Role of autophagy in retinal ganglion cell death following retinal ischemia in mice.

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Autophagy is an intracellular catabolic pathway responsible for degradation of cytosolic components through the autophagosomal-lysosomal system. Dysfunctional autophagy has been associated with alterated cellular homeostasis and neuropathological conditions. Retinal ganglion cells (RGCs) death is the cellular event responsible for the glaucoma-related visual field defect or blindness and is often associated with an increase of the intraocular pressure (IOP) that represent one of the main risk factors associated with the pathology. Recent studies described autophagic dysfunctions in several experimental models of glaucoma although their functional role is still debated.

Here we analyzed the expression of autophagy-related proteins (Atg) and the effect of autophagy modulation on RGCs survival following retinal ischemia/reperfusion, a common feature of ocular pathologies (i.e. glaucoma, anterior ischemic optic neuropathy and retinal vessels occlusion). Retinal ischemia was induced in C57BL/6J, GFP-LC3 transgenic and autophagy-deficient ($AMBRA1^{+/-}$) mice by acutely increasing the intraocular pressure and allowing the reperfusion for 1, 6 or 24 hours. Retinal ischemia induced a reduction of the autophagosome-associated form of LC3 (LC3II), while a significant accumulation of the protein was observed in the reperfusion phase. This event was associated with an initial decrease of the autophagic substrate p62 followed by a significant accumulation of the protein during the later phase of reperfusion suggesting a biphasic modulation of the autophagic pathway.

RGCs loss was increased in $AMBRA1^{+/-}$ mice, while treatment with the autophagy inducer Rapamycin improved RGC survival following retinal ischemia.

Altogether our data show that the balance of autophagic flux is altered under retinal ischemia/reperfusion injury and strengthen the hypothesis that pharmacological modulation of this pathway is a rational strategy for retinal neuroprotection.