Fibrin mediates metabolic changes the promote diet-induced obesity

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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. White adipose tissue (WAT) and liver from mice fed a high fat diet (HFD) and obese patients revealed extensive extravascular fibrin deposits that were not observed in control diet (CD)-fed mice or healthy patients. To determine the role of fibrinogen in promoting obesity, mice expressing fibrinogen variants were fed either a CD or HFD for 20 weeks. FibΔΕK mice that express a mutant form of fibrinogen ‘locked’ in the monomeric form gained less weight and were protected from fatty liver disease following HFD-challenge than wildtype mice. This suggests fibrin polymerization is a key mechanism driving obesity and associated pathologies. Further, Fibγ³⁹⁰–³⁹⁶A mice, that express fibrinogen with a mutated FXIII and β2 integrin binding motif, gained less weight and developed significantly diminished obesity-associated inflammation, reduced macrophage accumulation in the WAT, and were protected from fatty liver disease and changes in glucose dysmetabolism. Indirect calorimetry revealed significantly elevated energy expenditure in HFD-challenged Fibγ³⁹⁰–³⁹⁶A 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. Collectively, these data provide the proof-of-principle that targeting fibrin(ogen) may limit pathologies in obese patients.

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