One more trick in the regulation of PGC-1α

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PGC-1α is a transcription coactivator centrally involved in the regulation of energy balance and metabolism. A recent study in Cell Metabolism adds another role for Pgc-1α, namely gene regulation in mitochondrial maintenance and metabolic homeostasis. The latest findings indicate significant increases in levels of DNA methylation within the promoter region of the Pgc-1α gene within human skeletal muscles from subjects with impaired glucose tolerance or type 2 diabetes. The significance and implications of this discovery are discussed.

PGC-1α is a transcription coactivator of functional importance in the regulation of metabolism and other biological processes (1-4). A recent study by Barrès et al. in Cell Metabolism points to another new role of the Pgc-1α gene regulation in mitochondrial maintenance and metabolic homeostasis (5). The results showed significant increases of DNA methylation within the promoter region of the Pgc-1α gene in human skeletal muscles from subjects with impaired glucose tolerance or type 2 diabetes. Increased DNA methylation was detected in the promoter region between -337 and -37 from the transcription start site containing the consensus binding site for CREB and ATF2 transcription factors. Of particular note is that the enhanced methylation occurred primarily at non-CpG sites, which in turn led to reduced Pgc-1α transcription and mitochondrial density. The investigators further demonstrated that treatment of human skeletal muscle culture with free fatty acids and tumor necrosis factor-α (TNF-α) for 48 hours reproduced the hypermethylation
of the Pgc-1α promoter through DNA methyltransferase 3B (DNMT3B).

The experiment that demonstrated the direct link between levels of DNA methylation and Pgc-1α transcription was the reduced reporter gene activity in transfected muscle cells following in vitro methylation of the promoter at the CpG site at –260. Although mutation of each or all of the non-CpG sites to prove the importance of non-CpG methylation may not be technically feasible, pharmacological inhibition and promotion of methylation could be employed in cultured myocytes to address this important issue. Precedents have been set in studies in which maternal nutrient supplementation altered fetal epigenome and the coat color of the offspring and their susceptibility to obesity and type 2 diabetes (6,7). It would of great interest to know if dietary interventions would result in changes in non-CpG methylation in the Pgc-1α gene, which is responsible for the adult disease susceptibility phenotype, whereas methylation of the CpG sites within the Aγ intracisternal A particle (IAP) retrotransposon of the Agouti gene is known to be responsible for the agouti color coat phenotype. A genetic approach to alter the level of expression or enzymatic activity of DNMT3B within skeletal muscle may also provide additional functional information regarding the epigenetic regulation of the Pgc-1α gene in vivo. Hypermethylation at non-CpG sites within the Pgc-1α promoter appeared to occur rapidly during the methylation process, which questions the long-term impact and significance of non-CpG methylation. This issue is not only relevant in cultured cell models where DNA methylation and its impact upon gene expression may be assessed following withdraw of the stimulus, but also in the situation where its impact may persist over generations in animal models and humans.

Previous studies have revealed a great diversity in the regulation of PGC-1α function in decoding various cellular signals and controlling the phenotypic characteristics of various organ systems. For example, PGC-1α activity has been shown to be regulated by post-translational modification through phosphorylation (8), methylation (9), SUMOylation (10), and deacetylation (11). The Pgc-1α gene is also regulated at the transcriptional level by transcriptional control with an auto-regulatory loop (12). Functionally, reduced Pgc-1α gene expression has been shown to be associated with conditions of insulin resistance and type 2 diabetes (13), and a missense mutation of the Pgc-1α gene that leads to reduced expression of PGC-1α has been shown to be correlated with type 2 diabetes in certain populations (14-17). More recently, attentions have been directed toward epigenetic regulation of the Pgc-1α gene (5,18,19). The fact that variants of the Pgc-1α gene were only correlated with type 2 diabetes in certain population may suggest an environment-gene
interaction in the development of complex diseases in which genetic variation and environmental factors both contribute to the pathogenesis. Our challenge is not only to figure out how to apply this knowledge, but also to be prepared to learn of and from the ‘tricks’ inherent within our biological system to enable us to treat and prevent complex disease such as type 2 diabetes mellitus.

References


