Sox2 Necessity For Neural Development: A Step Closer To Curing Multiple Sclerosis

By Chris Croteau

A family member shrieks from across the room and that's when a loved one realizes their arm has been resting on a hot surface…and according to the burn it must have been there awhile. Normally there would be a quick reaction to move the arm away; however, this individual had no idea their arm was even touching a hot surface, much less resting on it. This is one of the first symptoms of Multiple Sclerosis (M.S.), a debilitating neurodegenerative disorder.

This horrific disease can progress rapidly; one day a person might be playing their favorite sport when all of a sudden they are unable to even walk without assistance. Many of the 2.5 million people affected worldwide by M.S. are burdened by a variety of health complications later in life (1). Lack of bladder control and buildup of food in the lungs (due to difficulties chewing and swallowing) can increase risk of bacterial infection and ultimately decrease life expectancies by an average of six years (2).

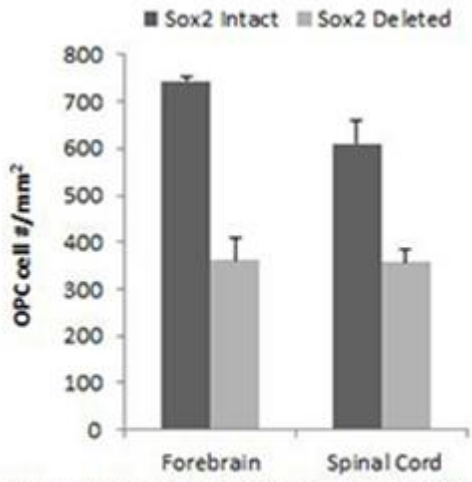

Figure 1: OPC in central nervous system upon sox2 deletion: The number of OPCs in the forebrain and spinal cord were declined after *Sox2* deletion.

Loss of sensory and motor control is caused by the destruction of a fatty sheath called myelin that covers neurons. Neuronal extensions termed axons are much like cables used to send a message. Myelin functions as the plastic coating to these cables. If you remove the plastic coating from cables, the signal goes haywire. Similarly, damage to myelin leads to inefficient communication between neurons.

To date (March 2016), there is still no approved treatment to promote the myelination of axons. Understanding myelin synthesis in the central nervous system will be crucial for generating therapies that can successfully remyelinate damaged regions of the brain and spinal cord.

So what do we currently know about myelination? A cell type called oligodendrocytes generates myelin (3). Mature myelinating oligodendrocytes can be formed in the adult brain from a source of cells termed oligodendrocyte progenitor cells (OPCs) (3). Unfortunately, the capacity for myelin repair is limited in M.S because few OPCs fully develop into mature myelinating oligodendrocytes at the damaged sites (3).

One of the most remarkable advances in stem cell biology was the discovery of *Sox2* being one of four genes necessary for reprogramming adult cells into an embryonic stem cell-like state(4). Stem cells are characterized by their unique ability to give rise to various specialized cell types while retaining the ability to generate more of themselves.

Remarkably, *Sox2* promotes neural development and represses non-neuronal cell fates in embryonic stem cells (5). Even though *Sox2* has been studied for its involvement in neural

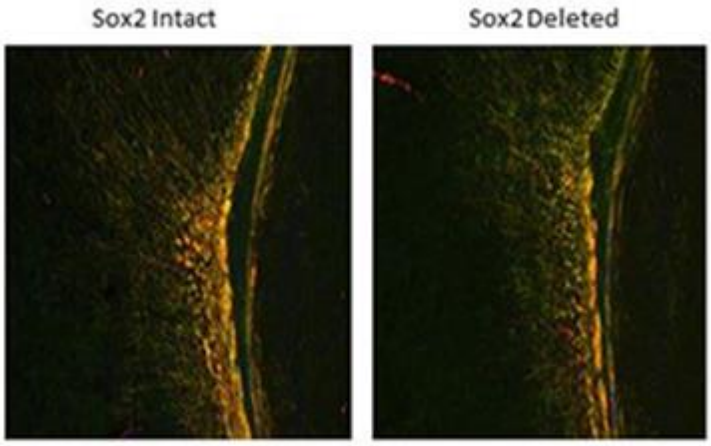

Figure 2 Myelination of the CNS. Images show a decline of CNS myelination in the forebrain when *sox2* expression is eliminated in oligodendrocytes.

development, less is known about how *Sox2* impacts oligodendrocyte development in the central nervous system.

In the laboratory of Dr. David Pleasure at the Institute For Pediatric Regenerative Medicine at Shriners Hospital For Children Northern California, I have been working with a team of scientists dedicated to seeking answers to this question.

Mice have many similarities to humans in how the brain and spinal cord develops making them an ideal model organism for our research.

To understand the function of *Sox2* in OPCs, the *Sox2* gene was specifically deleted in OPCs in newly born mice. Deleting *Sox2* in OPCs resulted in a drastic decline in the number of OPCs and mature oligodendrocytes. The number of self-renewing oligodendrocytes was also reduced.

In the surviving oligodendrocyte population, we found that loss of *Sox2* decreased expression of other genes responsible for myelin production.

Our findings suggest that *Sox2* is necessary for oligodendrocyte development, and is also vital for the extent of central nervous system myelination. The next step will be measuring what happens when oligodendrocytes produce excess *Sox2*. If overexpression of *Sox2* leads to increased oligodendrocyte development and myelin synthesis it could mean an effective treatment or even cure for MS might be around the corner.

References

1. Browne, P., Chandraratna, D., Angood, C., Tremlett, H., Baker, C., Taylor, B. V., & Thompson, A. J. (2014). Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. *Neurology*, *83*(11), 1022–1024.
2. Scalfari, A., Knappertz, V., Cutter, G., Goodin, D. S., Ashton, R., & Ebers, G. C. (2013). Mortality in patients with multiple sclerosis. *Neurology*, *81*(2), 184–192.
3. Huang, Hao, Zhao, Xiao-Feng, Zheng, Kang, & Qiu, Mengsheng. (2013). Regulation of the timing of oligodendrocyte differentiation: mechanisms and perspectives. *Neuroscience Bulletin, 29*(2), 155-164.

4. Takahashi, Kazutoshi, Tanabe, Koji, Ohnuki, Mari, Narita, Megumi, Ichisaka, Tomoko, Tomoda, Kiichiro, & Yamanaka, Shinya. (2007). Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors. *Cell, 131*(5), 861-872.
5. Rebecca, Valotta, Menella, Ferri, Anna L. M., Latorre, Elisa, Mariani, Jessica, Giachino, Claudio, . Nicolis, Silvia K. (2009). Hippocampal development and neural stem cell maintenance require Sox2-dependent regulation of Shh. *Nat Neurosci, 12*(10), 1248-1256.