The acquisition of myelin: An evolutionary perspective

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Abstract (216 words)

It has been postulated that the emergence of vertebrates was made possible by the acquisition of neural crest cells, which then led to the development of evolutionarily advantageous complex head structures (Gans & Northcutt, 1983). In this regard the contribution of one important neural crest derivative—the peripheral myelin sheath—to the success of the vertebrates has to be pointed out. Without this structure, the vertebrates, as we know them, simply could not exist. After briefly reviewing the major functions of the myelin sheath we will ask and provide tentative answers to the following three questions: When during evolution has myelin first appeared? Where has myelin initially appeared: in the CNS or in the PNS? Was it necessary to acquire a new cell type to form a myelin sheath? Careful examination of fossils lead us to conclude that myelin was acquired 425 MY ago by placoderms, the earliest hinge-jaw fishes. I argue that the acquisition of myelin during evolution has been a necessary prerequisite to permit gigantism of gnathostome species, including the sauropods. I propose that this acquisition occurred simultaneously in the PNS and CNS and that myelin forming cells are the descendants of ensheathing glia, already present in invertebrates, that have adapted their potential to synthesize large amount of membrane in response to axonal requirements.

Functions of the myelin sheath

Myelin has three major functions. Chronologically it was first described as a way to protect naked axons. It is Robert Remak who first reported, in 1838, the co-existence in peripheral nerves of two types of fibres, some being wrapped by a thick sheath (Remak, 1838). When in 1854 Virchow proposed to name **myelin** this sheath wrapped around axons (Virchow, 1854) this was at the time when the first communication cable was laid under the sea between France and England (1850) followed by the first transatlantic cable between Ireland and Newfoundland (1858). The heart of the cable was made of seven wires (axons) of copper, enrobed (wrapped) by three layers of gutta-percha (the myelin) to protect the copper wires. As Virchow wrote: "The medullary sheath serves as an isolating mass, which confines the electricity within the nerve itself and allows its discharge to take place only at the non-medullated extremities of the fibers." Later, Louis Ranvier extended the comparison to transatlantic cables: "Electrical wires immersed in a conductive medium need to be protected from this medium by a non-conductive sheath; it is on this principle that transatlantic cables are built." (Ranvier, 1878).

The second major function of myelin sheath is to accelerate the speed of conduction of nerve influx. There are only two ways transmission of action potential can be accelerated: increase the diameter of the axon and/or wrap the axon with a myelin sheath (Rushton, 1951). In most species (vertebrate and invertebrate) the axon diameter averages between 0.3 and 30μm. As a consequence, action potentials along non-myelinated invertebrate axons propagate at about 1m/s or less for an axon of about 10μm in diameter. This is sufficient, however, for routine conduction within the framework of animals of relatively small size (between 0.1 and 30 cm). Among invertebrates only the cephalopods (squid, octopus) have larger axons, but this large size is generally limited to those neurons involved in the rapid escape response. By increasing the diameter of key axons up to 1mm or more, cephalopods have increased action potential speed, and so have been able to evolve a larger body size. In vertebrates, the entire CNS is confined into

the skull (brain) and the vertebrae (spinal cord) rigid bony structures, which impose a physical constraint preventing the increase in axon diameter. It has been calculated that, in human, to maintain a speed of conduction of 50m/s, solely by increasing the diameter of axons, the spinal cord would reach a diameter of 1meter! Acquisition of the myelin sheath, by maintaining the axon diameter below 10 – 15 μm, permits to keep, in human, the width of spinal cord to a maximum of 6-7 cm. Plotting the speed of conduction against the axon diameter in non-myelinated and myelinated fibers shows that myelination is favored when the axon diameter is superior to 1μm (Rasminsky, 1971; Koles & Rasminsky, 1972; Moore et al., 1978).

