Targeting necroptosis to halt neural retina degeneration in the hOPA1delTTAG mouse model of Dominant Optic Atrophy

Comunicación Oral

Neurobiología de enfermedades - Neurobiology of disease

Macarena S Arrázola [1], Concepción Panadero-Medianero [1], Alexandra Iribarren [1].

(1) Universidad Mayor, Center for Integrative Biology, Faculty of Sciences, Camino la Pirámide 5750, Santiago, Chile.

arrazola.ms@gmail.com

Dominant Optic Atrophy (DOA) is a hereditary optic neuropathy caused by mutations within *OPA1* gene. Degeneration of retinal ganglion cells (RGC) and optic nerve (ON) leads to progressive blindness in DOA, although the underlying mechanism remains unknown. We previously identified necroptosis as a key regulator of axonal degeneration. Upon activation, the necrosome complex (RIPK1-RIPK3-MLKL) assembles, triggering membrane permeabilization and disrupting organelles such as mitochondria. The mitochondrial phosphatase phosphoglycerate mutase 5 (PGAM5) interacts with RIPK3, recruiting the necrosome to mitochondria and promoting mitochondrial fragmentation via Drp1 dephosphorylation. Whether necroptosis contributes to DOA pathophysiology by promoting optic nerve atrophy and loss of vision has not been previously explored.

Using*ex vivo* and *in vivo* approaches, we evaluated necroptosis activation in the retina and ON of hOPA1*delTTAG* mice. Accumulation and interaction of phosphorylated-RIPK3 and PGAM5 were detected in OPA+/- retina and in axonal projections of retina explants. Neuronal RIPK3 knockdown, achieved via intravitreal delivery of an AAV-PHP.be-shRipk3 vector in OPA1+/- mice- effectively delayed axonal degeneration in the ON, prevented RGC loss, and improved visual function assessed by the mice optomotor response. Pharmacologic inhibition of RIPK3 or PGAM5 similarly prevented retinal degeneration in OPA1+/- mice. Our preclinical study reveals necroptosis as a druggable target for treating optic neuropathies such as DOA, with potential relevance for other retinal diseases characterized by early and prominent optic atrophy.

Financiamiento:

Fondecyt 11220120