Enabling Neural Regeneration in a Model of Glial Scarring: Implications of Enhancing Retinoic Acid Signaling and Regulating NG2 Expression

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NG2-glia are a class of glial cells in the brain that play a critical role in synaptic regulation and myelination through their structural support of axons and oligodendrocytes. In the instance of neurotrauma, a neurochemical cascade is initiated and NG2-glia migrate to regions of trauma. Two major production pathways within NG2-glia are stimulated, causing increased production of retinaldehyde dehydrogenase 2 (RALDH2), an important enzyme in the oxidation of Vitamin A (retinol), and neuron-glial antigen 2 (NG2), a growth-regulating molecule. Increased production of NG2 contributes to the formation of glial scars, negatively impacting surrounding neurons and inhibiting axonal outgrowth. Increased RALDH2 production leads to increased retinoic acid receptor beta (RARβ) activity, which promotes axonal regeneration. However, due to a resource tradeoff, NG2 production outcompetes RALDH2 production, reducing RARβ activity and preventing post-trauma neurite development. Therefore, to create the most permissive environment for neuronal regeneration, a controlled investigation was conducted to determine the individual and combined effects of NG2-neutralizing antibodies and RARβ agonists on functional NG2 levels, RARβ activity, and neurite outgrowth. In vitro experimentation confirms that the application of RARβ agonists and NG2-neutralizing antibodies in mechanically traumatized neural cultures can profoundly assist in post-trauma CNS recovery. In vivo, this has the implication of preventing post-trauma neurodegenerative disorders such as Alzheimer's Disease. It is postulated that stimulating RARβ activity and/or functionally downregulating NG2 are potentially viable treatments for the degenerative processes caused by trauma to the human hippocampus and frontal lobe.