The third function of the myelin sheath has been illustrated only recently (Fünfschilling et al., 2012; Lee et al., 2012). These authors have suggested that myelin-forming cells provide nutrient and support the integrity of axons. In this respect it has to be reminded that body size is again an issue. Indeed, length of axons are easily 1 000 to 10 000 times higher than neuronal cell body. Transport along axons can be either fast or slow. Traffic of vesicles along the axons is relatively rapid, varying between 2 and 17mm/h. In contrast soluble molecules move slowly at a maximum of 300 μm/h. Therefore, for a human motoneuron, which axon can easily be 1m in length, it will take between 3 and 20 days for proteins trafficking using the fast moving vesicular cargoes. In contrast, for nutrients, such as glucose or lactate, transport from the neuronal cell body will take in the average 200 days to reach the neuro-muscular junction! Neurons are highly vulnerable to energy deprivation. Myelin forming-cells, have therefore a crucial role for axon function and survival by transferring energy metabolites (namely lactate) from their cell bodies to axons through monocarboxylate transporter (Morrison et al., 2013). It is likely that this transfer of lactate from oligodendrocytes to axons takes place at the paranodal loops of myelin wraps.

A key consequence of the acquisition of myelination has been the possibility to increase body size. In an interesting paper, Sander and Clauss proposed a set of factors that contributed to the evolution of massive body size in sauropods (Sander and Clauss, 2008). These authors suggested that « the unique gigantism of sauropods was made possible by a combination of phylogenetic

heritage (lack of mastication, egg-laying) and a cascade of evolutionary innovations (high growth rate, avian-style respiratory system, and a flexible metabolic rate". Surprisingly, a critical factor omitted from these authors' analysis was the introduction of the myelin sheath. Imagine a Diplodocus 40m in length bitten in the tail by a predator. Clearly, if Diplodocus had not been myelinated, nerve impulse along fibers whose diameters could without myelin ensheathment only support an extremely slow rate of conduction (~1 m/sec), a full 40 seconds would have been required for action potentials to ascend the length of this giant sauropod to its brain, and another 40 seconds for the return signal to the tail muscles - completely incompatible with fast reaction times necessary for escape. However, the same signal, traversing the same diameter myelinated axon, would make the 80 meters round trip at a speed of 100m/s and reach the tail musculature in only 800 milliseconds. Large predatory dinosaurs such as *Mapusaurus rosae* (13 m in length) (Coria and Currie, 2006) no doubt possessed myelinated nervous systems as well, since they also would have required millisecond reaction times to chase and snap at prey. Furthermore, and this is consistent with Sander and Clauss' analysis - a myelinated nervous system conserves metabolic energy.

Having set the scenery and outline the crucial role of acquisition of myelin as a pre-requisite to vertebrate increasing in size, we can ask when during evolution has myelin first appeared?

When during evolution has myelin first appeared?

Are only vertebrates myelinated?

Shortly after myelin has been described in peripheral nerves of vertebrates, Retzius (1888), Friedlander (1889) or Nageotte (1916) reported in some annelid and some crustaceans the presence of myelinated fibres. However, it is of note that not all annelids or crustaceans have wraps of membrane around their axons (e.g., leeches or lugworms for annelids, or augaptiloid copepods, Mantis shrimp, or benthic decapods (lobsters and crabs) for crustaceans do not present these myelin-like structures around axons)(see Fig. 3 in Hartline & Colman, 2007). Also

myelin or myelin-like structures have not been reported in mollusks or insects. In invertebrates having a myelin-like membrane ensheathing some axons, these membranes are often concentrically arranged and compactness is often incomplete. However these pseudo-myelin like structures can be super efficacious assuring for instance in copepods of the order calanoida an escape response of 200 body lengths per second within milliseconds (Davis et al., 1999). Using myelin-like sheath around axons the penaeid shrimp achieved speed of conduction of nerve impulse of $200ms^{-1}$, the highest speed of conduction reported among living species, twice more rapid than in the fastest reported myelinated axons in vertebrates (Hartline & Colman, 2007).

Are all vertebrates myelinated?

Among the phylum chordates (animals possessing a notochord, and hollow dorsal nerve cord) two subphyla have been identified: Cephalochordates (lancelet or amphioxus) and Craniates. Craniates include Mixinidae and Vertebrates. Depending on the absence or presence of a hinge-jaw, craniates can be divided in two groups: among the most primitive are the agnathans, which are jawless fishes, contrasting with gnathostomes, which have a hinge-jaw. Agnathans are a relatively small group of fishes comprising among living species hagfish (mixinidae), and lampreys (vertebrate). These species do not have myelinated axons. In the outgroups cephalocordates (lancelets), and hagfishes (jawless basal craniates), as well as lampreys (jawless basal vertebrates), axons are ensheathed by glial cells, but myelin is not present.

