PHERADOA - Pharmacological therapy to curtail visual loss in ADOA mouse model

Autosomal dominant optic atrophy (ADOA) is the most common hereditary neuropathy that affects 1:35.000 people worldwide. A progressive visual loss is a characteristic of ADOA, and a treatment is not available. Mutations in the nuclear gene Optic Atrophy 1 (OPA1) in ADOA patients promote low levels of OPA1 protein, causing Retinal Ganglion Cells (RGCs) degeneration leading to blindness. OPA1 is the key component for mitochondrial inner membrane fusion mechanism and controls cristae biogenesis and remodeling, affecting cytochrome c release and apoptosis. So, mutations in OPA1 in RGCs may affect mitochondria integrity and lead to insufficient energy supply in the optic nerve. The role of OPA1 in ADOA-RGCs remains elusive since ADOA mouse models show inconclusive and no RGCs specific results. To address this issue, Dr. Luca Scorrano developed an ADOA mouse model of conditional RGCs OPA1 depleted. In this model, RGCs show fragmented mitochondria and excluded from axon but combined with autophagosomes in the axonal hillock. But a genetic autophagy inhibition restores mitochondrial distribution in the RGCs axon and curtails visual loss in the ADOA animal. These data suggest that autophagosome accumulation reduced axonal mitochondria content in RGCs by an impairment of the mitochondrial traffic. Therefore, we propose that visual loss of ADOA mouse model will be prevented by restoring its axonal mitochondrial content through a local use of inhibitors of the autophagy process. This proposal aims to develop a pharmacological therapy to curtail ADOA mouse visual loss. For this, we will deliver autophagy inhibitors through vitreal nanocarriers implants in ADOA mouse model which is conditional RGCs-OPA1 depleted. This research will contribute to provide a pre-clinical approach for a potential pharmacological therapy to ADOA patients.

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