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Mitochondria and Cytoskeleton rearrangement in Drp1 overexpressing skeletal muscle

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In skeletal muscle mitochondrial fusion and fission define the mitochondrial network morphology regulating myofiber differentiation, muscle contraction and the response to stress conditions 1-3. Mitochondrial fission is mainly mediated by dynamin-related protein 1 (Drp1) which represents a critical player in myogenesis and its inhibition suppresses myotube formation 4-5.Our work is focused on a transgenic mouse overexpressing Drp1 specifically in skeletal muscle (Drp/MC). Drp/MC mice show growth defects starting from P7 mainly due to an impairment of glycolytic muscles development; indeed, in adult phase they display an overall 20% reduction of body weight and a drop of locomotor performance without any increasing in catabolic processes. Drp/MC mice exhibit low mitochondrial DNA levels which trigger mitochondrial stress and upregulate the unfolding proteins response (mtUPR) together with an impairment of Growth Hormone anabolic pathway. Interestingly, we observe a strong remodeling of mitochondria distribution with a depletion of inter-myofibrillar mitochondria and an enrichment of the sub-sarcolemmal pool. In parallel, we observe a perturbation of cytoskeleton framework characterized by the disruption of Desmin network (the main skeletal muscle intermediate filament connecting mitochondria to cytoskeleton) with the presence of Desmin aggregates inside myofibers and its accumulation beneath the sarcolemma. Moreover, in vivo time-lapse imaging of both skeletal muscle fibers and satellite cells-derived myotubes, indicates an increased mitochondrial mobility in Drp/MC mice; therefore, our aim is the evaluation of the role of different motor proteins, such as the kinesin (Kif5b and KLC1) and dynein, in the Drp/MC dysregulated muscular and mitochondrial phenotype.

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