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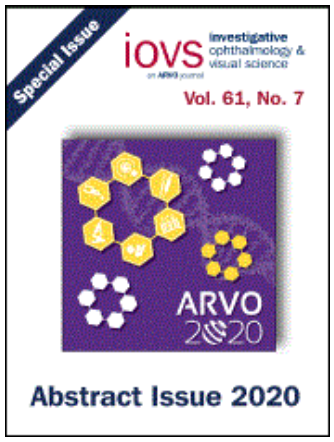

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Mechanism of Action of Risuteganib for Retinal Diseases through Protection of Retinal Pigment Epithelium (RPE) and Enhancement of Mitochondrial Functions

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Purpose : Risuteganib is a novel synthetic peptide that has advanced through Phase II clinical trials, showing promising efficacy in retinal diseases, including dry age-related macular degeneration (AMD) and diabetic macular edema (DME). This study is to explore the mechanism of action (MOA) of risuteganib by uncovering its functional target(s) and the associated cell layer.

Methods : Fluorescent staining of mouse and rat retinal cryo-sections was performed with risuteganib-dye conjugates and compared with control peptide. Protective effects against oxidative stress was studied in ARPE-19 cell line challenged with tert-Butyl Hydroperoxide (tBHP) using WST-1 assay and Caspase 3/7 apoptosis assay. Mitochondrial bioenergetics were measured using Seahorse XF cell mito stress test.

Results : Peptide-dye staining of animal retinal tissue indicated preferential localization of risuteganib in the RPE layer. 24hr risuteganib pretreatment significantly rescued ARPE-19 cells from tBHP-induced oxidative stress in WST-1 assay ($p<0.05$) and Caspase 3/7 apoptosis assay ($p<0.01$). Seahorse bioenergetics measurement of ARPE-19 cells showed that risuteganib dose-dependently enhanced mitochondrial basal, maximal and ATP-related respirations of RPE cells.

Conclusions : Oxidative stress is one of the hallmarks of retinal diseases AMD and DME, and is associated with impaired RPE function. The observations of preferential binding to RPE layers in retina and the protection of mitochondrial function in RPE cells against oxidative stress in vitro, suggest that the clinically observed therapeutic effect of risuteganib in dry AMD and DME may be associated with supporting RPE cells and maintaining mitochondrial stability and function. Such a novel MOA of risuteganib could lead to new strategies for treatment of retinal diseases.

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