CellPress

Opinion

Activity-Dependent and Experience-Driven Myelination Provide New Directions for the Management of Multiple Sclerosis

Samuel K. Jensen[1] and V. Wee Yong[1,*]

Despite an appreciation of the importance of myelination and the consequences of pathological demyelination, the fundamental mechanisms regulating myelination are only now being resolved. Neuronal activity has long been considered a plausible regulatory signal for myelination. However, controversy surrounding its dispensability in certain contexts and the difficulty in determining to what degree it influences myelination has limited its widespread acceptance. Recent studies have shed new light on the role of neuronal activity in regulating oligodendrogenesis and myelination. Further, the dynamics of myelin in adulthood and the association between skilled learning and myelination have become increasingly well characterized. These advances present new considerations for the management of multiple sclerosis and open up new approaches to facilitate remyelination following pathological demyelination.

Regional Heterogeneity and Structural Dynamicity of Myelination in Adulthood

Myelination of axons by oligodendrocytes occurs predominantly after birth and actively extends into the fourth decade of life in humans [1]. This prolonged period of myelin development opens a window where environmental cues and individual experiences can influence the regional pattern of myelination. However, the degree to which myelination differs both in structure and over time between different central nervous system (CNS) regions and between individuals has been challenging to investigate. The recent application of serial election microscopy and advanced *in vivo* imaging techniques has revealed significant structural heterogeneity and dynamicity of myelin throughout life.

The heterogeneity of white matter myelination has long been appreciated. Myelinated and unmyelinated axons commonly intermix within white matter tracts and the proportion of these two populations varies between different regions [2,3]. Generally, subcortical white matter structures contain more unmyelinated axons compared with deep white matter structures. This is particularly notable within the corpus callosum where approximately 30–50% of the axons are postnatally myelinated [2] (Figure 1A). By contrast, the axons within the optic nerve and spinal cord white matter are almost completely myelinated [3] (Figure 1B).

Trends

Myelin has been demonstrated to be a highly dynamic structure with a large degree of heterogeneity between different CNS regions.

Renewed evidence demonstrates that oligodendrocytes respond strongly to neuronal activity where increased activity promotes oligodendrogenesis, increases myelin thickness, biases axon selection towards active axons, and enhances myelinating potential.

White matter fractional anisotropy is positively correlated with skilled learning and adaptive myelination is required for motor skill learning. These changes are likely driven by alterations in neuronal activity patterns during learning.

Sensory and environmental input are required for the proper myelination of both sensory regions responsible for signal processing as well as associated higher order regions within the CNS.

[1]Hotchkiss Brain Institute and the Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta T2N 4N1, Canada

*Correspondence: vyong@ucalgary.ca (V.W. Yong).

 http://dx.doi.org/10.1016/j.tins.2016.04.003

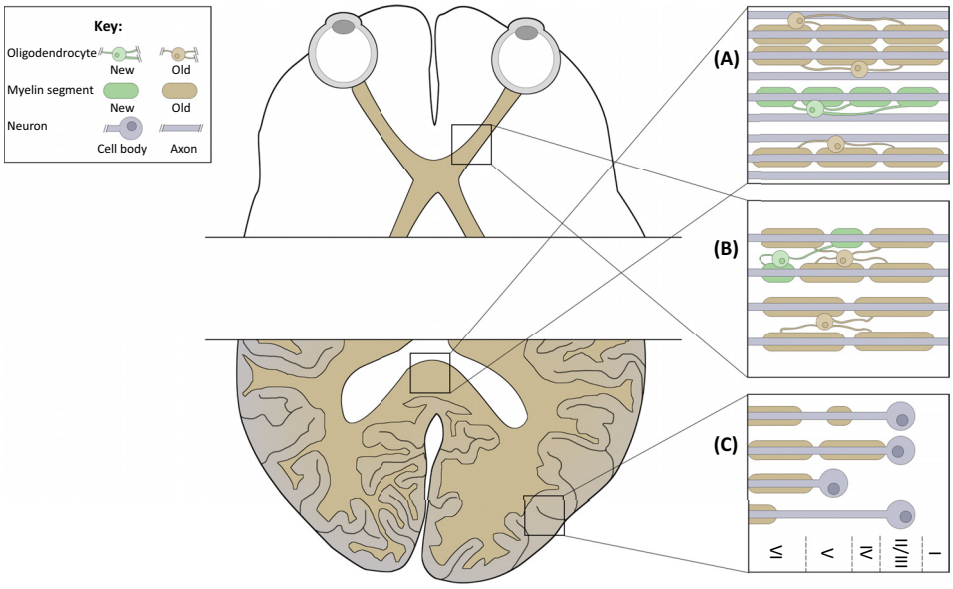

Figure 1. Structural Heterogeneity in Central Nervous System (CNS) Myelination. Significant regional variation in myelination has been described between both white and grey matter regions of the CNS. Further, myelin is continuously generated into adulthood and displays unique characteristics when compared with developmentally generated myelin. (A) Subcortical white matter structures and the corpus callosum are relatively unmyelinated structures. Here, only ~30% of axons are developmentally myelinated [2]. In rodents, significant oligodendrocyte generation is observed in adulthood (30%/year in rodents) [6]. The *de novo* myelination of previously unmyelinated axons (grey) is common. (B) In adulthood, the optic nerve is almost completely myelinated. Despite this, new oligodendrocytes are generated throughout adulthood (6.5%/year in rodents) [6]. These newly formed myelin segments (green) intercalate between previously generated internodes (gold). Overall, internodes formed in adulthood are shorter than their developmental counterparts. (C) Cortical myelination is considerably complex. While layer V projection neurons tend to be completely myelinated, myelination of upper layer neurons, particularly those in layer II/III, is variable [4]. Here, myelin segments can be separated by long stretches of unmyelinated axon. In addition, the distance between the axon hillock and the first myelin segment is highly variable. Roman numerals indicate cortical layer.

Recent high-resolution tracing of cortical neuronal projections has revealed unique patterns of myelination within the mammalian cortex [4] (Figure 1C). Axons originating from cell bodies residing in cortical layer II/III possess low levels of myelination. However, the degree of myelination gradually increases into the deeper cortical layers. In addition, single axon tracing reveals longitudinal heterogeneity in myelin distribution among single upper layer pyramidal neurons. The myelinated segments of layer II/III pyramidal neurons are significantly variable in length and often interrupted by long unmyelinated stretches. Further, myelination of these axons often does not begin at the soma and there is no uniformity in the distance from the axon hillock to the first myelin segment. These features are independent of axon calibre, soma size, or the availability of oligodendrocytes, and they are not maintained when cortical lamination is interrupted or altered developmentally.

The regional and structural features of myelination suggest that adult myelin is a more dynamic and variable structure than previously appreciated. Indeed, significant myelin remodelling has been described in the adult murine CNS accompanied by the widespread generation of new mature oligodendrocytes [5–7]. Strikingly, adult oligodendrocyte and myelin formation occurs in all myelinated tracts. In mice, approximately 30% of all mature oligodendrocytes in the corpus callosum are formed after 7 weeks of age [6]. In the mouse optic nerve, ~6.5% of all mature oligodendrocytes are adult-born. This suggests that even fully myelinated axons can incorporate new myelin segments in adulthood and that axons that have either discontinuous or no myelination are not the sole substrate for adult myelination.