A Microtubule-Myelination Connection

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https://doi.org/10.1016/j.cell.2019.08.046

Microtubules are critical for the extension of oligodendrocyte processes and myelin deposition, yet our knowledge of their microtubule biogenesis is limited. In this issue of *Cell*, Fu et al. (2019) identify an oligodendrocyte-enriched microtubule regulator that promotes microtubule growth from Golgi outposts and controls myelin sheath elongation, linking microtubule cytoarchitecture and myelination in the CNS.

The dictum "form ever follows function" was coined by the American architect Louis Sullivan with the advent of the skyscraper as an integral part of the modern American city. It is as true in biology as in architecture, from the tiniest molecular machine such as the rotary F0F1 ATPase to the different cell types that make up the tissues in our bodies. Neurons are asymmetric with long processes that can integrate and transmit thousands of inputs. Red blood cells are small and biconcave so that they can meander through tiny blood vessels to deliver oxygen. Muscle cells are highly elongated and packed with myofibrils specialized for contraction. But how do cells achieve the complex architectures optimized for their function? The morphological changes during differentiation are executed by the cytoskeleton, a highly integrated filamentous structure that forms a supportive meshwork for the cell. The microtubules are the stiffest components in this meshwork. In addition to guiding shape they also serve as tracks for the transport of cytoplasmic components including organelles, vesicles, and granules. Thus, defects in microtubule organization disrupt the precise and efficient transport of cellular components. While we know the identities and mechanism of many microtubule regulators, we still have much to learn about how cell-specific factors are used to build the diverse cytoarchitecture of differentiated cells. This is partly because discovery is frequently driven by investigations in simple, robust *in vitro* systems using immortalized cells and then back-engineered to try to understand more complex cell architectures. In this issue of *Cell*, Fu et al. (2019) identify an oligodendrocyte-enriched factor that controls myelin deposition by regulating the nucleation and organization of microtubules.

Oligodendrocytes extend growth cone-like processes that spiral around axons to wrap them in myelin. Myelin insulates axons and drastically increases the speed of action potentials. One oligodendrocyte can contact and insulate tens of axons in multiple layers of the central nervous system (Figure 1). The highly branched architecture of oligodendrocytes and the length and thickness of the deposited myelin sheets is critical for vertebrates because it supports a large number of neurons while preserving fast interconnectivity. Erosion of myelin sheaths causes multiple sclerosis, a disease that affects more than 2 million people worldwide. Fu et al. (2019) show that microtubules in oligodendrocytes nucleate not only in the cell body, but also from Golgi outposts found in both proximal and distal processes and identify tubulin polymerization promoting protein (TPPP) as important for this activity. In *Tppp* KO mice, nucleation from Golgi outposts decreases as judged from tracking end binding protein 3 (EB3) comets that follow the growing microtubule ends. Biochemical purification of *Tppp*-positive Golgi outposts failed to detect any γ-tubulin, and *Tppp* and γ-tubulin show no colocalization, suggesting that the nucleation process from these sites is not γ-tubulin dependent. Earlier electron microscopic studies visualized what looked like Golgi outposts in oligodendrocyte processes (de Vries et al., 1993) and Golgi outposts have been shown to be sites of microtubule nucleation in other cell types such as neurons (Ori-McKenney et al., 2012). However, such a role in oligodendrocytes has not been described until now.

In the absence of *Tppp*, oligodendrocytes have thinner and more numerous branches in proximal processes. Importantly, fewer microtubules are nucleated from Golgi outposts and these are no longer arranged in parallel bundles with their growing plus-ends distal, but show random polarity (Figure 1). Importantly, Fu et al. (2019) show that recombinant, purified *Tppp* concentrated on beads binds tubulin and is able to promote microtubule nucleation *in vitro* in the absence of any other factor. This provides a mechanistic link between biochemical activity and the observed *in vivo* phenotype. The clustering of *Tppp* on the beads likely mimics that on the Golgi membrane, although it is not yet clear how *Tppp* is recruited and organized on the Golgi outposts.

