Boosting Endogenous Repair in the Brain

Review of “[Inhibition of Gli1 mobilizes endogenous neural stem cells for remyelination](http://www.ncbi.nlm.nih.gov/pubmed/26416758)” from Stem Cells by Stuart P. Atkinson

In order to function properly, our nerves require an insulating layer of a protein called myelin. Loss of this myelin barrier can cause a number of neurodegenerative disorders, although the actions of oligodendrocyte progenitor cells (OPCs) and neural stem cells (NSCs) [1] can counteract this loss. While OPCs act locally to promote remyelination [2, 3], NSCs from the subventricular zone home towards demyelinated regions where they differentiate into oligodendrocytes to effect [4] to effect a certain level of repair.

However, the action of these NSCs is often not enough to completely replace lost myelin, as occurs in the inflammatory demyelinating disease multiple sclerosis (MS), and furthermore, the signals which recruit NSCs and enhance their oligodendrocytic differentiation are unknown. Some studies have linked NSC recruitment to activated sonic hedgehog (Shh) signaling [5], whose pathway activates the transcription of the Gli1 zinc-finger transcription factor.

In a new study published in Nature, researchers from the laboratory of [James L. Salzer](http://www.med.nyu.edu/biosketch/salzej01) (New York University School of Medicine, USA) studied the remyelination abilities of Gli1-positive NSCs, and in doing so, have found a simple and effective means to significantly boost their myelinating abilities [6].

Samanta et al first used genetic fate mapping to show that Gli1-positive mouse NSCs represented a distinct subset of NSCs which specifically homed towards a region of artificially induced demyelination in the mouse brain in response to Shh. Upon arrival, they differentiated into OPCs, oligodendrocytes, and astrocytes and mediated an increase in myelin levels. However, differentiation the cells corresponded to a reduced responsiveness to Shh and this in turn led to a dramatic reduction in Gli1 expression. This suggested that remyelination activity corresponds to a loss of Gli1 expression and that inhibition of Shh signaling may promote enhanced levels of remyelination, not the other way round as previously thought [5].

Indeed, the authors noted that remyelinating regions in Gli1-null mice contained a 7.5-fold higher number of oligodendrocytes and a higher level of myelin. However, loss of Shh signaling, further upstream, did not affect cell number or fate. Interestingly, enhanced Shh signaling in the presence of Gli1 enhanced OPC generation, but blocked their differentiation, while, in the absence of Gli1, this led to robust recruitment and enhanced oligodendrocyte differentiation and proliferation at the remyelination region.

Excitingly, the authors were next able to reproduce the effects of Gli1-knock out with a small molecule inhibitor (GANT 61 [7]) and then used it to successfully enhance remyelination and protect neurons in a physiologically relevant model of inflammatory demyelination and remyelination. This supports the clinical investigation of Gli1-inhibition in MS, and other associated neurological disorders, in order to enhance the body’s own reparative response to demyelination. This may be a safer option than cell transplantation, and provides an impetus to discover other signals which can mobilize other pools of endogenous repair cell types.

**References**

1. Xing YL, Roth PT, Stratton JA, et al. Adult neural precursor cells from the subventricular zone contribute significantly to oligodendrocyte regeneration and remyelination. J Neurosci 2014;34:14128-14146.
2. Gensert JM and Goldman JE Endogenous progenitors remyelinate demyelinated axons in the adult CNS. Neuron 1997;19:197-203.
3. Zawadzka M, Rivers LE, Fancy SP, et al. CNS-resident glial progenitor/stem cells produce Schwann cells as well as oligodendrocytes during repair of CNS demyelination. Cell Stem Cell 2010;6:578-590.
4. Menn B, Garcia-Verdugo JM, Yaschine C, et al. Origin of oligodendrocytes in the subventricular zone of the adult brain. J Neurosci 2006;26:7907-7918.
5. Ferent J, Zimmer C, Durbec P, et al. Sonic Hedgehog signaling is a positive oligodendrocyte regulator during demyelination. J Neurosci 2013;33:1759-1772.
6. Samanta J, Grund EM, Silva HM, et al. Inhibition of Gli1 mobilizes endogenous neural stem cells for remyelination. Nature 2015;526:448-452.
7. Lauth M, Bergstrom A, Shimokawa T, et al. Inhibition of GLI-mediated transcription and tumor cell growth by small-molecule antagonists. Proc Natl Acad Sci U S A 2007;104:8455-8460.