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MITOCHONDRIAL DISEASE: FROM MECHANISMS TO THERAPY

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Mitochondrial diseases are a large family of extremely heterogeneous disorders genetically determined by mutations in either the nuclear genome or the mitochondrial DNA. Most of the mitochondrial disease genes are expressed in all cell types. However, in many conditions, some cell types are more affected than others. However, the reasons for this tissue-specificity remain poorly understood. To investigate the functional basis of the striking tissue-specificity in mitochondrial diseases, we analyzed several bioenergetic parameters, including oxygen consumption rates, Q redox poise, and reactive oxygen species production in mouse brain and liver mitochondria fueled by different substrates. In addition, we determined how these functional parameters are affected by electron transport chain impairment in a tissue-specific manner using pathologically relevant mouse models lacking either *Ndufs4* or *Ttc19*, leading to complex I or III defects, respectively. No cure is currently available for most of the mitochondrial diseases. We previously showed that the coordinated activation of autophagy, lysosomal biogenesis, and mitochondrial biogenesis by rapamycin, ameliorated the myopathic phenotype of a muscle-specific knockout mouse for *Cox15* (*Cox15sm*), encoding an enzyme involved in heme A biosynthesis. However, the role of mitophagy has been poorly investigated. We found that urolithin A, a direct mitophagy inducer, improved motor performance and myopathy in the *Cox15sm* mice, without increasing the activity of the respiratory chain complexes in a 10 week-treatment. These results indicate that activation of mitophagy can be a suitable treatment to ameliorate mitochondrial myopathies.