction. We hypothesize that Protein S binds to a family of Tyrosine Kinase (Tyro3, Axl, and Mer) Receptors (TAM receptors) and induces signaling pathways to initiate clot retraction. Our objective is to identify the mechanism of how PS-binding to TAM receptors regulates clot retraction.

Method: Blood from healthy volunteers was collected in citrated tubes and platelet-rich plasma (PRP) was prepared. Clotting was initiated by adding 50 μ l thrombin (20 unit/ml) to a tube with 745 μ l Tyrode-HEPES Buffer, 200 μ l PRP, and 5 μ l red blood cells. Anti-Protein S antibodies (300 nM) were added to 6 tubes to deplete PS. To achieve a known concentration, PS was added to 300 nM to 6 tubes of platelets re-suspended in PS deficient plasma. Images and weights of the clots were taken as a function of time to measure the retraction rate. Apoptotic-like pathway induction was analyzed by immunoblots probed for p53, phosphorylated p53, and HSP27.

Results: Compared with the control sample, addition of PS to PRP promoted clot retraction. Conversely, clot retraction was delayed by the addition of anti-PS antibody. Accordingly, clot weights gradually decreased with time when the clots retracted in the presence of 300 nM PS. These data indicated that PS promoted clot retraction. To determine the PS-mediated mechanism of clot retraction, we dissolved clots formed in the presence and absence (\pm anti-PS antibody) of PS and subjected the samples to immunoblotting. We found that the amount of phosphorylated p53 and HSP27 decreased when the clot was retracted in the presence of PS

Conclusion: Our data support a critical function of Protein S in promoting clot retraction. Thus, Protein S is a key factor that prevents stroke and cardiac arrest that can result from impaired clot retraction.