Even the lamprey is not myelinated, despite the detection of cross-immunological reactivity with myelin proteins from bovine or teleost (Waehneldt et al., 1987). In contrast, among gnathostomes, even the most ancient chondrichtyes (cartilaginous fishes such as rays or sharks) are myelinated. And so are the osteichthyes (bony fishes). Several authors have studied myelin in sharks and rays and have pointed the cellular similarities, and sequence homologies with myelin in mammals (Agrawal et al., 1971, Kemali et al., 1983; Tai & Smith,1984; Kitagawa et al., 1993, Saavedra et al., 1989; Gould et al., 1995). Although chondrichtyes are the most ancient living myelinated species, it is of note that they are already myelinated both in the CNS and in the PNS

with cells alike oligodendrocytes, i.e., multibranched cell myelinating several internodes and Schwann cell type cell, i.e., cells myelinating a single internode, in the CNS and PNS, respectively. Examination of the composition of PNS and CNS myelin constituents across species show similarities and differences; among similarities are the high concentration and unique expression of galactosphingolipids: galactocerebroside and sulfatide. It appears that the presence of galactosphingolipids is necessary for compaction and stability of myelin membrane. In contrast the choice of proteins is more versatile. From an evolutionary point of view it is of interest to note that in fishes the major myelin protein is P0 (P zero) both in the PNS and CNS. It is only with amphibian that CNS myelin looses the expression of P0 and chooses PLP and MBP as major protein constituents, with remarkable sequence conservation across species.

In vertebrate myelin was acquired by Placoderms

These observations on living species lead us to raise the question of when during evolution has myelin appeared. In the annelid and crustacean, I would have the tendency to consider the described wraps around axons as a myelin-like structure, mostly because in most species the extensive membranous around axons are concentrically deposited (in contrast with spirally wrapping in vertebrates) and not very compact with frequent interlamellar inclusion of cytoplasm. Another feature is that having these myelin-like structures has not been adopted by increasing numbers of these family members. This is in contrast with the situation of vertebrates since from fishes to primates, all the species are myelinated. Another interesting observation is that looking at the evolutionary trees from crustacean, annelid and craniate, it is clear that as proposed by B. Roots, the synthesis by glial cells of these multilamellar sheath of membrane has occurred separately and at least on three different occasion (Roots et al., 1991). This would have happen in canaloid copepod for the crustaceans, and earthworm for annelid. In vertebrate, since there is no living species between the lamprey (non myelinated agnathans) and fully myelinated shark or ray, we questioned when during evolution of vertebrates has myelin been acquired. In

the absence of living species, we turn towards fossils. It occurred to us that fossil fishes might harbor some clues as to whether their nerves were myelinated or not. It has been suggested that the dual, apparently unrelated acquisitions of myelin and the hinged jaw were actually coupled in evolution (Zalc & Colman, 2000). If so, it would be expected that myelin was first acquired during the Devonian period by the oldest jawed fish, the placoderms (Grassé, 1975). It might be anticipated that in non-myelinated species, the nerve length:diameter ratio would be smaller than in a myelinated organism, as is found to be the case when this comparison is made amongst living animals. Indeed, axon diameter is relatively constant among species (between 0.3 and 30μm) and in the average around 1μm. This constrast with the length of axons, which in invertebrates (with the exception of cephalopodes) do not exceed 25-30cm, while in vertebrates, depending on the body size, axons are much longer. For instance, in human, axons travelling from the motor cortex to the spinal cord, can easily reach a length of 100cm. Accordingly, we set out to determine this ratio for Paleozoic vertebrate fish (osteostraci and placoderms) that were contemporaneous, and for whom well-preserved fossilized skulls exist. Although myelin itself is not retained in the fossil record, within the skulls of well-preserved fossilized vertebrate fish are exquisitely preserved imprints of cranial nerves and the foramina they traversed. We have measured the length and diameter of oculomotor nerve in specimen of ostracoderm and placoderm of about the same body size. In placoderms, the first hinge-jawed fish, oculomotor nerve diameters remained constant, but nerve lengths were 10 times longer in comparison with the jawless osteostraci. In order to accommodate this 10-fold increase in length while maintaining a constant diameter, we conclude that the oculomotor system in placoderms must have been myelinated to function as a rapidly conducting motor pathway (Zalc et al., 2008). Significantly, it is highly likely that as the first fish with a hinged jaw, and taking into account the fact that certain placoderms grew to formidable lengths (up to 9 meters), necessitating a rapid conduction system, the placoderm was also the first organism possessing myelinated axons in the craniate lineage (Fig. 1). In contrast, their fellow ostracoderm were most probably not myelinated and in line, it is

