Title: Introduction to the Special Issue on Myelin Plasticity in The Central Nervous System

Guest Editors

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Myelin, as defined in textbooks, is the “fatty” insulation surrounding axons necessary for saltatory nerve conduction. Myelin is formed by the membrane extension of specialized cells called oligodendrocytes in the central nervous system, and Schwann cells in peripheral nerves. Since not all axons are myelinated, nerve fibers have been classified either as myelinated fast-conducting or as unmyelinated and slow-conducting. In the central nervous system, areas with abundance of myelinated axons are called white matter, while the rest is referred to as gray matter. Myelin formation has been traditionally viewed as a pre-established developmental program, and myelin itself as an unchanging structural component of the nervous system. However, a number of recent seminal discoveries have substantially challenged this static model and revealed a dynamic interplay between experiences and the generation of new myelin, the generation of new myelinating oligodendrocytes from progenitor cells, and the remodeling of existing myelin sheaths. This paradigm shift provides new ways to understand how the nervous system responds to and is changed by experience.

Two critical discoveries that challenged the notion of myelination as a fixed process were reports showing that social isolation of adolescent mice impairs myelin formation (Makinodan et al., 2012), and that depriving mice of social contact during adulthood prevents formation of new myelin in the prefrontal cortex (Liu et al., 2012). These studies also showed that the isolation-driven myelin alterations lead to cognitive and behavioral impairments, highlighting the importance of myelin plasticity for brain function. Subsequent studies underscored the importance of myelin formation for motor learning, e.g. adult mice taught to use a complex running wheel were unable to properly

learn if new myelin generation was prevented by genetic manipulations (McKenzie et al., 2014). Furthermore, studies using optogenetic stimulation showed that electrical activity modulated myelin thickness (Gibson et al., 2014). Collectively, these studies reinforced the concept that new generation of oligodendrocytes underlies new myelin formation in the adult brain. However, they also raised the question of whether this process is necessary to replace myelin that has been either damaged or simply replenished over time, or whether there maybe axons or axonal segments within the CNS that become myelinated at late stages. A study based on the serial sectioned-based ultrastructural analysis of single myelinated axons revealed the myelination of central axons can be indeed discontinuous, in the sense that some axons can have some myelinated segments interspersed with unmyelinated ones (Tomassy et al., 2014). Because myelin provides insulation, and therefore modulates axonal conductance, this report suggested that myelin serves as an important mechanism to modulate the flow of neural activity by regulating the speed of axonal conductance and therefore suggested a purpose for the formation of new myelin during learning paradigms.

As knowledge on myelin and its plasticity continues to grow, this special issue of Developmental Neurobiology assembles a series of articles that discuss and review some of the recent progress in the understanding of mechanisms and roles of myelin plasticity and the experimental approaches and systems that can be used to study them.

The review by Long et al (Long et al., 2017) uses the auditory system to highlight the critical role that myelin plays in regulating the flow of acoustic information in the brain, where binaural hearing is critically dependent on very accurate timing of nerve conduction. This paper also reviews emerging evidence that, like other experiential deprivation, sensory acoustic deprivation impairs myelination of the auditory pathways. The original report by Liu et al (Liu et al., 2017) identifies stress as another type of experience that influences myelination, demonstrating that stressors modulate myelin gene expression in a region-specific fashion and lead to defects in oligodendrogenesis and to myelin formation impairment.

Two papers review the mechanisms of myelin development and plasticity. Bechler et al. (Bechler et al., 2017) discuss the idea that developmental myelination is regulated by the interplay of two processes; on one hand an intrinsic program leading to the formation of myelin-forming oligodendrocytes wrapping axons based on their diameter, a.k.a. “innate“ myelination; on the other hand, a process of “adaptive” myelination, where the timing of myelination and myelin thickness are regulated by the electrical activity of axons, providing a basis for why more active fibers are myelinated prior to those less active. Then, the review by deFaria et al. (de Faria et al., 2017) explores the molecular mechanism of activity-dependent myelination, discussing current evidence that this process is mediated by the interplay of ion channels, neurotransmitters and growth factors.

Two reviews explore the impact of myelin plasticity in pathological scenarios. On one hand, the review by Kondiles et al. (Kondiles and Horner, 2017) discusses how myelin plasticity and new myelin formation in the context of traumatic brain injury favors repair, and how this process is facilitated by neural inputs. The authors suggest that manipulation of neural activity might provide therapeutic strategies aimed at favoring remyelination after injury. On the other hand, the review by Gibson et al. (Gibson et al., 2017) discusses the potential contributions of mechanisms regulating myelin plasticity to the pathogenesis of brain disorders. The authors propose the concept that in brain cancer and some psychiatric or neurological disorders, maladaptive utilization of mechanisms involved in myelin plasticity might exacerbate these pathologies.

While work with animal models have provided mechanistic, structural and functional insights into myelin plasticity, human studies support the notion that myelin plasticity is part of human biology. For example, piano practicing during childhood (Bengtsson et al., 2005), working memory training (Takeuchi et al., 2010), and learning to juggle (Scholz et al., 2009) or to read (Carreiras et al., 2009) have been shown to change human white matter structure. The review by Heath et al. (Heath et al., 2017) provides a in depth discussion of the imaging methods that are currently used to analyze myelin and white matter structure in the human brain, their power and limitations.

Together, these studies highlight the exciting recent progress in the understanding of the mechanisms of myelination, the degree of plasticity that myelination possesses, and

the impact of myelin on brain and cognitive function and its potential relevance to neurological and neuropsychiatric disorders as well as to cancer.

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