Our panel of experts highlight the most important research articles across the spectrum of topics relevant to the field of regenerative medicine

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Gas6 promotion of remyelination
Evaluation of: Goudarzi S, Rivera A, Butt AM, Hafizi S. Gas6 promotes oligodendrogenesis and myelination in the adult central nervous system and after lysolecithin-induced demyelination. *ASN Neuro*. doi:10.1177/1759091416668430 (2016) (Epub ahead of print).

Oligodendrocyte precursor cell recruitment to lesions of multiple sclerosis (MS) is a target of many papers. The factors driving the maximization of cellular recruitment involve extracellular and axonal derived factors. The driving force of remyelination's eventual demise is in part due to lack of differentiation and support. Factors related to the differentiation of oligodendrocyte precursor cells have been studied extensively. The researchers of the current paper analyze the role of Gas6 protein which signals to Tyro3, Axl, Mer (TAM) family of receptor tyrosine kinase. These particular receptor tyrosine kinases participate in a number of cellular processes including immune system regulation and activation in addition to regulation of cell survival. In a previous paper, the Gas6–TAM signaling has been shown to play a role in another model of MS.

Initially the researchers concluded via quantitative PCR, that TAM and Gas6 to be expressed in the cortex, cerebellum and optic nerve of the mouse brain at various time points in development. The three TAM receptors were expressed differentially with age as confirmed by Western blot protein. They were able to discern the expression

of Axl and Tyro3 to be in all mouse brain regions at the various ages, however, Tyro3 was significantly higher in cortical regions in the aging animal, whereas Axl decreased with age. The role of Gas6 was analyzed by utilizing the Sox10–EGFP reporter mice, where the reporter is expressed in a bulk of the myelinating oligodendrocytes. By using the optic nerve, they were able to maintain an organotypic culture for 3 days to study myelination. After 3 days, with or without medium containing Gas6, the optic nerves were fixed. The results show that Gas6 increased the number of Sox10–GFP positive cells and this was blocked with inhibitors of the vitamin K-dependent pathway.

Importantly, the researchers utilized a lysolecithin toxic demyelination model with a cerebellar slice culture model. This model involves a fast demyelination which will then have spontaneous repair, similar to MS. Myelin loss was quickly observed in the control cultures with lysolecithin, however, cultures containing Gas6 in the medium has a significant reduction in demyelinated axons. Analysis of downstream signaling demonstrates STAT3 protein to be activated in the organotypic optic nerve cultures with Gas6 stimulation in the cultures, which is indicative of oligodendrocyte regeneration. Further analysis via immunocytochemistry revealed phosphorylated STAT3 protein to be expressed in mature oligodendrocyte, preferentially in the Gas6-treated cerebellar sections. Activation of phosphorylated STAT3 was seen after just 3 h of Gas6 treatment. Additionally, activated Tyro3 was

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seen in Gas6 stimulated optic nerves. Small molecule inhibitors of Axl were unable to block the myelination effect seen by the Gas6 stimulation, therefore, myelination must be due to the Tyro3 activation by Gas6. MS related gene expression was analyzed and indicated by a number of genes associated with MS to be downregulated with Gas6 stimulation of the optic nerves.

The study outlined came to the conclusion that Gas6 protects the oligodendrocytes from damage due to lysolecithin. Gas6 was unable to promote remyelination 3 days after lysolecithin treatment. Therefore, it would not be able to be used as a therapy for MS. However, the time frame of treatment needs to be better investigated. The researchers also failed to analyze the

role of Mer in microglia in the TAM-mediated signaling. This could also play a role in the remyelination process. On the other hand, this work demonstrated a role for Gas6 in promotion of remyelination in a couple models of MS.

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