of note that none of the osteostraci fossils reported have a size exceeding 70cm. The myelin sheath in vertebrates arose in conjunction with the neural crest, which gives rise to the jaw apparatus and most of the peripheral nervous system. The myelin sheath was an extraordinary enabling acquisition in this regard, facilitating both predatory and escape behaviors, and permitting the evolution of very large vertebrate body sizes such as were featured in the placoderm repertoire, the first jawed fishes arising as early as the middle Silurian period some 425 million years ago (Zalc et al., 2008). To explain the apparent close developmental relationship between oligodendrocytes and motor neurons in the ventral spinal cord WD Richardson has put forward a parallel view that myelin first evolved not for predation, but for escape from predators (Richardson et al., 1997; Li & Richardson, 2009).

Where has myelin initially appeared: in the CNS or the PNS?

Many axons run both in the CNS and the PNS. For instance nerves conducting the eye motility, which originates in the III, IV and VI nuclei and are myelinated by oligodendrocytes during their intracerebral travel, and then exit the CNS to become myelinated by Schwann before reaching the oculo-motor muscles. Similarly motor fibres from spinal cord motoneurons have a short pass in the CNS before exiting the spinal cord by the ventral root to form the motor contingent of peripheral nerves. They are initially myelinated by oligodendrocytes and then by Schwann cells after crossing the ventral root. Alternatively, sensitive axons, which cell body is in the dorsal root ganglion are initially myelinated by Schwann cells, and after entering the CNS, oligodendrocytes are assuming their myelination. In demyelinating disease like MS a partial demyelination, as far as a sufficient number of adjacent internodes are concerned, results in a block of conduction. Therefore if myelination had started in the PNS only, the nerve impulse circulating at high speed would be stopped when entering the unmyelinated CNS. Of note, in the retina, axon of the retinal ganglion cells are not myelinated, except in the rabbit, in their retinal portion and start to be myelinated only after they cross the papilla to form the optic nerve. Therefore the nerve influx must propagate slowly in the retina and then is suddenly accelerated when in the optic nerve.

Starting slow and then moving fast is fine, but a rapid conduction does not accommodate a brutal slowing down. The only way it could adapt is by dramatically increase the axon diameter, an impossible solution (see above) due to the physical constraint of the skull or the vertebrae. Following a slightly different reasoning, based on the hypothesis that evolutionary pressure for primitive vertebrates to get moving in order to escape predators preceded the advent of the vertebrate jaw, Li and Richardson argue that "once the myelinating program started to evolve in one cell type, all or part of the program could have been activated in other cells, given appropriate cues. Therefore, evolution of CNS and PNS myelin would have gone largely hand in hand" (Li & Richardson, 2008). Both hypotheses are complementary. Hence it is most likely that during evolution, myelination has started simultaneously in the PNS and the CNS.

Was it necessary to acquire a new cell type dedicated to myelination?

Oligodendrocytes have a multiple origin.

It is now well established that even though the myelin sheath looks everywhere the same in the CNS, whether in the spinal cord, brain stem, mesencephalon, diencephalon or telencephalon, the oligodendrocytes differs depending on their origin. These differences are of three types:
Difference depending on their dependence on growth factors: It is well established that the majority of oligodendrocytes depends on PDGF-AA for their survival, proliferation and even migration (Richardson et al., 1988). It has however been demonstrated that there exists subpopulation of oligodendrocytes that are independent on PDGFRα signaling (Spassky et al., 2001).

