Reprogramming of PPARγ super-enhancers during browning of human adipocytes

Susanne Mandrup

Department of Biochemistry and Molecular Biology, University of Southern Denmark

The emergence of brown in white (brite)/beige adipocytes in white adipose tissue (WAT) is associated with protection against obesity and metabolic dysfunctions in rodents. Recent results indicate that brite adipocytes also play an important role in human energy metabolism, and strategies to induce such browning in humans therefore hold promise as future means to alleviate obesity. Using genome-wide technologies we have investigated the transcriptional processes underlying browning of human multipotent adipose-derived stem cells (hMADS). Rosiglitazone-induced browning of these cells activates a comprehensive gene program that is linked to increased mitochondrial function. Once induced this gene program is maintained independently of rosiglitazone, suggesting that additional browning factors are activated. Browning is associated with reprogramming of PPARγ binding to form brite-selective PPARγ super-enhancers that appear to play a major role in activation of key brite-selective genes. Based on the association with a brite-selective PPAR super-enhancer, we have identified an evolutionarily conserved metabolic regulator, KLF11, as a novel browning transcription factor in human adipocytes required for rosiglitazone-induced

browning. KLF11 is directly induced by PPARγ and appears to cooperate with PPARγ in a feed forward manner to activate and maintain the brite-selective gene program.