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Myelin in Cartilaginous Fish

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Abstract

Myelin is probably one of the most fascinating and innovative biological acquisition: a glia plasma membrane tightly wrapped around an axon and insulating it. Chondrichthyans (cartilaginous fishes) form a large group of vertebrates, and they are among oldest extant jawed vertebrate lineage. It has been known from studies 150 years ago, that they are positioned at the root of the successful appearance of compact myelin and main adhesive proteins in vertebrates. More importantly, the ultrastructure of their compact myelin is indistinguishable from the one observed in tetrapods and the first true myelin basic protein (MBP) and myelin protein zero (MPZ) seem to have originated on cartilaginous fish or their ancestors, the placoderms. Thus, the study of their myelin formation would bring new insights in vertebrate's myelin evolution. Chondrichthyans central nervous system (CNS) myelin composition is also very similar to peripheral nervous system (PNS) myelin composition. And while they lack true proteolipid protein (PLP) like tetrapods, they express a DM-like protein in their myelin.

Keywords

myelin; chondrichthyans; elasmobranchs; mbp; PLP; DM20; myelin protein zero

INTRODUCTION

Myelin is probably one of the most fascinating and innovative biological acquisition: a cell (glia) wraps around an axon and insulates/protects it. Its plain simplicity has enthralled many biologists and fostered research: how one cell's plasma membrane arrangement provided the key evolutionary advantage of rapid nerve conduction in larger organisms (chordates).

Chondrichthyans are probably one of the oldest, longest studied organisms in the field of zoology, likely because their interesting nature and availability of embryos. Starting with Balfour's classic description on their development (Balfour, 1874; Balfour, 1880) and ending with more current descriptions on their nervous system morphology and development

(Ari and Kalman, 2008; Bullock and Northcutt, 1984; Gillis et al., 2012). They encompass elasmobranchs (sharks, skates and rays) and Holocephali (chimeras). Chondrichthyans stand at a crossroad in vertebrate evolution: they are fully endowed chordates (head, big brains, jaws and large mobile trunks) while still exhibiting lesser evolutionary aspects compared with osteichthyans (cartilaginous versus bony skeleton, dermal denticles versus scales, etc.). More importantly, they are the earliest extant gnathostomes, the product of more than 400 million years of evolution.

The field of myelin morphology and evolution research has a long history in neuroscience. Starting with early 20th century studies on myelin's importance for nerve conduction (Eveleth and Biester, 1937), followed by identification of its lipid composition (Erskine, 1946; Margolis and Pickett, 1956; Smith and Quigley, 1937) and the classic studies on its morphology from microscopy studies (Fernandez-Moran and Finean, 1957; Peters, 1960; Schmitt, 1950). The purpose of this review is to give an overview of what we currently know regarding the appearance and uniqueness of myelin in cartilaginous vertebrates.

Morphology

Myelin, because it is made by tightly apposed glial plasma membranes, provides insulation to nerve action potentials. It is precisely this insulating function that makes it an evolutionary success story across several Lophotrochozoan and Ecdysozoan lineages in addition to Deuterostomia (Castelfranco and Hartline, 2015; Davis et al., 1999; Hartline and Colman, 2007; Zalc, 2006). Thus, copepods (Davis et al., 1999), earthworms (Roots et al., 1991) and shrimps (Hsu and Terakawa, 1996), have myelin-like structures. However, myelin is not identical across these lineages; some organisms have loosely wrapped membranes while others have compact myelin (Waehneldt, 1990). Hence, there is not one way to make myelin, but several (Hartline and Colman, 2007). However, what is uncanny is how little compact myelin has changed since its appearance upon the arrival of chondrichthyans, how unchanged its structure has remained morphologically and molecularly across all gnathostomes vertebrates.

While agnatha (lampreys and hagfish) lack any kind of myelin, chondrichthyans have well developed compact myelin (Bullock et al., 1984; Waehneldt et al., 1984). This "sudden" appearance led many to hypothesize that myelin must have first appeared in placoderms, an extinct lineage before chondrichthyans (Zalc, 2006). It was not until Colman and colleagues looked closely into placoderm fossil skulls (measuring cranial nerves preserved imprints and their foramina) to place this hypothesis under a stronger footing (Zalc et al., 2008).

As mentioned above, the ultrastructure of chondrichthyans compact myelin is practically identical to the one observed in tetrapods. While we have electron microscopy studies of compact myelin for chicken and reptiles from mid 1950s (Geren and Raskind, 1953; Robertson, 1955), it was not until 2006 that the first elasmobranch electron microscopy images were published by Schweigreiter and co-workers (Schweigreiter et al., 2006). Although Kemali et al. published a short description of EM in the ancient shark *Scyllium stellare* (Kemali et al., 1983), Schweigreiter's study is the single most detailed study so far on shark myelin ultrastructure.