TPPP is expressed at high levels in oligodendrocytes and very low levels in other cell types in the CNS. Notably, TPPP expression increases during myelination (Zhang et al., 2014). By culturing oligodendrocytes on 3D microfibers that mimic axons, Fu et al. (2019) find that in the absence of *Tppp*, myelin sheath length is cut in half and thickness is also dramatically reduced, without affecting overall sheath number (Figure 1). Strikingly, the authors find Golgi outposts along growing myelin sheaths. In the absence of *Tppp*, the microtubules in the sheaths are highly disorganized and possibly shorter, although better insight into their organization will require higher-resolution imaging. Thus, *Tppp* affects myelin sheath elongation, but not myelin sheath initiation along axons. Fu et al. (2019) see the same

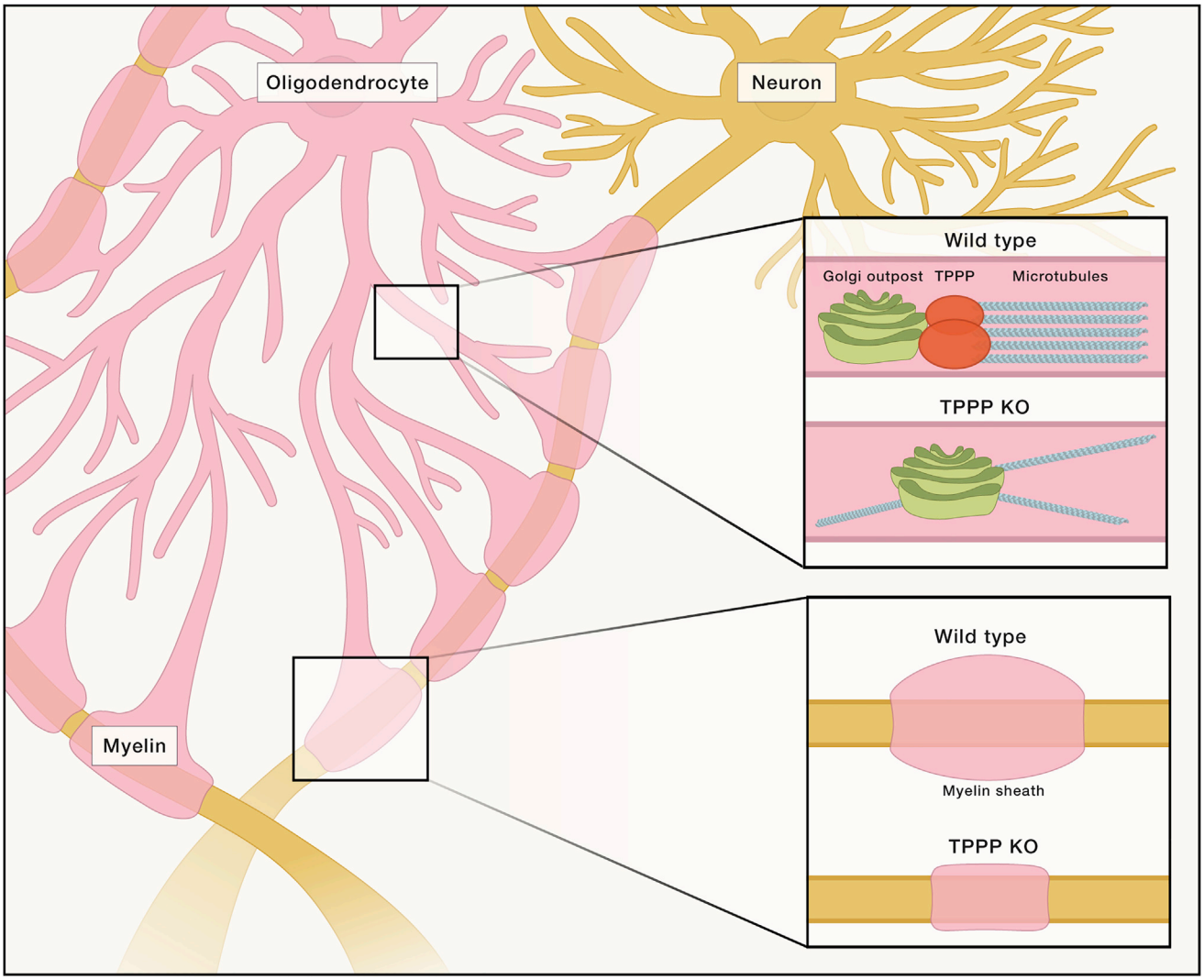

Figure 1. *Tppp* Helps Nucleate and Organize Microtubules from Golgi Outposts to Control Myelin Sheath Length and Thickness

