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Myelination

J.L. Salzer¹ and B. Zalc²

¹New York University School of Medicine, Neuroscience Institute, Departments of Physiology and Neuroscience, NYU School of Medicine, New York, NY 10016, USA.

Electronic address: james.salzer@nyumc.org

²Sorbonne Universités, UPMC Paris06, Inserm U1127, CNRS UMR 7225, Institut du cerveau et de la moelle épinière (ICM), GH Pitie-Salpêtrière, 75651 Paris cedex 13, France

Electronic address: bernard.zalc@upmc.fr

Myelin is a key evolutionary acquisition that underlay development of the large, complex nervous systems of all hinged-jaw vertebrates. By promoting rapid, efficient nerve conduction, myelination also made possible development of their large body size. In addition to increasing the speed of nerve conduction, myelination has also emerged as a source of plasticity in neural circuits that is crucial for proper timing and function. Here we briefly describe the organization of myelin, and of myelinated axons, the functions of myelin in nerve conduction and neural circuits, and consider its potential evolutionary origins.

Formation and organization of myelinated fibers

Myelin is formed by Schwann cells in the PNS and oligodendrocytes in the CNS. Each Schwann cell forms a single myelin sheath around an axon. In contrast, each oligodendrocyte forms multiple sheaths (up to 30 or more) around different axons (see Fig. 1). Along the same axon, sequential myelin sheaths are formed by different oligodendrocytes. Myelin itself forms by the spiral wrapping of an enormously expanded glial plasma membrane around an axon which then compacts. Topological considerations, recently corroborated by live imaging studies, indicate the inner turn of this spirally wrapped glial membrane advances around the apposed axon to form the multilamellar, myelin sheath; as it expands radially, it also expands longitudinally.

Electron micrographs of compact myelin demonstrate the familiar appearance of interperiod lines, representing the apposition of the extracellular leaflets of the glial plasma membrane, alternating with major dense lines, resulting from the tight apposition of the cytoplasmic leaflets. The final compact myelin sheath can be comprised of as many as 40 or more lamellae. The thickness of the myelin sheath is tightly regulated and is highly correlated to the diameter of the axon it surrounds; this is conventionally expressed as the g ratio (the axon diameter/total fiber diameter).

Myelin is unique among plasma membrane equivalents in its unusually high lipid content (~70%), which includes galactosphingolipids, certain phospholipids (correspondingly named sphingomyelin), saturated long-chain fatty acids and, in particular, cholesterol; the latter is required for myelin sheath assembly. Myelin is also highly enriched in a relatively few proteins; the composition of these proteins overlaps but is distinct between PNS and CNS myelin. PNS myelin proteins include P0, a transmembrane adhesion molecule and a member of the immunoglobulin gene superfamily, which promotes apposition of the extracellular leaflets via homophilic adhesion. Another key protein is myelin basic protein (MBP), that binds to and neutralize the charges of the phospholipids (e.g. phosphatidylserine) on the inner leaflet of the plasma membrane. MBP is a major component of both PNS and CNS myelin. Finally, proteolipid protein (PLP), which has 4 membrane spanning segments, is a major component of CNS myelin. In the adult, these myelin proteins exhibit very little turnover indicating that the mature myelin sheath is normally quite stable. Recent proteomic studies have identified many additional, minor components of the myelin sheath whose functions are still being elucidated but likely contribute to the organization and integrity of the sheath.

With myelination, the glial cell also drives a reorganization of the axonal proteins into a series of specific domains (Fig. 2). Notably, myelination results in the accumulation of voltage gated sodium channels at the nodes of Ranvier - the gaps on the axon in between the myelin sheaths. Nodes are ~ 1 μm in length, corresponding to <1% of the territory of the myelinated axon. They

are flanked by specialized paranodal junctions, which are the sites of closest apposition between axons and myelinating glia. Due to its circumferential wrapping, the outer, uncompacted edge of the glial cell has the appearance of a series of loops invaginating the axon. A characteristic of the paranodal junctions, as visualized by EM, are regularly spaced, transverse septae that emanate from the axon. The paranodal junctions serve as a membrane diffusion barrier that promotes the accumulation of the voltage gated sodium channels at the node and separates them from potassium channels (i.e. Kv1.1 and Kv1.2) in the juxtaparanodes. In contrast to this highly organized structure, unmyelinated axons exhibit a diffuse distribution of voltage gated channels and various adhesion molecules consistent with their conduction of action potentials by cable propagation.