In their book chapter, Schweigreiter and colleagues analyzed the development of CNS and PNS myelin of the spiny dogfish *Squalus acanthias*. Spinal cord sections showed a somewhat reminiscent version of the butterfly grey matter portion found in tetrapods (encompassing dorsal and ventral horns), surrounded by many myelinated tracts. Higher power images showed oligodendrocytes adjusting myelin sheath thicknesses to axon caliber. Interestingly, the dogfish had larger number of myelinated fibers in the ventral spinal cord compared with same region in a rat spinal cord. A novel finding was presence of many Schmidt–Lanterman incisures (SLI) in the spiny dogfish, a contrast with mammals, where SLI in the CNS are rare (Blakemore, 1969). The structure of nodes and paranodes was virtually indistinguishable from the ones seen in mammals.

In addition to regular myelin observations, Schweigreiter et al. looked at the development of myelination during embryogenesis and found that they follow the same pattern of formation as other vertebrates: with myelination beginning in the ventral funiculus (Kitagawa et al., 1993; Rotenstein et al., 2009). Dogfish PNS myelin followed suit as in other vertebrates: a) nerves are covered with a basal lamina, b) are surrounded by collagen, c) have many SLI and d) their nodes of Ranvier look like PNS nodes in mammals and other vertebrates. In summary, shark myelin morphology is practically identical to osteichthyes.

Myelin Composition

Studies on myelin composition (lipids and proteins) began in the 1960s from a biochemical perspective: separating the lipid fraction from other axonal components followed by electrophoresis (Adams and Fox, 1969; Wolfgram, 1968). Thus biochemists found that myelin is made up of 70% lipids and only 30% proteins (Folch-Pi, 1971; Folch et al., 1957; Siegel et al., 2006). The first studies on elasmobranchs myelin composition began in the 1970s by isolating it using Folch-Pi now classic method: myelin isolation by centrifugation on sucrose gradient, followed by SDS-PAGE gels and looking at major protein bands distribution (Folch et al., 1957; Norton and Poduslo, 1973). The first such study was by Agrawal and co-workers on the dogfish *Scyliorhinus canicula* myelin (Agrawal et al., 1971). They observed bands in their dogfish gels that were not similar to the ones from other vertebrates. This led them – mistakenly with our 20–20 hindsight - to conclude that “there is a greater species variation in myelin than previously suspected” (Agrawal et al., 1971).

Thomas Waehneldt carried out the most comprehensive comparative studies using the Norton’s method on myelin composition across evolution in the 1980s (Waehneldt, 1990). He isolated myelin proteins from several bony fishes, elasmobranchs and agnathans: sterlet (*Acipenser rhuthenus*), carp (*Carassius carassius*), trout (*Salmo gairdneri*), dogfish (*Scyliorhinus canicula*), ray (*Raja clavata*), electric ray (*Torpedo marmorata*), lamprey (*Petromyzon fluviatilis*) and hagfsih (*Myxina glutinosa*). He observed Wolfgram protein (now referred as 2′-3′CNP), myelin associated glycoprotein (MAG), proteolipid protein (PLP), DM20, and several bands corresponding to myelin basic protein (MBP) isoforms in cartilaginous fishes at comparable positions with mammals. In this now classic study, he also ran gels of *Torpedo* CNS myelin and compared it with the PNS myelin from rabbit and found a strong similarity between elasmobranch’s CNS proteins with rabbit’s PNS. This led him to hypothesize that; a) the CNS myelin of elasmobranchs and bony fishes uses

glycoproteins that run very similar to myelin protein zero (MPZ, or “old” Po) of tetrapods PNS and b) the transition of Po to PLP between fishes and tetrapods as the main CNS myelinating protein.

Waehneldt also noted that although elasmobranchs’ myelin proteins looked very similar across different species, lamprey’s CNS isolated proteins using Norton’s method gave a completely different profile suggesting that agnathans lack myelin (Franz et al., 1981). This was later confirmed by Bullock’s electron microscopy studies: neither lamprey (Cyclostomes) nor hagfish (Myxini) have myelinated axons (Bullock et al., 1984).

However, doubt remained regarding some of the bands observed in agnathans. This led Waehneldt’ studies to further look into the nature of those proteins with western blots using antibodies that recognized tetrapod myelin proteins. His initial findings led him to deny the presence of myelin proteins in agnathans in 1986 to later acknowledge the presence of a Po-like protein and absence of PLP and MBP in 1987 (Waehneldt et al., 1986; Waehneldt et al., 1987).

In summary, it was agreed that elasmobranchs had both MPZ and PLP-like proteins in the CNS and PNS. However, we did not know which protein was responsible for myelination in the CNS until Colman and co-workers cloned the DM20 family and Saavedra isolated MPZ and MBP in elasmobranchs (Kitagawa et al., 1993; Saavedra et al., 1989).

