Journal Club

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Cytoskeletal Regulation of Oligodendrocyte Differentiation and Myelination

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Review of Shao et al.

Cells in the developing nervous system must navigate diverse environments, interpret local signals from the extracellular matrix and neighboring cells, and migrate to their final destination to perform cellular functions. After reaching their final destination, cells continue to extend processes throughout their environment, gathering information and obtaining their mature morphology. For example, in the CNS, oligodendrocyte precursor cells (OPCs) must proliferate, migrate, and differentiate through multiple developmental stages to become myelinating oligodendrocytes that ensheath axons, increasing the speed of action potential propagation as well as providing metabolic and tropic support to neurons (Fünfschilling et al., 2012). As in other cells, precise regulation of the actin cytoskeleton coordinates migration and morphological changes in oligodendrocytes. In particular, recent data demonstrate that actin assembly (polymerization) is required for oligodendrocyte process extension during differentiation and that actin turnover through actin disassembly (depolymerization) and reassembly is required for myelin wrapping (Nawaz et al., 2015; Zuchero et al., 2015). Many proteins regulate actin polymerization and depolymerization, but those that regulate the actin cytoskeleton before and during myelin production remain unclear. Understanding the regulation of the actin cytoskeleton throughout this differentiation process is important because increases in oligodendrocyte density and myelination are associated with learning complex motor tasks (McKenzie et al., 2014), whereas disruption of myelin causes neuropathy and cognitive decline in diseases such as multiple sclerosis (MS; for review, see Hauser and Oksenberg, 2006).

In a recent publication, Shao et al. (2017) investigated cytoskeletal regulators in oligodendrocytes. They first measured the effects of an antibody against LINGO-1, a negative regulator of oligodendrocyte differentiation (Mi et al., 2005), on protein and RNA expression in cultured oligodendrocytes. LINGO-1 inhibition increased mRNA and protein expression of the actin-severing protein gelsolin (GSN) and increased phosphorylation of cofilin, another actin-severing protein. Anti-LINGO-1 treatment also increased expression of myelin basic protein (MBP), one of the major myelin proteins, and increased oligodendrocyte process extension. This indicates that inhibiting LINGO-1 leads to an increase in OPC differentiation, as well as an increase in actin severing proteins.

Two forms of gelsolin have previously been identified: a cytoplasmic form (cGSN), which plays a role in intracellular actin dynamics and prevents apoptosis, and a secreted form (pGSN), which breaks up extracellular actin networks (Kwiatkowski et al., 1988; Li-ChunHsieh et al., 2015). Shao et al. (2017) asked which of these forms of gelsolin is involved in OPC differentiation. Treatment with cGSN siRNA prevented OPC differentiation induced by anti-LINGO-1 treatment, and overexpression of cGSN, but not pGSN, increased OPC differentiation. This indicates that cGSN, but not pGSN, is necessary and sufficient for oligodendrocyte differentiation *in vitro* and acts downstream of LINGO-1. This is consistent with previous work which indicates that gelsolin expression increases during OPC differentiation *in vitro* and *in vivo* (Léna et al., 1994; Zhang et al., 2014). Determining the mechanism by which LINGO-1 acts on gelsolin will be important for future investigations. In particular, coimmunoprecipitation experiments should address whether LINGO-1 directly regulates gelsolin or if gelsolin increases as a consequence of OPC differentiation. These experiments may provide insight into the molecular regulation of gelsolin and the mechanism by which LINGO-1 inhibits differentiation.

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A major hurdle for repair in demyelinating disorders is failure of OPCs to differentiate at the site of demyelination (Chang et al., 2000). The underlying mechanisms of this failure are multifaceted and may involve aberrant signaling cascades in OPCs or failure of other glia to manage inflammation or debris clearance. For this reason, understanding which elements of developmental myelination affect remyelination efficacy is crucial for creating more useful therapies for demyelinating disorders. To that end, Shao et al. (2017) investigated the regulation of gelsolin in both the hypomyelinating *shiverer* mouse (which lacks MBP) and human MS patients. LINGO-1 was elevated in MS patients, whereas gelsolin expression was lower in both MS patients and *shiverer* mice than in healthy controls, supporting the hypothesis that LINGO-1 negatively regulates cGSN. However, gelsolin expression was variable in MS patients. All MS patients appeared to express lower GSN levels than sex- and age-matched controls, which may reflect oligodendrocyte loss in lesions. However, MS patients with active and chronic active lesions, characterized by acute white matter dysfunction, showed the highest levels of GSN compared to MS patients with chronic or inactive lesions. Given that the authors demonstrated that cGSN is necessary and sufficient for OPC differentiation, expression of cGSN in MS patients with active lesions may suggest an attempt of oligodendrocytes to differentiate and remyelinate axons following white matter damage. It is worth noting that this study demonstrates that either loss of MBP or gelsolin individually appears sufficient to cause loss of the other. This may reflect the fact that gelsolin and MBP are part of a suite of myelin-promoting proteins that must coordinate their activity for myelination to progress, rather than being activated sequentially.

