Class IIa histone deacetylase control of muscle metabolism

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In type 2 diabetes, skeletal muscle displays transcriptional and metabolic remodeling that is thought to contribute to impaired oxidative metabolism, lipid accumulation and insulin resistance. The molecular mechanisms contributing to this response are, however, unknown. Here we present evidence to suggest that the class IIa histone deacetylases (HDACs) are key regulators of muscle metabolism that contribute to the transcriptional and metabolic remodeling seen in type 2 diabetes. The class IIa HDAC family members HDAC4 and 5 are increased in skeletal muscle of diabetic mice. Increasing HDAC4 and 5 expression in muscle cells phenocopies muscle in the diabetic state, including reduced metabolic and mitochondrial gene expression, impaired oxidative metabolism, lipid accumulation, insulin resistance and metabolic inflexibility. Conversely, genetic ablation of class IIa HDAC activity in the skeletal muscle of diabetic mice enhances skeletal muscle metabolic gene transcription and insulin action, and reduces lipid accumulation.

As no current diabetes therapies target skeletal muscle metabolism, we sought to determine whether HDAC inhibition could be an effective therapy to normalize muscle metabolism in metabolic disease states. After small scale *in vitro* screening of a number of HDAC inhibitors, each with different inhibitory properties towards different HDAC isoforms, for their ability to enhance metabolic gene expression and metabolism, we selected Scriptaid for further *in vivo* studies. Daily Scriptaid treatment in chow and diet-induced obese mice enhanced exercise performance, metabolic gene expression and insulin action, and reduced lipid accumulation in skeletal muscle. Scriptaid also reduced obesity-induced cardiac hypertrophy and normalized cardiac function. At a whole body level, Scriptaid enhanced energy expenditure, but had no effect on whole body glucose tolerance, due to hepatic insulin resistance.

Following from these studies, we sought to determine the functional advantage for increasing skeletal muscle class IIa HDACs in diabetes. Comparative transcriptomics from cells overexpression HDAC4 and 5 and the skeletal muscle of diabetic mice in which these HDACs are increased revealed significant suppression of a gene set involved in apoptosis. Experiments in muscle cells over expressing HDAC4 and 5 showed that these cells are resistant to apoptosis and cell death in response to apoptosis agents and metabolic insults that are thought to mediate metabolic dysregulation in diabetes, such as saturated fatty acids and inflammatory cytokines. We also show that regulation of metabolism and protection from apoptosis by the class IIa HDACs occurs via distinct enzymatic functions. We are currently designing novel small molecules that exploit this divergence in class IIa HDAC function to enhance metabolism, without altering muscle cell sensitivity to apoptosis, as a novel potential therapeutic strategy to normalize muscle metabolism in type 2 diabetes.