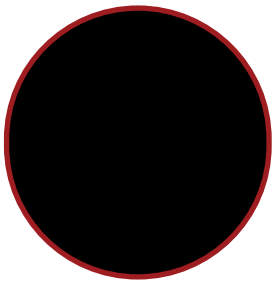

Qian Wang

iLab Research Institute, USA

Arbutin Mitigates Oxidative Stress–Associated Transcriptomic Alterations in Retinal Pigment Epithelial Cells

Abstract:

Background: Dry age-related macular degeneration (AMD) is a leading cause of irreversible central vision loss and is marked by progressive dysfunction of the retinal pigment epithelium, photoreceptor degeneration, and extracellular deposit accumulation. Oxidative stress is a central contributor to AMD pathogenesis, making antioxidant-based approaches promising candidates for disease prevention and intervention. Hydrogen peroxide (H_2O_2)–induced oxidative injury in RPE cells is a well-established in vitro model for investigating molecular mechanisms underlying AMD-related degeneration.

Objective: To characterize the transcriptomic effects of arbutin on hydrogen peroxide–induced oxidative stress in retinal pigment epithelial (RPE) cells using RNA sequencing.

Methods: Publicly available RNA-sequencing data from ARPE-19 cells (GSE265933) were reanalyzed. Cells were treated with 600 µM H_2O_2 for 24 hours, with a subset receiving 100 µM arbutin pretreatment for 24 hours prior to oxidative stress exposure. Filtered and annotated gene count data were normalized, log transformed and analyzed using DESeq2. The differentially expressed genes (DEGs) were identified. Functional interpretation was conducted through Gene Ontology and pathway enrichment analyses using clusterProfiler, and data visualization included principal component analysis (PCA), heatmaps, volcano plots, and enrichment plots.

Results: H_2O_2 exposure induced transcriptomic remodeling in ARPE-19 cells, characterized by marked enrichment of pathways involved in RNA metabolism and translational control, including RNA helicases, spliceosomal components, ribosome biogenesis factors, and nonsense-mediated decay regulators. These changes are consistent with suppression of global protein synthesis and activation of RNA quality control mechanisms under oxidative stress. Prominent activation of DNA damage response pathways was observed, with enrichment of genes involved in genome surveillance and repair, including ATM, ATR, PRKDC, and WRN. Antioxidant and redox homeostasis pathways were strongly

represented, particularly components of the NRF2–KEAP1 axis (NFE2L2, KEAP1, TXN, GCLC, NQO1). In addition, significant alterations were detected in genes governing proteostasis and autophagy (SQSTM1, ULK1, AMBRA1), endoplasmic reticulum stress signaling (ERN1, XBP1), and mitochondrial maintenance (TFB2M, TWNK). Several regulatory genes previously implicated in retinal and neurodegenerative disorders, including CD2AP, EP300, CREBBP, and NOTCH1, emerged as key integrative nodes linking oxidative stress to AMD-relevant molecular pathways.

Conclusion: Arbutin exposure was associated with modulation of core oxidative stress–responsive transcriptional programs in RPE cells, affecting redox balance, RNA quality control, DNA repair, and proteostasis. These findings provide transcriptomic evidence supporting the protective potential of arbutin against oxidative injury relevant to AMD and offer mechanistic insight into antioxidant-based strategies for retinal degeneration.