MTPHAGYTREAT - Study of the role of mitophagy and lysosomal biogenesis in COX deficiency: a new model for drug discovery

Mutations in COX15 are associated to cytochrome c oxidase (COX) deficiency (OMIM: 220110), a mitochondrial disease characterized by inefficient energy production due to the accumulation of impaired mitochondria. The phenotype of a muscle-specific Cox15 knockout (Cox15sm/sm), a model of severe mitochondrial myopathy characterized by profound COX deficiency, was previously shown to be ameliorated by the coordinated induction of autophagy and lysosomal biogenesis via TFEB activation. Stimulation of mitophagy, a selective degradation of mitochondria by autophagy, is one attractive possibility to induce the elimination of damaged mitochondria and be used as a broad-spectrum treatment for mitochondrial dysfunctions. However, the role of mitophagy in this mitochondrial dysfunction was not investigated in detail. To clarify the role of mitophagy in the amelioration of Cox15sm/sm mice phenotype and explore its therapeutic potential, a Cox15sm/sm mito-QC reporter mouse has been created in the host laboratory. Mito-QC, a pH-sensitive mitochondrial targeted probe, will allow to assess unambiguously mitophagy at single cell resolution by the quantification of the number of mitolysosomes in COX-deficient myocytes. Likewise, the investigation of the mitophagy role in muscle regeneration in the Cox15sm/sm mice can have a high impact in mitochondrial diseases. MTPHAGYTREAT will thus create a new myoblast model for the evaluation of autophagy/mitophagy role in muscle regeneration. In addition, we will take advantage of Cox15sm/sm myoblasts and advanced imaging techniques to fast track the discovery of new drugs for the treatment of mitochondrial diseases by screening a library of natural compounds previously shown to be safe for humans, thus facilitating the eventual translation to the patients.

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