Myelin and the need for speed

An increase in the speed of nerve conduction represents an obvious evolutionary advantage by enabling rapid monitoring of and response to the external environment. During evolution, there were two distinct strategies for achieving increased conduction velocity: i) increasing axon size and thereby decreasing the axial/interior resistance of the axon - which is inversely proportional to axon cross sectional area and ii) decreasing the trans-fiber capacitance of the axon via myelination.

An increase in axon diameter was a strategy largely adopted by invertebrates and is best illustrated in cephalopods (squid, octopus, cuttlefish, etc) - species in which some giant axons reach a diameter of between 0.5 and 1 mm, allowing a conduction velocity of 25 m/s. However, there are clear spatial and energetic disadvantages to increasing axon diameter. Thus, the unmyelinated squid giant axon occupies 15,000 times the space of a comparably conducting myelinated mammalian nerve and requires several thousand fold more energy. Extrapolating to humans, it has been estimated the human spinal cord would be nearly a meter across if it relied on increased axon diameters. Thus, while increasing axonal diameter represents a solution adopted by many invertebrates, it is not compatible in vertebrates given the physical constraints imposed on the CNS by the skull and vertebral column.

Myelination of axons, a key vertebrate acquisition, also enabled rapid action propagation via saltatory conduction. This increase in the speed of conduction results from the dramatic and cooperative changes in the glial cell and the organization of the axon discussed above. The compact myelin sheath increases the local resistance of the axon and reduces membrane capacitance by several orders of magnitude. Voltage gated sodium channels are concentrated at nodes of Ranvier and downregulated along the internodal axolemma ensuring that current flow is spatially restricted to the nodal region. Paranodal junctions function as an electrical seal that limit current leakage underneath the sheath. Together, these changes in the architecture of myelinated fibers result in dramatic increases in conduction velocity. Both strategies – increased axon diameter and myelination - are characteristic of the fastest conducting vertebrate axons, e.g. motor fibers.

Despite the clear advantages myelination provides, not all vertebrate axons are myelinated. In the PNS, small caliber fibers, e.g. those subserving pain and temperature as well as post-ganglionic autonomic nerve fibers, remain unmyelinated. The ensheathment fate of axons in the PNS, i.e. whether they are myelinated or remain unmyelinated is dictated by whether they express

threshold levels of neuregulin 1, a membrane-tethered member of the EGF superfamily, on their surface. In the CNS, certain fiber tracts, also remain unmyelinated, e.g. dopaminergic axons in the medial forebrain bundle and parallel fibers in the cerebellum. In the CNS, myelination appears to be more of a default pathway for oligodendrocytes. Recent studies suggest that selection of fibers that will remain unmyelinated, e.g. a subset of axons and of all dendrites, is dictated by the presence of as yet unknown inhibitory signals on those fibers.

Adaptive myelination and neural circuits

Importantly, myelin does not simply maximize conduction velocity, it also provides a substrate for additional control of the timing of inputs during development and in adult neural circuits. Precise control of timing is essential not only for motor skills and sensory processing but also for higher integrative functions including cognition. As an indication that myelin likely has broader functional relevance, it constitutes ~ 15% of the weight of the rodent brain and ~50% of that of humans. Myelin is present not just in white matter but is also an important component in the cortex and deep grey nuclei in agreement with its role in more complex neural functions.

At the cellular level, timing must be regulated for proper coincidence detection, proper sequencing of excitatory and inhibitory inputs and spike-timing-dependent plasticity that underlie Hebbian learning. In addition, there are numerous examples of synchronous activation of spatially dispersed targets in which variation in conduction velocity is critical. A notable example is the synchronous activation of cerebellar Purkinje cells by climbing fibers – despite being at varying distances from the inferior olivary nucleus.

In many cases, timing involves slowing or speeding action potential propagation of some axons relative to other axons. Such variation in conduction speed could result from alterations in individual anatomical parameters of myelinated axons. These include axon diameter, differences in internode length (increasing the length increases conduction until a maximum is achieved), myelin sheath thickness or potentially even node diameter and length. These parameters can vary between axons and potentially even along the length of the same axon. Evidence that these structural parameters of myelinated axons can be tuned to optimize conduction velocity that is important for temporal processing has been shown in the auditory system. Thus, axons responding best to low-frequency sounds have a larger diameter than high-frequency axons but, surprisingly, shorter internodes.

