Journal Club

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Uncovering the Role of Sox2 in Oligodendroglia

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Review of Zhang et al

In the CNS, oligodendrocytes are responsible for the formation of myelin. To build these insulating sheaths surrounding axons, cells of the oligodendrocyte lineage must go through an intricate and temporally matched sequence of proliferation, migration, differentiation, and myelination (Michalski and Kothary, 2015). This process is tightly regulated through the interaction of various transcription factors and chromatin regulators (Hernandez and Casaccia, 2015). For example, Sox8, Sox9, and Sox10, which are members of the SoxE family of transcription factors, are well established players in the development of oligodendrocytes (Weider and Wegner, 2017). Some studies suggest that Sox2, a member of the SoxB1 family, is also involved in oligodendrocyte development, but its role is less clearly defined.

Sox2 is a well characterized transcription factor best known as one of the four reprogramming factors essential for generating induced pluripotent stem cells (Takahashi and Yamanaka, 2006). Originally, it was identified as a key factor for induction and maintenance of pluripotency in embryonic and neural stem cells (Graham et al., 2003; Masui et al., 2007). Sox2 expression persists in neural progenitor cells (NPCs), where it regulates the proliferation and maintenance of neural progenitor properties (Bylund et al., 2003). After neuronal differentiation, Sox2 expression decreases in most neurons. However, Sox2 expression is maintained in other cells derived from SoxB1-expressing NPCs, including oligodendroglia (Hoffmann et al., 2014; Dai et al., 2015). Recent studies have reported somewhat conflicting results regarding the function of Sox2 in the oligodendrocyte lineage. Whereas Hoffmann et al. (2014) showed that Sox2 is involved in terminal differentiation of oligodendrocytes and does not affect oligodendrocyte precursor cell (OPC) proliferation or migration in the embryonic and perinatal spinal cord, Zhao et al. (2015) proposed a role for Sox2 in the recruitment of OPCs to demyelinated spinal cord lesions (Hoffmann et al., 2014; Zhao et al., 2015).

In a recently published article in *The Journal of Neuroscience,* Zhang et al. (2018) further addressed the functions of Sox2 in myelination and remyelination by using several conditional knock-out mouse strains. In contrast to the findings of Zhao et al. (2015), Zhang et al. (2018) showed Sox2 expression not only in early postnatal OPCs, but also in adult OPCs in the brain. Furthermore, Sox2 was transiently upregulated in newly differentiated oligodendrocytes. Specific deletion of Sox2 in mature oligodendrocytes revealed reduced oligodendrocyte differentiation and myelination in the brain. Surprisingly, this effect was not seen in postnatal spinal cord, suggesting that the regulation of oligodendrocyte differentiation by Sox2 is region-specific. A potential explanation for this difference is that the loss of Sox2 in the spinal cord may be partially compensated for by Sox3, another member of the SoxB1 family (Hoffmann et al., 2014).

Next, the authors selectively knocked out Sox2 in OPCs, which are characterized by the expression of platelet-derived growth factor receptor α (PDGFRα). This reduced the number of OPCs in the subcortical white matter and subsequently decreased oligodendrocyte differentiation and myelination. This effect most likely results from reduced proliferation of OPCs rather than an increase in apoptosis. Finally, as the results from these stage-specific Sox2 ablation experiments imply, the deletion of Sox2 in all oligodendrocyte lineage cells severely affected brain developmental myelination. CNS hypomyelination was evident at the behavioral level by tremor, ataxia, and motor impairment and was confirmed at protein and mRNA levels.

