

Wednesday, September 25, 2019

LSC 3 | 1:00 - 2:00PM



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“Hepatocyte tPA: From Liver to Blood and Beyond”

Fibrinolysis is initiated by tissue plasminogen activator (tPA) and inhibited by its serpin inhibitor PAI1. The balance of tPA and PAI1 is critical for preventing excessive clotting without compromising hemostasis. Despite an increase in plasma tPA protein, obesity lowers blood tPA activity and fibrinolysis, but the mechanism is unknown. We have shown in lean mice that hepatocytes contribute substantially to basal plasma tPA and fibrinolysis and that hepatocyte tPA expression is repressed by DACH1 (Zheng Z. et al, *Blood*, 2019). Moreover, liver DACH1 correlates with body mass index in humans and body weight in mice, suggesting a possible mechanism that limits tPA in obesity. In humans, tPA activity in plasma and liver was negatively correlated with liver DACH1, consistent with liver DACH1 as a negative regulator of tPA.

An imbalance of hepatocyte PAI1 and tPA contributes to decreased systemic fibrinolysis in obesity. However, the fibrinolysis defect in obesity is limited by a novel compensatory pathway in which PAI1, increases hepatocyte tPA expression by activating a LRP1-CREB1 pathway. Therapeutic boosting of this compensatory pathway, inhibition of the DACH1-tPA repression pathway, and/or inhibition of hepatocyte PAI1 expression may provide novel means to restore fibrinolytic balance in obesity.

Please note that due to some technical difficulties we are unable to webcast this seminar.