An alternative mechanism for adjusting conduction velocity is by adding new myelin sheaths to axons. It has generally been thought that axons are either uniformly myelinated or entirely unmyelinated and thus propagate action potentials exclusively by saltatory conduction or by cable propagation, respectively. Unexpectedly, recent data indicates that CNS axons of young adult rodents are often inconsistently myelinated. In particular, layer II and III projection neurons harbor large, unmyelinated gaps along their length and thus likely use a combination of cable propagation and saltatory conduction. Modulation of conduction velocity might, accordingly, result from ongoing myelination of unmyelinated gaps. In agreement with this notion, recent studies indicate that new myelin continues to form much later into adulthood than previously realized – in rodents up to 8 or 9 months and in humans well into the 40s. Whether this represents the gradual filling in of unmyelinated gaps, or possibly intercalation into existing myelinated fibers is not yet known.

An emerging consensus is that there is activity-dependent control of myelination during development and in the adult and that this late myelination is important for the acquisition of new (motor) skills. Studies in both mice and zebrafish indicate that oligodendrocytes are biased to myelinate electrically active axons. Neuronal activity promotes proliferation of oligodendrocyte progenitors and stabilizes axon-oligodendrocyte interactions. The mechanisms by which neuronal activity drives these events is yet to be established but may involve glutamatergic signaling. In humans, MRI data also supports the notion that activity predisposes specific motor tracts for myelination. Importantly, formation of new myelin from local progenitors in the CNS appears to be required for the acquisition of complex motor skills in the adult rodent. While this is likely to involve enhanced conduction speeds of the cognate motor circuits, this remains to be shown.

Myelin and metabolic support of axons

Myelinating glia cover nearly the entirety of the axon presenting axons with the challenge of accessing a source of metabolites. While myelination markedly reduces the energy requirements for action potential propagation, energy is still required for transport, metabolism and action potential regeneration at nodes. In addition, body size is an additional, formidable issue as the length of axons are easily 1000 to 10,000 times greater than that of the neuronal cell body. Typically, axon components are replenished via transport from the soma. While trafficking of vesicles along the axons is relatively rapid, soluble molecules including metabolites move much more slowly with a maximum rate of 300 $\mu\text{m}/\text{h}$. For a human motoneuron, whose axons can easily be 1 meter in length, it would take between 3 and 20 days for trafficking of proteins via fast, vesicular transport. For metabolites required for aerobic metabolism, such as glucose or lactate, transport from the neuronal cell body would take on average 200 days to reach the axon terminal!

A solution is provided by the myelinating glia themselves, which serve as conduits for metabolic support for the axon along its length. Myelinating glia have been found to be critical for transferring energy metabolites (i.e. lactate) to axons through monocarboxylate transporters which are present on the inner membrane of the glial sheath and on the axon. Neurons are known to be highly vulnerable to energy deprivation. In agreement, a hallmark of myelin disease is axonal/neuronal degeneration which likely results, at least in part, from disruption of this metabolic support from the glial cell.

Evolutionary considerations

Among extant species, the great majority although not all vertebrates are myelinated: axon myelination is present in gnathostomes, i.e. fish with a hinged jaw but not in agnatha, i.e. jawless fish (Fig. 3). It has been suggested that the dual, apparently unrelated acquisitions of myelin and the hinged jaw may even have been coupled in evolution. If so, myelin would have first appeared in the oldest jawed fish, the placoderms, during the Devonian period some 425 million years ago. Indeed, examination of the exquisitely preserved imprints of cranial nerves and the foramina they traversed on the inner face of the skull of placoderms and jawless osteostraci fossils supports the conclusion that the oculomotor system in placoderms must have been myelinated to function as a rapidly conducting motor pathway, particularly given the formidable

lengths (up to 9 meters) that some placoderms achieved. Thus, the first fish with a hinged jaw, the placoderms, were likely the first organisms possessing myelinated axons in the craniate lineage.

Myelin provided an extraordinary evolutionary advantage, facilitating both predatory and prey/escape behaviors. Given its inherent advantages, myelination - once established - became widespread throughout all gnathostome phyla. The rapid conduction velocity provided by myelinated fibers also made feasible the large increase in body size achieved by vertebrates, which reached its apotheosis in the Sauropods. At nearly 60 meters in length, these were the largest vertebrates to have existed (today's blue whales reach a length of 30 meters). Based on estimated nerve lengths in the motor circuits of these enormous vertebrates, and known conduction velocities in present day nerves, it would have required response times of minutes for motor pathways in the PNS if unmyelinated vs. a second or two for comparably sized myelinated nerves. Thus, it seems highly likely that myelination was a critical factor enabling organismal gigantism.