Oligodendrocytes are also diverse depending on molecular cues necessary for their emergence, whether on the ventro-dorsal or the rostro caudal axis. For instance it was for a longtime believed that in the spinal cord oligodendrocytes originate solely from the ventral portion, following an induction by the morphogen Sonic Hedge Hog (Shh) in a restricted ventral ventricular territory expressing Olig2 and Nkx2.2. More recently it has been shown that subpopulation of oligodendrocytes also emerge from more dorsal territories relatively distant

from sites of expression of Shh and expressing Msx-3 and Dbx-1 (Vallstedt et al., 2005; Fogarty et al., 2005). Similarly, it has been shown in the telencephalon that oligodendrocyte can have a ventral, alar or dorsal origin. Ventrally, they are characterized by the expression of Nkx2.1, those emerging from the alar territory expresses Gsh-2, while dorsally they are Emx-1 positive (Kessaris et al., 2006). Finally differences along the rostro-caudal axis are illustrated by the role of Hox gene family: in rhombomeres 2 to 4, Hoxa2 inhibits oligodendrogenesis, while in rhombomere 4, Hoxb2 increases oligodendrogenesis (Miguez et al., 2012). It is of note that while Hoxb2 has a restricted pattern of expression limited to rhombomere 4 and that *hox* gene family are not expressed more rostrally than rhombomere 2. Therefore from rhombomere 1 and more rostrally, oligodendrogenesis is not influenced by the *hox* genes. Finally, depending on their site of origin oligodendrocyte precursor cells respond differently to guidance cues controlling their migration towards their final destination. This has been shown for members of the semaphorin family (semaphorin 3A and 3F), for netrin 1, but also for some members of the Eph/Ephrin family (Sugimoto et al., 2001; Spassky et al., 2002; Tsai et al, 2003; Prestoz et al., 2004). Because of this vast variability on their origin it would have been necessary to generate a large number of different oligodendrocytes. On the other hand, one can argue that during evolution, it was necessary to generate only one type of oligodendrocyte and that the diversity observed on present living species would have been the result of further successive adaptations.

However, a series of observations and experimental data do not favor the necessity to acquire a new cell type for myelination to occur. As we shall explain in the following section, there is evidence that ensheathing glial cells in invertebrate have the capacity to synthesize large amount of membrane, and in drosophila as a consequence of a neuronal mutation these glial cells even wrap around axons. Therefore, it is most likely that myelination has occurred in response to the appearance of neuronal signals.

Myelination depends on an axonal signal

In vitro, myelination has been observed on all sort of artificial structures and in particular on electron-spun nanofibers of varying sizes substitute for axons as a substrate for oligodendrocyte myelination (Lee et al., 2012). However in co-culture of neurons and oligodendrocytes, oligodendrocyte processes myelinate only axons and never dendrites (Lubetzki et al., 1993). *In vivo*, not all axons are myelinated. For instance dopaminergic neurons are not myelinated. In the medial forebrain bundle dopaminergic axons forming the nigrostriatal contingent navigate in close vicinity to motor descending fibers and oligodendrocytes myelinate the later but never the former, suggesting the presence of either a positive attracting signal on axons to be myelinated or a repulsing signal on fibers that do not need to be myelinated.

What is the nature of this axonal signal?

In the PNS, it has been elegantly demonstrated that Neuregulin-1 type III determines the ensheathment fate of axons by Schwann cells (Michailov et al., 2004; Taveggia et al., 2005). Axons from sympathetic neurons do not express Neuregulin-1 type III. However, if following transfection of the corresponding sequence, sympathetic neurons are forced to express Neuregulin-1 type III, then their axons are recognized and myelinated by Schwann cells (Taveggia et al., 2005). What has been demonstrated for Schwann cells does not occur for oligodendrocytes and a possible positive or negative signal is still awaiting discovery. Another signal is driven by the electrical activity along the axons. In the optic nerve of rodents, all axons are myelinated. In the mouse, myelination in the optic nerve begins at around P7, the developmental stage when retinal ganglion neurons acquire a repetitive pattern of firing concomitant to changes in density and activation kinetics of tetrodotoxin-sensitive Na_v currents, which paralleled changes in firing thresholds and size of action potentials (Rothe et al., 1999). The link between neuronal activity and myelination has been clearly demonstrated some 20 years ago (Demerens et al., 1996). To investigate the role of electrical activity on myelin formation, these authors have used highly specific neurotoxins, which can either block (tetrodotoxin) or increase (α-scorpion toxin) the firing of neurons. They have shown that, both *in vitro* and *in vivo*,

