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Abstract

Background Glaucoma is a leading cause of irreversible blindness, characterized by the loss of retinal ganglion cells (RGC) in primary open-angle glaucoma (POAG).

Purposes To identify novel gene and protein targets associated with glaucoma and gain insights into the underlying mechanisms of the disease, we utilized various analysis methods. These methods included differential analyses, pathway enrichment analysis, metabolic flux simulation, and metabolomics analysis.

Methods The primary datasets we used included RNA-seq data from a glaucoma mouse model and metabolomics data from glaucoma patients. Principal component analysis (PCA) was used to assess sample characteristics, and we applied support vector machines (SVM) for classification. We also performed custom-made in-silico metabolic flux simulations. Metabolite samples from the aqueous humor were prepared and analyzed using gas chromatography/time-of-flight mass spectrometry (GC/TOF MS).

Results Our analysis revealed down-regulated pathways in glaucoma, including synapse organization, reduced blood flow to the optic nerve, mitochondrial dysfunction, and pathways related to peroxisomes and hypoxia-inducible factors. Up-regulated pathways in glaucoma included mitophagy and energy metabolism-associated pathways, particularly oxidative phosphorylation. Furthermore, we found that the levels of threose, mannitol, and urea were significantly lower in the POAG group compared to the control group, indicating impaired osmotic regulation and altered metabolic processes in the eye.

Conclusions In the glaucoma mouse model, we observed transcriptional changes in the oxidative phosphorylation (OXPHOS) pathway and signs of mitochondrial damage, suggesting potential mitochondrial dysfunction. Metabolomics analysis revealed increased levels of specific lipid compounds associated with oxidative stress in POAG patients, implying a role of oxidative stress in the disease.