In an effort to translate the finding that cGSN is necessary and sufficient for oligodendrocyte differentiation from basic biology to a disease context, Shao et al. (2017) used viral injection to overexpress gelsolin in rats treated with lysolecithin, a demyelinating chemical. This improved remyelination efficacy as measured by an increased number of remyelinated axons. Notably, previous work has shown that the secreted form of gelsolin (pGSN) mitigates the cellular and clinical pathology of the experimental autoimmune encephalomyelitis (EAE) model of MS (Li-ChunHsieh et al., 2015). Thus, it is possible that the effect of gelsolin on remyelination is twofold: cGSN may promote differentiation and actin rearrangement, whereas pGSN may help to clear the extracellular environment for repair processes. It would be interesting to measure the differential effect of cGSN, pGSN, and total GSN induction or loss in an *in vivo* demyelinating model.

It should be noted that Shao et al. (2017) performed their virus injection 2 weeks before inducing demyelination, which suggests that cGSN levels were enriched in healthy tissue before myelin loss, making it difficult to determine whether it promotes myelin protection or remyelination. This is particularly important because gelsolin-mediated actin remodeling has been shown to inhibit apoptosis in a variety of cell types (Ohtsu et al., 1997; Leifield et al., 2006), including neurons (Harms et al., 2004). Similarly, in a mouse model of Alzheimer's disease, lentiviral injection of cGSN proved to be neuroprotective and to reduce the effects of Aβ on the brain (Antequera et al., 2009). Because most MS lesions are identified after demyelination, studies of gelsolin induction after demyelination will provide mechanistic insight and clinical relevance. It will also be necessary to determine whether expressing gelsolin after demyelination measured both by the number of myelinated axons and myelin thickness, and to determine how cGSN induction affects other cell types, in particular, neuronal populations.

As mentioned above, although Shao et al. (2017) demonstrate that inhibiting LINGO-1 leads to OPC differentiation and increases in gelsolin, future investigations will need to determine whether LINGO-1 directly regulates gelsolin or whether gelsolin increases as a consequence of OPC differentiation, which is in turn regulated by LINGO-1. Alternatively, gelsolin might be regulated through axo-glial interactions, specifically the influx of calcium. It is well established that calcium can bind to gelsolin, leading to major conformational changes that allow gelsolin to bind and sever actin (for review, see Sun et al., 1999). Multiple lines of evidence demonstrate that calcium transients regulate OPC differentiation (Martinez-Lozada et al., 2014; Cheli et al., 2015; Gautier et al., 2015; for review, see Bakiri et al., 2009) and more recent data show that knocking out a voltage-gated calcium channel in OPCs ($Ca_V1.2$) leads to thinner myelin in the corpus callosum (Cheli et al., 2016). Stimulating axons in the optic nerve also leads to glutamate release and subsequent calcium influx in myelin (Micu, 2016). Together, these data suggest that activity-dependent myelination may be regulated by calcium influx into the myelin sheath, which then binds and activates gelsolin, allowing for F-actin severing in the leading edge to drive myelin wrapping.

These results add to growing evidence that the actin cytoskeleton plays an integral role in the differentiation and myelination by oligodendrocytes (Nawaz et al., 2015; Zuchero et al., 2015). They also demonstrate that targeting actin regulators is a potential mechanism to promote remyelination in disease. This study and others have identified cGSN as a regulator of oligodendrocyte function and a potential therapeutic target for neurological diseases. Future investigations of cGSN regulation and activity throughout oligodendrocyte development may lead to better therapeutics and remyelinating therapies for diseases such as MS.

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