Critical role of AMP-activated protein kinase in the balance between mitophagy and mitochondrial biogenesis in MELAS disease

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Abstract

MELAS syndrome is a mitochondrial disorder that is caused mainly by the m.3243A>G mutation in mitochondrial DNA. Here, we report on how the severity of pathophysiological alterations is differently expressed in fibroblasts derived from patients with MELAS disease. We evaluated mitophagy activation and mitochondrial biogenesis which are the main mechanisms regulating the degradation and genesis of mitochondrial mass in MELAS fibroblasts and transmitochondrial cybrids. Our results suggest a critical balance between mitophagy and mitochondrial biogenesis which leads to the expression of different degrees of pathological severity among MELAS fibroblasts cell lines according to their heteroplasmy load and the activation of AMP-activated protein kinase (AMPK). AMPK-activators such as 5-aminoimidazole-4-carboxamide 1-β-D-ribofuranoside (AICAR) or coenzyme Q10 (CoQ) increased peroxisome proliferator-activated receptor alpha (PGC-1α) nuclear translocation, mitochondrial biogenesis, antioxidant enzyme system response, autophagic flux and improved pathophysiological alterations in MELAS fibroblasts with the most severe phenotype. Our findings support the hypothesis that mitochondrial biogenesis, increased antioxidant response and autophagy clearance serve as compensatory mechanisms in response to mitophagic degradation of dysfunctional mitochondria and point out that AMPK is an important player in this balance.

