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Metabolic reprogramming of human cells in response to oxidative stress: implications in the pathophysiology and therapy of mitochondrial diseases.

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Abstract

Mitochondria are the organelles producing most of the energy and play important roles in a variety of biochemical functions in human cells. Mitochondrial defects can cause ATP deficiency and overproduction of reactive oxygen species, which are the major hallmarks of mitochondrial diseases. Abundant evidence has suggested that mitochondrial dysfunction-elicited oxidative stress can play an important role in the pathogenesis and progression of mitochondrial diseases. Mitochondria can respond to energy deficiency by the retrograde signaling to trigger a number of molecular events to help the human cells to cope with physiological or environmental changes. In this article, we first describe oxidative stress-induced cellular responses including metabolic adaptation, compensatory increase of mitochondrial biogenesis, upregulation of antioxidant enzymes, and alteration of protein acetylation in human cells with mitochondrial dysfunction. In this regard, we review recent findings to elucidate the mechanisms by which human cells motivate their mitochondria and the antioxidant defense system to respond to energy deficiency and oxidative stress, which contribute to the adaptive metabolic reprogramming in mitochondrial diseases. In addition, we emphasize the critical role of the activation of AMPK, Sirt1 and Sirt3 in the metabolic adaptation of human cells harboring mitochondrial DNA mutations. Recent studies have revealed that AMPK and sirtuins-mediated signaling pathways are involved in metabolic reprogramming, which is effected by upregulation of antioxidant defense system and mitochondrial protein acetylation, in human cells with mitochondrial dysfunction. Finally, we discuss several potential modulators of bioenergetic function such as coenzyme Q10, mitochondria-targeting antioxidants, resveratrol, and L-carnitine based on recent findings from studies on human cells and animal models of mitochondrial diseases. Elucidation of the signaling pathway of this adaptive response to oxidative stress triggered by mitochondrial dysfunction may enable us to gain a deeper insight into the communication between mitochondria and the nucleus and guide us to develop novel therapeutic agents for effective treatment of mitochondrial diseases.

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