CBR

The Centre for Blood Research Seminar Series

Wednesday, January 13, 2016
LSC 3 - Life Sciences Centre
2350 Health Sciences Mall
12-1pm

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"Mechanism of Thrombin Activable Fibrinolysis Inhibitor Activation and Its Influence on Clot Degradation"

Fibrinolysis is triggered when activators such as t-PA convert plasminogen to plasmin, the main enzyme that breaks down fibrin clots. Fibrin matrix acts as a cofactor in plasminogen activation, thus enhancing its own degradation. This process is enhanced even further by the initial digestion of fibrin as the proteolytic cleavage generates new carboxyl-terminal lysine residues; additional sites to which plasminogen and t-PA can bind. This feedback is regulated by activated thrombin activable fibrinolysis inhibitor (TAFIa), which down-regulates fibrinolysis by removing these newly exposed lysine residues and decreasing the cofactor activity of fibrin. While TAFI can be activated by thrombin and plasmin, thrombin complexed with thrombomodulin (T-TM) is thought to be the physiologically relevant activator. The mechanism of how TM enhances the activation process, however, still remains unclear. By analyzing TAFI structure, we identified the activation peptide region of TAFI to be important for the expression of TM cofactor activity towards TAFI activation. Specifically, we have identified the triple lysine residues at positions 42, 43, and 44 to be important for TAFI activation. By altering the number of lysine residues through point mutation, we were able to modulate TAFI activation rates. Similarly, by using synthetic peptides that mimic this region of TAFI, we were able to inhibit and modulate TAFI activation in a lysine-dependent manner. The functional importance of these residues was then investigated in a clot lysis model, where once again, we were able to modulate the extent of clot lysis based on the number of lysine residues. Thus, these lysine residues of TAFI are the key residues involved in expressing TM-dependent cofactor activity during TAFI activation by thrombin.

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