dramatic effects on myelination in tissue sections from *Tppp* KO mice. Consistent with this, the *Tppp* KO mice have coordination defects. Why is myelin sheath elongation impaired? Are components of the myelin sheath not getting there? A major component of myelin is myelin basic protein (MBP). Its mRNA is transported to distal processes where it is locally translated. In the absence of *Tppp*, the authors find that MBP mRNA forms aggregates and is not uniformly distributed as in the wild-type, indicative of defects in transport. Thus, while the gross branched architecture of the oligodendrocyte is largely undisturbed in the absence of *Tppp*, like the corridors of a building which are designed for optimal traffic, perturbation of the microtubule organization close to sites of myelin sheath deposition results in disorganized traffic and defects in myelin formation.

Previous work has shown that actin disassembly is needed to initiate myelin wrapping around axons (Zuchero et al., 2015). The cytoplasm is squeezed out as it wraps around the axon with the help of MBP, which zippers up the membranes and possibly contributes to the release of actin disassembly factors. Thus, MBP could also provide the propulsive force for membrane extension and wrapping around the axon, especially since sheath elongation happens in the absence of assembled actin (Zuchero et al., 2015). In the absence of TPPP, MBP is no longer uniformly distributed, but shows accumulations. Thus, the failure to provide the required concentrations of MBP at sheath initiation sites could directly affect membrane expansion in the early stages of sheath formation.

Myelin is actively remodeled by synaptic activity (reviewed in Kaller et al., 2017) and recent work shows that myelin sheaths are able to regrow after targeted damage (Auer et al., 2018). How the position and activation of microtubule nucleating Golgi outposts in oligodendrocytes is controlled through cell-autonomous and -extrinsic signals will be a fascinating area of future exploration. Interestingly, the *Tppp*-positive Golgi outposts that are microtubule nucleation competent are stationary,

suggesting that they are anchored to an underlying structure. Those that are not stationary have weak nucleating activity. Fu et al. (2019) performed proteomic analysis of the Golgi outposts and identified non-conventional myosin Myo18, previously implicated in Golgi dispersal (Farber-Katz et al., 2014), as well as several molecules that could be involved in signaling. Mining the proteome of the *Tppp*-positive Golgi outposts will undoubtedly provide many more interesting insights into how oligodendrocytes organize and activate their non-centralized microtubule organizing centers to control myelin deposition and how this process can be harnessed to regrow myelin destroyed in diseases such as multiple sclerosis.

ACKNOWLEDGMENTS

A.R.M. is supported by the intramural programs of the National Institute of Neurological Disorders and Stroke (NINDS) and the National, Heart, Lung and Blood Institute (NHLBI).

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Crenarchaeal 3D Genome: A Prototypical Chromosome Architecture for Eukaryotes

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https://doi.org/10.1016/j.cell.2019.08.045

In this issue of *Cell*, Takemata et al. demonstrate that coalescin (ClsN), an archaeal condensin ortholog, facilitates higher-level organization of chromosomes in crenarchaea that bears greater similarity to metazoans than bacteria. Their study unravels biological function for chromosome organization in Archaea and provides insights into the evolution of eukaryotic chromosomal compartmentalization.

Since its invention by Lieberman-Aiden et al. (2009), the Hi-C chromosome conformation capture assay has been conducted in several representative organisms in bacteria and eukaryotes. In eukaryotes, these studies have revealed three distinctive levels of three-dimensional (3D) genome topology: (1) the uppermost level of chromosome compartmentalization, in which chromosome compartments of transcriptionally active and inactive chromatin regions are segregated into different nucleus locations; (2) the second level, which is the formation of topologically associated domains (TADs) that appear as squares of enriched contact frequency with sharp boundaries; and (3) the basic level of interactions, called peaks or loops, which are often visible as focal enrichments at the corners of TAD squares (Bonev and Cavalli, 2016). In bacteria, however, higher-level chromosome organization is limited to the formation of self-interacting domains, appearing as extrusion loops (Marbouty et al., 2015). Intriguingly, in this issue of *Cell*, Takemata et al., (2019) show, through their study of 3D genomes of *Sulfolobus*, a crenarchaeon in Archaea, the third domain of life, that crenarchaeal chromosomes are organized into two compartments with different spatial distribution in the cell. This demonstrates that crenarchaea, although prokaryotic, may have adopted all three levels of chromosome organization observed in eukaryotes, in strict contrast to the