An intriguing question is how myelin itself evolved. Myelin would have arisen in the context of a world in which axons were already ensheathed by glia – a characteristic of the nervous systems of virtually all phylogeny and thus evolutionary ancient. Generation of a spirally wrapped glial process appears to be a relatively modest transition from this starting point. Thus, recent studies have shown that activation of PI 3-kinase and its effector Akt are sufficient to induce ensheathing Schwann cells to generate elaborate, spirally wrapped (albeit non-compacted) membrane sheaths around axons. Expression and recruitment of myelin proteins under the control of appropriate transcriptional cascades, would likely drive their compaction. It has also been shown that regulation of the actin cytoskeleton (i.e. inhibition of an effector of Rho GTPase) can induce Schwann cells to generate multiple myelin sheaths akin to that of oligodendrocytes. Thus, modest changes in intracellular signaling pathways result in dramatic transitions in glial morphology resembling those of myelination. Further, key molecular complexes characteristic of the myelinated axon: e.g. the sodium channel complex and the paranodal complex, likely antedated myelination during evolution. The sodium channel complex (e.g. sodium channels, adhesion molecules and Ankyrin G) almost certainly evolved to generate action potentials at the axon initial segment and was likely repurposed later for its analogous role at nodes. The paranodal junctional complex (e.g. the adhesion molecules Caspr, contactin, and a 4.1B-based cytoskeleton) also antedates myelin as it is molecularly and functionally orthologous to invertebrate septate junctions. Thus, modest changes in glial morphology and repurposing of existing molecular complexes could have readily generated a precursor to today's familiar vertebrate myelin sheath.

Based on the appearance of several key proteins during evolution, myelin may have evolved in early gnathostomes in a common glial precursor that later gave rise to the distinct Schwann cell and oligodendrocyte lineages, ensuring that both the CNS and PNS were concurrently myelinated. However, there are important differences between Schwann cells and oligodendrocytes that are not readily reconciled with the notion of a common glial precursor. These include distinct embryological origins (neural crest vs. neuroectoderm, respectively), distinct transcriptional cascades that regulate myelination in these cells (Sox10, Pou3F1, Egr 2 vs. Sox10, Olig1/2, MYRF) and even distinct mechanisms of wrapping. These considerations raise the possibility of convergent evolution in distinct glial lineages.

Indeed, evolution is not a linear process and myelin-like structures have appeared multiple times during evolutionary history. Notably, among invertebrates some crustacea (arthropods) and some annelids (lophotrochozoa) have axons that are wrapped by processes of glial cells. In the case of arthropods, these myelin-like structures consist of concentric ensheathment by multiple flattened glial processes of separate glial cells. Annelids do form a multilammellar, spiral wrap which are mostly uncompacted. Even though these myelin-like structures are not consistently compacted as they are in vertebrates they are highly efficient. Although nodes of Ranvier could not be demonstrated morphologically in these species, electrophysiological recordings strongly suggest that conduction is saltatory in these giant fibers. For example, in the *Kuruma* shrimp impulse conduction velocities range between 90 – 200 m/sec in axons 10 μm in diameter and covered by a 10 μm thick myelin-like sheath - the fastest velocities known among all animal species.

Interestingly, in this subphylum of arthropods, only some shrimp and some copepods present these pseudo-myelin structures. Similarly, in the phylum Annelida, only some species have myelin-like structures ensheathing axons, while other members of the same phylum do not. It has been proposed that cutting the response time by increasing the speed of conduction was first developed for escape from predators, which is in agreement with the observation that the territory of extension of myelinated copepods is much larger than that of their non-myelinated “cousins”.

Perspectives

Given its essential roles in increasing conduction velocity and providing metabolic support, acquisition of myelin was a critical event in the evolution of the large, complex neural circuits of vertebrates. Myelin is also now appreciated to be surprisingly dynamic, regulated by neuronal activity, that contributes to the timing and plasticity of neural circuits, that would also contribute to the evolution of neural circuits. This progress in understanding of myelin’s more complex roles in the vertebrate nervous system raise additional, important questions. What are the molecular mechanisms by which activity regulates myelination? Is activity-dependent regulation of myelination a feature of all oligodendrocytes and all circuits, or is it more restricted - in particular, might regulation of myelination contribute to the development of behavior and learning in the adult. Answers to these questions are likely to provide important insights into acquisition of complex behaviors as well as a variety of neurologic and neuropsychiatric disorders.

