Impact of Drp1 activation and fission induction in the pathogenesis of DMD progression

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Loss of function mutations in *DMD* gene encoding for dystrophin protein cause Duchenne Muscular Dystrophy (DMD) a severe progressive neuromuscular disease. Despite remarkable progress has been made in genetic approaches to restore dystrophin, or its function, new therapeutic strategies are needed. In this view, muscle weakness in DMD is thought to be dependent, at least in part, on damaged mitochondria and compromised bioenergetics.
Consistently mitochondria are an attractive target for therapeutic interventions. Dystrophic fibers show marked mitochondria fragmentation, however, few studies have addressed the relevance of mitochondrial shape in the muscle damage progression.
Accordingly, we generated a DMD mouse model with intrinsically fluorescent mitochondria, the *mdx*-PhAM mouse, to precisely define mitochondrial dynamics during DMD progression and we confirmed the existence of a less interconnected mitochondrial network in *mdx* single fibers by 3-dimensional reconstruction. In agreement, Western blot experiments showed a significant upregulation of pro-fission proteins, Drp1 and its receptors, in *mdx* muscles starting from 3 months of age, suggesting the shifting of mitochondrial dynamics towards Drp1-mediated mitochondrial fission. This can potentially contributes to DMD pathological fibrosis and inflammation by triggering the activation of specific signaling pathways, such as inflammation by DAMPs (mtDNA) release and UPR response.
Therefore, to assess the relevance of Drp1-dependent fission enhancement in DMD pathogenesis we treated *mdx* mice with MDIVI-1, a specific Drp1 inhibitor. We have obtained encouraging results as for muscle functionality and phenotype, thus confirming the relevance of Drp1 as a therapeutic target in DMD.