Persistent inhibition of mitochondrial biogenesis in Limb Girdle Muscular Dystrophy 2D: identification of nitric oxide-dependent salvage pathway

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Mitochondria are pivotal players in skeletal muscle bioenergetic and mitochondrial dysfunction has long been suspected to be an important pathogenetic feature in muscular dystrophies even if their role is not fully understood. In Limb Girdle Muscular Dystrophy (LGMD) the loss of Î± sarcoglycan (Î±-SG), as the loss of dystrophin or other components of the dystrophin-glycoprotein complex, leads to a severe alteration in the physical properties of the sarcolemmal and to mitochondria swelling and dysfunction triggering a 'metabolic crisis'. An important aspect in dystrophic skeletal muscle, including LGMD-2D, is the displacement of the muscle specific variant of the enzyme neuronal nitric oxide (NO) synthase (nNOSμ), usually localized at the sarcolemma in close contact with the sarcoglycan-dystroglycan complex, with reduced generation of NO. NO in skeletal muscle regulates metabolism and energy expenditure, coupling energy demand and supply, through a variety of actions. In addition, NO stimulates mitochondrial biogenesis regulates mitochondrial dynamics and contributes to muscle physiological growth and repair. Normalization of NO production slows disease progression in mouse models of muscular dystrophies and it is currently investigated in therapeutic perspective.
Here we characterize the mitochondrial profile of a mouse model of LGMD-2D, the Î±-SG null mice, finding out an impairment in the oxidative capacity of dystrophic muscles dependent on a reduced mitochondrial mass. Since defect of NO generation is a key pathogenic event in muscular dystrophies, we treated dystrophic animals with NO-donor Molsidomine to evaluate a possible impact on mitochondrial content and activity.
Of interest, long term treatment with Molsidomine do not affect mitochondrial biogenesis, but increases mitochondrial efficiency in dystrophic muscles, promoting oxidation of fatty acid and inducing a shift toward more oxidative muscle fiber types. Molsidomine acts as SIRT1 activator favoring deacetylation of PGC1Î± protein and inducing metabolic adaptation with activation of AMP-activated protein kinase.
These results highlight the important role of mitochondrial metabolism in muscular dystrophy; thus, we identify in Î±-SG null mice a NO-dependent salvage pathway able to overcome the persistent mitochondrial defects and explaining why NO donation has therapeutic effects in muscular dystrophies.