The Centre for Blood Research

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1:30pm
in LSC3

Life Sciences Centre
2350 Health Sciences Mall

"Caught in the middle: The diverse roles of activated TAFI in Coagulation, fibrinolysis and inflammation"

TAFIa (activated thrombin-activatable fibrinolysis inhibitor) is a plasma carboxypeptidase B-like enzyme that removes C-terminal basic residues from plasmin-modified fibrin and anaphylatoxins, C3a and C5a. The physiological role of TAFI was assumed to be in clot maintenance and clot stability which ultimately promotes hemostasis. The lack of an overt bleeding phenotype in the TAFI knockout mouse, however, has led many to reconsider the physiological role of TAFIa, if it has one, during normal hemostasis. We have elucidated the kinetics of lysine cleavage from plasmin-modified fibrin by TAFIa. In doing so, we have clarified the mechanism of fibrin cleavage by TAFIa. The relatively high catalytic efficiency of lysine removal from fibrin by TAFIa suggests that it might competitively inhibit anaphylatoxin inactivation by TAFIa. Hemostasis requires that a delicate balance between coagulant and fibrinolytic events be achieved. In bleeding pathologies, such as hemophilia, thrombin generation and the quality of fibrin are significantly impaired thus disrupting the balance between coagulation and fibrinolysis.

We have observed that the severity of bleeding in hemophilia is significantly and negatively correlated with the extent of TAFI activation. This suggests that TAFI may be targeted to stabilize fibrin thus promoting hemostasis by restoring the balance between coagulant and fibrinolytic processes. We have determined the extent to which TAFI activation is decreased in hemophilia and show that enhancing TAFI activation with Solulin, a thrombomodulin analogue, increases clot strength and stability ex vivo in hemophilia patient blood and in vivo/ex vivo in canine hemophilia. All together, our data suggest that TAFIa is an active player in abnormal hemostasis and its well-characterized role as an anti-fibrinolytic in normal or pro-coagulant states may have downstream consequences in inflammation.

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Host: Dr. Ed Conway, CBR Director, Professor of Medicine, UBC

Refreshments will be served 10 minutes before the seminar
Seminar information: 604 822 7407