REGULATION OF MITOCHONDRIAL BIOENERGETIC FUNCTION BY SIRT3-MEDICATED POST-TRANSLATIONAL PROTEIN MODIFICATIONS IN HUMAN CELLS

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Introduction: Sirt3-mediated lysine acetylation is a new type of regulation of enzyme function, but where and how acetylation affects mitochondrial function and oxidative metabolism is not fully understood. (27)

Objectives: To explore how Sirt3 regulates mitochondrial function, we analyzed the acetylation levels of respiratory enzymes in human cells harboring mtDNA mutation by immunoprecipitation, immunoblotting and proteomics. (26)

Methods: Acetylation of lysine residues on mitochondrial enzymes was identified by mass spectrometry. Moreover, Sirt3 was knocked down in human cells by shRNA to examine the effect of Sirt3 deficiency on the acetylation levels of the oligomycin sensitivity conferring protein (OSCP) of F⁰F¹ATPase and pyruvate dehydrogenase. (45)

Results: We showed that Sirt3 interacts with OSCP and leads to its subsequent deacetylation and activation of F⁰F¹ATPase. Loss of Sirt3 decreased the activity of F⁰F¹ATPase and respiratory function, and compromised metabolism of 143B cells. Importantly, we proved that increased intracellular reactive oxygen species impaired Sirt3 regulation of F⁰F¹ATPase by reducing Sirt3 in human cells harboring 85% mtDNA with 4977 bp deletion that causes CPEO syndrome. On the other hand, we found that the expression levels of Sirt3 and pyruvate dehydrogenase activity were decreased in human cells carrying the MERRF-associated A8344G mutation of mtDNA. The protein level of Sirt3 was decreased with the increase of mtDNA with A8344G mutation. Interestingly, we found that Sirt3 expression was down-regulated in mutant cybrids due to increase in the intracellular levels of hydrogen peroxide. In addition, the Sirt3 level and pyruvate dehydrogenase activity were concomitantly increased by addition of N-acetylcyesteine to mutant cybrids. (148)

Conclusion: These findings suggest that oxidative stress is involved in the pathophysiology of CPEO and MERRF syndromes, respectively, via the regulation of Sirt3-mediated deacetylation and that the bioenergetic functions of mitochondria can be recovered by antioxidants through upregulation of Sirt3 in the therapy of mitochondrial diseases caused by mtDNA mutations. (49)

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Key Words
Sirt 3, Deacetylation, Mitochondria