



Wednesday, April 25, 2018

LSC 3 | 12:00 - 1:00PM

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"Fibrin mediates metabolic changes that promote diet-induced obesity"

Obesity promotes a chronic inflammatory and hypercoagulable state that drives cardiovascular disease, type 2 diabetes, fatty liver disease, and several cancers. Association studies in humans suggest the thrombin-fibrin(ogen) axis is linked to exacerbation of obesity-driven 'metabolic inflammation', but specific mechanisms remain largely undefined. Fibrin(ogen) has been shown to promote pro-inflammatory activity through engagement of the leukocyte integrin receptor $\alpha_{\text{M}\beta_2}$ /Mac-1. $\text{Fib}^{\text{390-396A}}$ mice carrying a mutant form of fibrinogen incapable of binding leukocyte $\alpha_{\text{M}\beta_2}$ -integrin revealed these animals were significantly protected from high fat diet (HFD)-induced weight gain and elevated adiposity. HFD-fed $\text{Fib}^{\text{390-396A}}$ mice had markedly diminished systemic, adipose, and hepatic inflammation with significantly reduced macrophage counts within white adipose tissue, as well as near complete protection from development of fatty liver disease and glucose dysmetabolism. Indirect calorimetry revealed significantly elevated energy expenditure in HFD-challenged $\text{Fib}^{\text{390-396A}}$ mice compared to HFD-challenged wildtype mice. Notably, NMR-based metabolomic analyses of plasma, white adipose tissue, and liver indicated a prominent shift in glucose, glucose derivatives and other metabolites associated with development of obesity and hepatic steatosis. In separate experiments, mice were treated with the direct thrombin inhibitor dabigatran etexilate (DE), and DE treatment limited HFD-induced obesity development. In rescue experiments, DE suppressed progression of sequelae in mice with established obesity. Collectively, these data provide the proof-of-principal that targeting thrombin or fibrin(ogen) may limit pathologies in obese patients.

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