Therapeutic Remodeling of Adipose Tissue

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The ongoing pandemic of obesity has increased the need to develop new therapeutic targets to counteract this disease and other obesity-related metabolic diseases. Obesity is characterized by abnormal accumulation of adipose tissue, and adipose tissue dysfunction is one of the risk factors associated with a high incidence of metabolic diseases. However, therapeutic strategies to specifically target adipose tissue catabolic metabolism have not been fully established yet. Adipose tissue is a major metabolic organ that can be subdivided into the following two types: white adipose tissue (WAT); and brown adipose tissue (BAT). WAT stores and mobilizes lipids to maintain energy homeostasis, and BAT is responsible for non-shivering thermogenesis. Importantly, recent studies have demonstrated that adipocytes exhibit drastic plasticity with respect to anabolic and catabolic phenotypes. Reduction in BAT mass and activity has been associated with aging and obesity in rodent models and humans. There is accumulating evidence suggesting that interventions to enhance BAT and mitochondrial mass/function in adipocytes lead to the improvement of systemic metabolic function and insulin sensitivity. Our recent work demonstrated that STK3/STK4 (MST2/MST1) are key physiological suppressors of mitochondrial capacity in brown, beige, and white adipose tissues. Genetic inactivation of STK3/STK4 increases mitochondrial mass and function, stabilizes uncoupling protein 1 in beige adipose tissue, and confers resistance to metabolic dysfunction induced by high fat diet feeding. STK3/STK4 expression levels are elevated in human obesity and pharmacological inhibition improves metabolic profiles in a mouse model of obesity, suggesting STK3/STK4 as potential targets for treating obesity-related diseases.