Roles Of Retinoic Acid Signaling In Neuritogenesis During Light-Induced Retinal Degeneration

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Purpose: Work in our laboratory and others has revealed striking neuritogenesis in the neural retina subsequent to photoreceptor stress and degeneration. While the initiators of this process remain unknown, our data indicate that major changes in retinoid processing occur prior to neuritogenesis. We hypothesize that alterations in retinoid acid (RA) signaling may influence the evolution of neuritogenesis and subsequent retinal remodeling.

Methods: Adult balbc albino mice were exposed to constant intense light (24 h) by excluding one normal night cycle (12 h) to establish the light-induced retinal degeneration (LIRD) animal model. Retinas were harvested at various post-light exposure day (pLX) 0, 1, 7, 30, 60, 90 and 120 for RA signaling analysis by morphological, metabolic and protein profiling.

Results: Cellular retinoic acid-binding protein II (CRABP II, a transcriptional regulator), RA receptors α, β (RARα, β), and retinoid X receptors α, γ (RXRα, γ) were expressed in inner nuclear layer (INL) and ganglion cell layer (GCL). RXRβ was not detected in control retina. The protein levels of CRABP II, RXAR, RXRα, RXRγ, and RORy were fluctuated in the neural retina after light stress, while RARα levels had no alteration. These changes were followed by bipolar cell neuritogenesis revealed by PKCα staining in the survivor zone where the gross histology of the neural retina seemed normal. However, signals of the examined RA signaling components were reduced in the inner light-direct loss (LD) zone, where photoreceptor loss and early dendritic remodeling occurred. Nevertheless, we observed neuritogenesis revealed by SV2 staining in INL of the LD zone, where ganglion cells showed strong signals of RA signaling.

Conclusions: RA signaling displays large alterations early in retinal degeneration, suggesting RA signaling pathways may be responsible for survival-related neuritogenesis and reactive neuronal plasticity. Deficiencies in RA signaling may contribute to neurite degeneration.

Background Retinoic acid (RA), a biologically active metabolite of vitamin A (retinol), is one of the most ubiquitous inductive signals, and is involved in retinal and eye development. RA controls the transcription of its target genes by binding to a sequence of DNA known as the RA-response element (RARE). This binding activates β, retinoid X receptors (RXRα, γ, CRABP I, II). The other superfamily encodes RA receptors (RARα, β, γ) and retinoid X receptors (RXRα, β, γ), which themselves heterodimerize and bind to a sequence of DNA known as the RA-response element (RARE). This binding activates the transcription of target genes and influences adult phenotypic attributes.

In the adult brain, all-trans RA increases neurite outgrowth and restores neurogenesis in vitamin A-deprived animals. RA modulates neurite outgrowth in dissociated embryonic brain cultures, retinal explants, and olfactory receptor neurons. Neuritogenesis, a striking feature of retinal degeneration, is a pathologic process of neuroplasticity and a barrier to therapeutic strategies.

Pathways for the synthesis and mechanism of action of RA.

Light stress induced photoreceptor death and retinal degeneration in adult mice

Immunolocalization of retinoic acid receptors and retinoid X receptors in adult mice retina

Alterations in protein levels of retinoic acid receptors and retinoid X receptors in adult mice retina after light stress

Neuritogenesis occurred in inner nuclear layer of the light-damage zone

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