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PARP inhibitors: The protective ways on retinal degeneration

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Abstract

Purpose: Inherited retinal degenerations lead to irreversible loss of visual function by progressive degeneration of rod and/or cone photoreceptors. It was shown that increased Poly-ADP-ribose polymerase (PARP) activity is involved in photoreceptor degeneration and PARP inhibition as potentially beneficial for the course of disease. Currently PARP inhibitors are in clinical trials for cancer and offer rapid therapeutic strategy for retinal degenerative diseases. Repositioning of PARP inhibitors has real promise for the therapy of non-oncological diseases. Here, we compared the effects of PARP inhibitors on degenerative process of retina

Methods: rd1 mouse retinae were explanted together with retinal pigment epithelium (RPE) at postnatal day (PN) 5. Retinal explants were treated with different concentrations of PARP inhibitors (PI1 and PI2) starting at PN7. Treatment was terminated at PN11. TUNEL, PAR, GSH, GSK3, beta catenin staining as well as Protein-Ligand Docking simulations were performed with GOLD (Genetic Optimization for Ligand Docking, v.5.3) docking program for the assessment of dying cells, PAR, GSK, beta catenin expression and to estimate the binding poses and affinities, respectively.

Results: Detection of degenerating cells using the TUNEL assay showed low number of TUNEL positivity and maximum number of photoreceptor rows were appeared for 100 nM PI1 (TUNEL; untreated: 5.6 ± 0.3 SEM, n=15, PI1: 3.8 ± 0.2 SEM, n=6, $p \leq 0.01$; PI2: 3 ± 0.1 %; n=6; $p \leq 0.0001$). In addition, there was a significant decrease in PAR signal for 100 nM PI1 and PI2 (untreated: 1.9 ± 0.2 SEM, n=6; PI1: 1.2 ± 0.1 SEM, $p \leq 0.05$; PI2: 0.4 ± 0.1 SEM n=5, $p \leq 0.001$). Both PI1 and PI2 were at 100 nM significantly increased the level of reduced-GSH in cultured rd1 retinal explants (untreated: 18.6 ± 2.5 nmol/mg protein, n=6; 100 nM PI1: 35.1 ± 6.6, n=4, $p \leq 0.05$; 100 nM PI2: 35.5 ± 5.1, n=6, $p \leq 0.05$). The PARP1 inhibitors were docked to the homology model of GSK3α and crystal structure of GSK3β (PDB ID:1q5k) targets via GOLD docking program in order to estimate the binding poses and affinities. It was found that PARP1 inhibitors have similar docking scores with the known GSK3β inhibitors at both targets GSK3α and GSK3β.

Conclusions: PARP may have important functions in neuroprotection and regulate cellular components during photoreceptor cell death. Repurposing of PARP inhibitors may facilitate a translation into a treatment for inherited diseases of the retina.

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