Histone modifications and skeletal muscle metabolic gene expression

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Skeletal muscle oxidative capacity plays an important role in human health and performance. Impaired oxidative capacity has been implicated in contributing to the development of insulin resistance and type 2 diabetes (Mootha *et al.,* 2001). Skeletal muscle oxidative capacity is also a key determinant in endurance exercise performance, and is chiefly determined by the expression levels of a broad set of metabolic and mitochondrial enzymes, which are largely regulated at the level of transcription.

Gene transcription is highly dependent on local chromatin structure, which is related to post translational modifications of the histone proteins that form the nucleosome core. Many histone modifications have been characterised, including acetylation, methylation, ubiquitination and phosphorylation (Berger, 2007). The greatest challenge for the area of genetics in the post genome sequencing era will be to determine how these modifications interact to regulate gene expression. However, it is generally recognized that acetylation of lysine residues within histone 3 are required for transcriptional initiation (Guenther *et al.,* 2007). Histone acetylation neutralizes the positive charge carried by lysine residue side chains, thereby breaking the electrostatic interaction between histones and the negatively charged phosphate backbone of DNA. This results in unraveling of the local chromatin, allowing transcriptional regulators such as the transcription initiation complex access to DNA promoter regions. Histone acetylation is regulated by the balance in activities between histone acetyl transferase and histone deacetylase (HDAC) enzymes (McKinsey *et al.,* 2001).

Using cell systems expressing either wild type or deacetylase defective HDAC4 and 5, we have showed that the class IIa HDACs regulate the expression of metabolic and mitochondrial enzymes involved in glucose and lipid transport and substrate oxidation. As compromised oxidative capacity has been implicated in contributing to peripheral insulin resistance, we are currently testing the hypothesis that pharmacological inhibition of HDACs might protect against diet-induced insulin resistance. *In vivo*, inhibition of HDAC repressive function is regulated by either phosphorylation dependent nuclear export or ubiquitin mediated proteasomal degradation. We have recently found that the AMP activated protein kinase (AMPK) is a HDAC5 kinase. In addition, we have also found that considerable redundancy exists between AMPK and protein kinase D in signaling to HDAC5 under conditions of cellular stress. Finally, we have evidence implicating heat shock protein 70 (HSP70) in mediating proteasomal degradation of the class IIa HDACs. Importantly, HSP70 is dysregulated in insulin resistance and type 2 diabetes and through the class IIa HDACs could contribute to the oxidative dysfunction seen in these diseases.

Together, these data suggest that the class IIa HDACs are key regulators of metabolic and mitochondrial gene expression in skeletal muscle and that these enzymes could be potential therapeutic targets for the treatment of diseases such as insulin resistance and type 2 diabetes. Understanding the regulation of these enzymes will uncover mechanisms regulating oxidative capacity.

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