Using two different demyelination approaches, Zhang et al. (2018) went on to show that Sox2 was involved in oligodendrocyte regeneration and remyelination. Specifically, they showed that cuprizone-induced demyelination and $MOG_{35–55}$ peptide-induced experimental autoimmune encephalomyelitis (MOG-EAE) increased the numbers of $Sox2^+$ cells in the corpus callosum and spinal cord, respectively. Moreover, conditional ablation of Sox2 in OPCs resulted in reduced numbers of newly regenerated oligodendrocytes and proliferating OPCs in the corpus callosum in the remyelination phase of the cuprizone model. Similarly, Sox2 deletion in OPCs diminished the density of OPCs, the number of proliferating OPCs and newly

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regenerated oligodendrocytes in the spinal cord after MOG-EAE. Collectively, the study by Zhang et al. (2018) demonstrated a region- and time-specific involvement of Sox2 in the regulation of OPC proliferation, oligodendrocyte differentiation, and myelination.

There is evidence that Sox2, in addition to being a transcriptional regulator, may act as a pioneer factor that prepares genes on the epigenetic level for regulation by other factors (Wegner, 2011). For instance, Zhang et al. (2018) propose an interaction of Sox2 with chromodomain helicase DNA binding protein 7 (Chd7), a chromatin-modifying enzyme, previously identified as a transcriptional cofactor of Sox2 in neural stem cells and of Sox10 in oligodendrocyte lineage cells (Engelen et al., 2011; He et al., 2016). Indeed, the interaction of Sox2 and Chd7 in OPCs was recently reported by Doi et al. (2017). That study provided evidence for a role of the Sox2-Chd7 complex in OPC activation and identified two proteins—regulator of cell cycle (Rgcc) and protein kinase Cθ (PKCθ)—as two possible downstream targets (Doi et al., 2017). These proteins are involved in the regulation of cell proliferation in different cell types (Badea et al., 1998; Pfeifhofer et al., 2003; Ou et al., 2008; Fosbrink et al., 2009). Consistent with this, knockdown of Rgcc and PKCθ in OPC cultures decreased the percentage of EdU$^+$, Ki67$^+$, PDGFRα^+, or Sox10$^+$ cells, indicating their requirement for OPC proliferation (Doi et al., 2017). However, it is necessary to verify these findings *in vivo* and to further test the hypothesis that Sox2 promotes OPC proliferation **via** activation of Rgcc and PKCθ. In this context, it would be reasonable to investigate the effect of Sox2 deletion on the expression of these candidate factors in the spinal cord and brain at different developmental stages of oligodendrocyte lineage cells. Moreover, using different conditional genetic mutants for Rgcc and PKCθ in OPCs would provide further insight about their role in oligodendrocyte development *in vivo*.

Another way that Sox2 might function in OPC differentiation was proposed by Hoffmann et al. (2014). Their study implicated Sox2 as a potential regulator of microRNAs (miRNAs) and identified miRNA145 as a possible target. Repression of this miRNA results in the activation of several factors involved in oligodendrocyte development and differentiation, such as Myrf (myelin regulatory factor) and Med12 (Emery et al., 2009; Vogl et al., 2013; Hoffmann et al., 2014). Loss of Sox2 in OPCs might enhance miRNA145 levels, thereby inhibiting the translation of these prodifferentiation factors. Interestingly, Zhang et al. (2018) reported an effect of Sox2 deletion only on oligodendrocyte differentiation in the brain, not in the spinal cord. Therefore, the role of Sox2 in oligodendrocyte differentiation in this CNS region remains to be specified. Nevertheless, this hypothetical mechanism is worth further investigation, for example by determining the influence of Sox2 deletion on miRNA145 and its targets during development, as well as in demyelinating conditions in the brain.

Efficient progression of oligodendrocyte lineage cells is vital for the formation of new myelin during development, as well as for remyelination. In some demyelinating disorders, such as multiple sclerosis, this process is severely affected. Yet, no potent treatment that directly enhances repair is available (Plemel et al., 2017). Therefore, to develop new therapies, it is necessary to gain further insights into mechanisms preventing demyelination and promoting remyelination. The work by Zhang et al. (2018), together with other previous studies, helps to elucidate the function of Sox2 in the complex regulatory network controlling the generation of myelinating oligodendrocytes, thus identifying a possible target for regulating OPC activation and for fostering functional recovery in demyelinating diseases.

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