Increased mitophagy in the skeletal muscle of spinal and bulbar muscular atrophy patients

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Résumé en anglais	Spinal and bulbar muscular atrophy (SBMA) is a neuromuscular disorder caused by polyglutamine expansion in the androgen receptor (AR) and characterized by the loss of lower motor neurons. Here we investigated pathological processes occurring in muscle biopsy specimens derived from SBMA patients and, as controls, age-matched healthy subjects and patients suffering from amyotrophic lateral sclerosis (ALS) and neurogenic atrophy. We detected atrophic fibers in the muscle of SBMA, ALS and neurogenic atrophy patients. In addition, SBMA muscle was characterized by the presence of a large number of hypertrophic fibers, with oxidative fibers having a larger size compared with glycolytic fibers. Polyglutamine-expanded AR expression was decreased in whole muscle, yet enriched in the nucleus, and localized to mitochondria. Ultrastructural analysis revealed myofibrillar disorganization and streaming in zones lacking mitochondria and degenerating mitochondria. Using molecular (mtDNA copy number), biochemical (citrate synthase and respiratory chain enzymes) and morphological (dark blue area in nicotinamide adenine dinucleotide-stained muscle cross-sections) analyses, we found a depletion of the mitochondria associated with enhanced mitophagy. Mass spectrometry analysis revealed an increase of phosphatidylethanolamines and phosphatidylserines in mitochondria isolated from SBMA muscles, as well as a 50% depletion of cardiolipin associated with decreased expression of the cardiolipin synthase gene. These observations suggest a causative link between nuclear polyglutamine-expanded AR accumulation, depletion of mitochondrial mass, increased mitophagy and altered mitochondrial membrane composition in SBMA muscle patients. Given the central role of mitochondria in cell bioenergetics, therapeutic approaches toward improving the mitochondrial network are worth considering to support SBMA patients.
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