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Acetyl-CoA as a Link between Metabolism, Chromatin and Gene Expression

Ales Vancura* and **Ivana Vancurova**
St. John's University, USA

Histone acetylation is a dynamic modification that affects chromatin structure and regulates diverse cellular functions, such as gene expression, DNA repair and cell proliferation. Perturbation of the balanced action of his tone acetyl transferases (hats) and histone deacetylases (hdacs) alters the expression pattern of genes involved in cellular growth, resulting in tumor genesis. Histone acetylation depends on intermediary metabolism for supplying Acetyl-CoA in the nucleocytosolic compartment. Acetyl-CoA is thus a key metabolite at the crossroads of metabolism, chromatin structure and transcriptional regulation. Our results show that decreased synthesis of nucleocytosolic acetyl-CoA in yeast leads to histone hypoacetylation, decreased expression of histone genes, decreased nucleosome occupancy, globally altered chromatin structure and altered transcriptional regulation. In addition, decreased expression of histones or a defect in nucleosome assembly result in increased mtDNA copy number, oxygen consumption, ATP synthesis and expression of genes encoding enzymes of the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS). This represents a novel signaling mechanism, where by decreased histone transcription and globally altered chromatin structure triggers mitochondrial respiration and increased synthesis of ATP. The metabolic shift from fermentation to respiration induced by altered chromatin structure is associated with induction of the retrograde pathway and requires the activity of the Hap2/3/4/5p complex as well as synthesis of theme. Together, our data indicate that altered chromatin structure relieves glucose repression of mitochondrial respiration by inducing transcription of the TCA cycle and OXPHOS genes encoded by both nuclear and mitochondrial DNA.

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Biography:

Ales Vancura, Ph.D., is a Professor of Biological Sciences and Chairman of the Department of Biology at St. John's University in New York. Dr. Vancura is the author of more than 60 peer-reviewed publications. His research focuses on understanding of the interdependency between metabolism, chromatin structure and transcriptional regulation. One of the current research efforts in his laboratory is directed at the role of chromatin structure in regulation of mitochondrial biogenesis and respiration. Dr. Vancura has trained many doctoral and undergraduate students and his research is funded by the National Institutes of Health.