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FIGURES

Figure 1: A comparison of myelination in the PNS and CNS

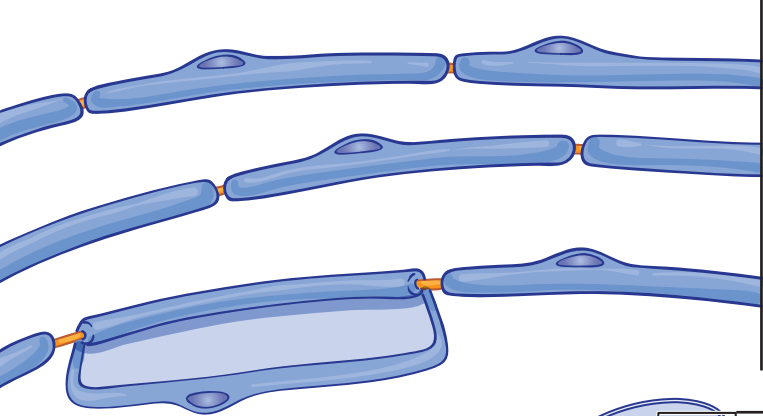
Schwann cells form individual myelin sheaths (blue) around axons (orange) whereas oligodendrocytes form multiple myelin sheaths (purple) each on separate axons. Schwann cell nuclei are located on the outside of the sheath. One myelinating Schwann cell is shown partially unrolled: the light central area is the topological equivalent of the compact myelin sheath, the darker edges represent belts of cytoplasm along the cell border. In the CNS, a stretch of unmyelinated axon is shown in agreement with recent evidence that some axons are inconsistently myelinated. A cross-section of a myelin sheath is illustrated at the bottom demonstrating the origin of interperiod line, formed by apposition of the extracellular leaflets, and the major dense line formed by the tight apposition of the cytoplasmic leaflets. Myelin grows by the spiral wrapping of the inner turn (arrow) around the axon.

Figure 2: Organization of the domains of myelinated axons in the PNS and CNS

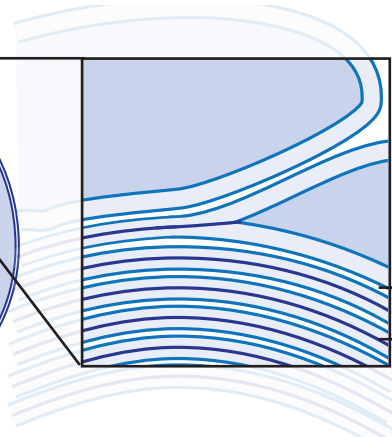
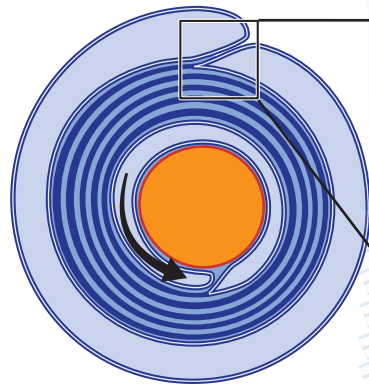
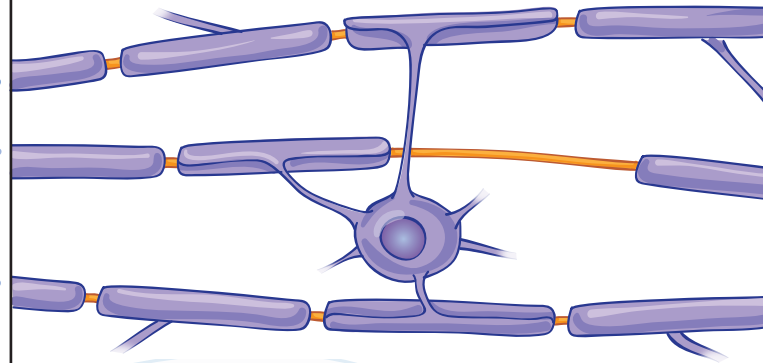
A longitudinal cross section through a myelinated axon in the PNS (top) and CNS (bottom) is schematically illustrated. The axon, with intracellular organelles/mitochondria concentrated in the nodal region, is in red and myelinating glial cells and sheaths are in blue. The node of Ranvier is demarcated in purple. In the PNS, the node is contacted by microvilli arising from the outer collar of the Schwann cell; in the CNS, it is frequently contacted by a process of a specialized glial cell. The paranodal junctions (magenta), with their transverse bands, flank each side of the node. The location of the juxtaparanodes (green) and internode (orange) located under the compact myelin sheath are also shown. Schwann cells are surrounded by a basal lamina, unlike oligodendrocytes.

Figure 3: A Cladogram of Craniate Myelination. Myelinated species are in purple, non-myelinated species are in green. Species listed in *italics* followed by † indicate fossils for which it is assumed they were myelinated (in purple) or not myelinated (in green).

PNS



CNS



Intraperiod line

Major dense line

