Epigenetic Changes and Photoreceptor Neuroprotection in a Mouse Retinitis Pigmentosa Model

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Abstract: DNA methylation is an epigenetic repressor mark for transcription dynamically regulated in neurons without altering the DNA sequence. DNA methylation plays a significant role in the development and differentiation of photoreceptors. To investigate the methylation patterns during the degeneration of photoreceptors and their involvement in photoreceptor plasticity of the degenerating retina, we analyzed the regulation of DNA methylation during the progress of retinitis pigmentosa (RP) in mice. RP is a group of sight-threatening hereditary retinal dystrophies characterized by progressive degeneration of photoreceptor cells, which results in debilitating visual impairment. Genetic defect modulated the expression of factors controlling DNA methylation and exerted similar effects on DNA methylation and the hydroxy-methylation state of the retina. Our data found elevated levels of DNMTs and DNA methylation during photoreceptor degeneration in the classic model of RP, mouse strain with rhodopsin deficiency (*Rho*$^{-/-}$). Blockage of the methyl transferase DNMTs by weekly decitabine treatment (intravitreous injection) led to significant improvement in visual function in *Rho*$^{-/-}$ mice, as evidenced by electroretinogram (ERG), spectral-domain optical coherence tomography (OCT), and optomotor response-based visual behavior assays (OMR). Concurrently, assessment of outer nuclear thickness and immunofluorescence for the cone photoreceptor cell marker PNA demonstrated pronounced increases in the survival of cones and improvement in the morphology of the outer segments. DNA methyltransferase (DNMT) inhibition blocked the molecular, morphologic, and visual functional effects of photoreceptor genetic defect, partially reversing the genetic defect-caused photoreceptor degeneration.