Obesity Inhibits Angiogenesis Through TWIST1-SLIT2 Signaling

Authors: Tendai Hunyenyiwa, Kathryn Hendee, Kienna Matus, Priscilla Kyi, Tadanori Mammoto, and Akiko Mammoto

Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI

Angiogenesis is required for functional adipose tissue remodeling and expansion. Physiologically balanced adipogenesis and angiogenesis are inhibited in subcutaneous adipose tissue in obese humans. Transcription factor TWIST1 controls angiogenesis and vascular function. TWIST1 expression is lower in obese adipose tissues. However, the role of endothelial TWIST1 in the impairment of angiogenesis in obese adipose tissue remains unclear. Here we found that the levels of TWIST1 and the guidance molecule SLIT2 that also controls angiogenesis are lower in endothelial cells (ECs) isolated from obese (BMI >30) human subcutaneous adipose tissues compared to that from lean (BMI <30) individuals. Overexpression of TWIST1 restores SLIT2 expression in obese adipose ECs. Angiogenic activities such as EC migration and DNA synthesis are inhibited in obese human subcutaneous adipose ECs compared to lean adipose ECs, while TWIST1 overexpression restores the effects. When we examine the effects of obesity on vascular formation using subcutaneous implantation of fibrin gel supplemented with lean vs. obese human ECs on mice, obese adipose ECs inhibit blood vessel formation in the gel. Overexpression of TWIST1 in obese ECs restores blood vessel formation in the gel, while SLIT2 knockdown inhibits the effects. These findings suggest that obesity impairs adipose tissue angiogenesis through TWIST1-SLIT2 signaling. Modulation of TWIST1-SLIT2 signaling in ECs could be a novel therapeutic strategy for obesity and obesity-associated diseases.