A fundamental system of cellular energy homeostasis regulated by PGC-1α

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Maintenance of ATP levels is a critical feature of all cells. Mitochondria are responsible for most ATP synthesis in eukaryotes. We show here that mammalian cells respond to a partial chemical uncoupling of mitochondrial oxidative phosphorylation with a decrease in ATP levels, which recovers over several hours to control levels. This recovery occurs through an increased expression of the transcriptional coactivator peroxisome proliferator-activated receptor-coactivator 1α (PGC-1α) and mitochondrial genes. Cells and animals lacking PGC-1α lose this compensatory mechanism and cannot defend their ATP levels or increase mitochondrial gene expression in response to reduced oxidative phosphorylation. The induction of PGC-1α and its mitochondrial target genes is triggered by a burst of intracellular calcium, which causes an increase in cAMP-response-element-binding protein and transducer of regulated cAMP-response-element-binding proteins actions on the PGC-1α promoter. These data illustrate a fundamental transcriptional cycle that provides homeostatic control of cellular ATP. In light of this compensatory system that limits the toxicity of mild uncoupling, the use of chemical uncoupling of mitochondria as a means of treating obesity should be re-evaluated.

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