Paving the Path to the Impossible: Regenerating Neurons Using Prostaglandin E2 Regulation as a Therapeutic Strategy

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Nerve degeneration, due to acute injury and chronic neurodegenerative disease, causes devastating symptoms for millions of patients worldwide. No therapeutics to regenerate neurons exist, meaning that patients with chronic neurodegeneration may never regain lost neurological functions. This project aimed to investigate the role of the glia-secreted lipid signaling molecule PGE2 in nerve regeneration to determine if modifying PGE2 signaling or applying it as a therapeutic would promote axonal re-extension. PGE2 is secreted by both Schwann cells and astrocytes, though its exact role in neurodegeneration and repair is unclear. Using in vitro injury paradigms, PGE2's impact on axonal regeneration was explored. A 1 uM dosage of dmPGE2 was found to promote regeneration following injury (with an average axonal length increase of 126.29%), showing promise for promoting cell survivability following injury. The 1 uM dmPGE2 treatment was also found to boost excitability in an RNA Scope analysis. As an orthoganal method to verify the impacts on axonal regrowth, Brainbow AAV transfection and a lift-replate assay were used for total axotomy. Next, to explore how PGE2 may interact with other receptors in the complex in vivo system, molecular docking was used. Finally, a GWAS-based analysis found that genes involved in prostaglandin production and signaling are upregulated in Multiple Sclerosis patients compared to healthy patients, suggesting that PGE2's role in inflammatory environments may be a natural response by glia meant to protect remaining neurons. Overall, this project suggests that targeting PGE2 signaling as a neuroregenerative therapy may save and improve millions of lives.

Awards Won: