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MAGIC - Targeting the pathological molecular mechanism behind axonal mitochondria depletion in ADOA retinal ganglion cells

Autosomal dominant optic atrophy (ADOA) is the most common form of hereditary optic neuropathy characterized by the progressive bilateral loss of vision. This rare disease affects 1:35,000 person worldwide for which no treatment exists. Symptoms appear in children aged 4-6 y/o and the care they require represent an emotional and financial burden on themselves, their caregivers and on the health system. This project therefore contributes to the European effort to advance research and develop treatments for ADOA which will materially improve the health and wellbeing of patients and alleviate the cost of care on health system. ADOA is associated with mutations in the nuclear gene encoding the mitochondrial protein Optic Atrophy 1 (Opa1) which affect primarily Retinal Ganglion Cells (RGCs). Upon RGC death, the optic nerve composed of RGC axons degenerates resulting in blindness. Prof. Scorrano's lab showed that Opa1 mutated RGCs exhibit excessive levels of autophagy with axonal hillock autophagosome accumulation and axonal mitochondria depletion, and that the loss of vision in an ADOA mouse model generated by Opa1 conditional deletion in RGCs was accompanied by the same abnormal features. Remarkably, genetic inhibition of excess autophagy rescues not only mitochondrial distribution but also vision in the ADOA mice. These data suggest that the axonal hillock accumulation of autophagosomes driven by autophagy hyperactivation creates a physical barrier preventing free mitochondrial traffic along axons. The molecular mechanisms behind this pathological cascade of events are, however, unclear. This proposal aims at (i) clarifying which proteins are involved in such cascade, (ii) whether their inhibition can decrease autophagy and curtail axonal mitochondrial depletion, and (iii) identifying FDA approved drugs which can rescue axonal mitochondrial content in ADOA RGCs, hence showing promising potential for ADOA treatment.