myelination can be inhibited by blocking the action potential of neighboring axons, or enhanced by increasing their electrical activity, clearly linking neuronal electrical activity to myelinogenesis. More recently, it has been shown, using optogenetic stimulation of the premotor cortex in awake, behaving mice that neuronal activity increases myelination within the deep layers of the premotor cortex and subcortical white matter and that this neuronal activity-regulated myelination is associated with improved motor function of the corresponding limb (Gibson et al., 2014).

Glial cells that do not myelinate under "normal" conditions, myelinate when confronted to proper axons.

Olfactory ensheathing cells (OECs), derived from the olfactory placode, are the cells that ensheath the axons within the olfactory nerve and constitute the major glial component of the superficially located nerve fiber layer of the olfactory bulb. OECs ensheath the axons forming the olfactory nerve, but never wrap spirally to form a myelin sheath. However, OECs myelinate axons when transplanted into foci of persistent demyelination in the adult rat spinal cord (Franklin et al., 1996). The myelination achieved is remarkably similar both morphologically and biochemically to that achieved by Schwann cells.

Axons of insects, and among them Drosophila, are unmyelinated (see above). In the drosophila mutant *Swiss cheese* (sws) the *sws* gene codes for a neuronal esterase, which Vertebrate's ortholog is « Neuropathy Target Esterase ». Mutation of *sws* induces the wrapping of axons by ensheathing glia. In late pupae, glial processes form abnormal, multilayered wrappings around neurons and axons, and in the adult, the number of glial wrappings increases with age (Kretzschmar et al., 1997). More recently, using loss- and gain-of-function studies in drosophila, the group of Christian Klämbt has shown that the homeodomain protein Cut is required for glial differentiation and is sufficient to instruct the formation of membrane protrusions, a hallmark of wrapping glial morphology, demonstrating the progression of a naïve perineurial glia towards the fully differentiated wrapping glia (Bauke et al., 2015). Altogether, these data show that ensheathing glial cells from invertebrates can synthesize large amount of membrane, and can

form a pseudo-myelin sheath, provided they are in the proper environment, i.e., «receptive» axons.

From ensheathing glial cells towards Schwann cells.

In Drosophila, peripheral glial cells ensheath bundles of axons as part of a peripheral nerve fascicle. This is reminiscent of non-myelinating Schwann cells engulfing a group of non-myelinated axons, known as Remak bundles in the adult. In some instances, Drosophila axons are ensheathed individually by glial membranes, similar to myelinating Schwann cells selecting the axon to be myelinated. From these similarities between invertebrate peripheral glia and Schwann cells in myelinated species, it is tempting to propose that myelin-forming cells have evolved from invertebrate ensheathing glial cells.

Conclusion

It is likely that during evolution the synthesis by glial cells of a multilamellar sheath of membrane has occurred separately and at least on three different occasions, in some annelids, some crustacean and most vertebrates. In the latter lineage, starting with the placoderm 425 MY ago, myelin has been adopted by all the vertebrates. Altogether, these data suggest that myelin forming cells are the descents of ensheathing glia that have adapted their properties in function of axonal requirements. I hypothesize that the first myelin-forming cell was more likely of a Schwann cell type, i.e., establishing a 1 to 1 relation with axons, using P0 as a major myelin protein, as it is the case in teleost. As for the transition from Schwann cell in the PNS to oligodendrocyte in the CNS, the group of Jim Salzer has shown that it is sufficient to inhibit a Rho kinase activity for a Schwann cell to emit several processes and myelinate several internodes on different axons, similar to an oligodendrocyte (Melendez-Vaquez & Salzer, 2004).

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Legend to Figure 1

Frontal view of a specimen of placoderm exposed in the Museum d'Histoire Naturelle in Paris. The hinge-jaw, separated on the mid-line is clearly visible. It is estimated that the length of this specimen must have been comprised between 7 and 9 meters ; (Human being serve as a scale)

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Figure 1