Myelin Lipids

Studies on myelin showed that myelin lipids make the larger proportion of myelin component totaling a 70% of dry weight compared to 30% from proteins. While there are no absolutely myelin-specific lipids, galactosyl ceramide (cerebroside) is the most common lipid across species (Thompson and Kies, 1965). Morell’ studies showed that in addition to cerebroside the other predominant lipids in myelin are cholesterol and phospholipids (Morell, 1977). Morell found that myelin has a set of minor lipid components including esters of cerebroside and galactosyldiglycerides (diacylglyceryl-galactoside and monoalkyl-monoacyl-glycerylgalactoside). He also found that mammal’s myelin contains 0.1 to 0.3% gangliosides in different proportions: myelin is very rich in GM1, relative to other brain membranes, which are enriched in the polysialo species. Looking across different species he observed that, rat myelin has less sphingomyelin than cows or humans, and regional differences, spinal cord myelin has a higher lipid-to-protein ratio than brain myelin from the same species (Morell and Quarles, 1999). All these findings strongly suggest that there might be differences across cartilaginous fish myelin lipids as well, however we do not have such detailed studies yet.

The oldest study in chondrichthyans was a seminal paper in 1952 by McColl and Rossiter looking at lipid composition across evolution (McColl and Rossiter, 1952). Here they looked at the amounts of cerebroside, cholesterol. phospholipin, sphingomyelin, lecithin and kephalin in the brains of Dogfish, Sand shark, Skate and Sting ray and compared them with actinopterygians, amphibian, reptile, birds and mammals brains. They found that 1) the chemical nature of the lipids in the brains of the earlier vertebrates differs from that in mammalian brain, 2) the relative amount of myelin in mammalian brains was greater than in

elasmobranch brains and 3) the concentration of those lipids differed greatly across species, especially elasmobranchs (McColl and Rossiter, 1952).

Waehneldt study the lipid composition of myelin across vertebrates in hope of finding an evolutionary trend, however, he found that the main difference across species was in the proportion of cerebrosides. These decreased in the sequence rat > Xenopus > Torpedo > trout, thus placing Torpedo closer to tetrapods than to trout (Burgisser et al., 1986). Interestingly acquisition of galactolipids is what seemed crucial for compact myelin formation: studies on myelin lipids evolution showed an evolutionary trend from gluco- to galactocerebrosides, which corresponds with changes in the nervous system from loosely structured membrane-enwrapped axons to multilamellar highly structured myelin (Okamura et al., 1985).

There are other studies looking in detail at cartilaginous fish tissue composition. One is by Aveldaño and co-workers. Here they studied the lipid composition of the electric organ in three elasmobranch fish and found species-related variations in the ratios between some phospholipid and in the relative abundance of major polyunsaturated acyl chains of phospholipids (Rotstein et al., 1987). The other by Koizumi and co-workers, looked at the differences among four shark species in muscle lipid composition. They found higher levels of ether glycerol-phospholipids in the muscle of four sharks compared to muscles of bony fish, and found specific characteristics in alk-l′-enyl and alkyl chains of ether glycerophospholipids in shark muscles (Jeong et al., 1996).

What is relevant within the big picture of myelin evolution is that findings from knockout mice suggest that proteins are less important than the lipids. Thus we find that the homozygous double mutant mouse line (plp−/−, mbp−/−), is viable and fertile. The triple mutant plp−/−mbp−/−mag−/− has a normal longevity, despite hypomyelination of CNS axons (Stoffel et al., 1997; Uschkureit et al., 2000). In contrast, myelin the ultrastructure of mice lacking the enzyme UDP-galactose:ceramide galactosyltransferase (CGT), required for GalC synthesis was normal. However, these mice had severe clinical and electrophysiological alterations not attributable to myelin structure. More important their life span does not exceed 30 days (Coetzee et al., 1996). Altogether, these findings point to an intrinsic role for lipids in the insulative properties of myelin and stability of CNS functions. These set up a challenge: when did these lipid enzymes appeared in evolution and are they expressed in the glial cells that make “loose” non-compact myelin in agnathans or earlier organisms?

Myelin Protein Zero

Myelin protein zero is a highly conserved cell adhesion molecule responsible for the compaction of the intraperiod line (Filbin et al., 1990; Filbin and Tennekoon, 1992; Martini et al., 1995; Shapiro et al., 1996). MPZ very likely first appeared 440 million years ago in cartilaginous fish or in placoderms, recent analysis of Ciona, lancelet (urochordate) and lamprey fully sequenced genomes has not shown any MPZ orthologs or paralogs. These absence of MPZ orthologs in taxa older than chondrichthyes supports the old hypothesis put forth by Colman that MPZ evolved from an ancient immunoglobulin protein after acquiring myelin functionality (Shapiro et al., 1996; Yoshida and Colman, 1996).

Cloning of elasmobranch and bony fish MPZ confirmed the hypothesis that this gene was responsible for the myelin compaction in this taxa as it is in tetrapods, given its identity to mammalian MPZ is around 50% (Fig. 1) and its presence in the ventral funiculus myelin tracts (Bai et al., 2011; Rotenstein et al., 2008; Saavedra et al., 1989).

What is unique of chondrichthyans and osteichthyans is that MPZ is the major adhesive myelin protein component of their PNS, but also of their CNS (Jeserich and Waehneldt, 1986; Rotenstein et al., 2008; Saavedra et al., 1989; Stratmann and Jeserich, 1995). The first studies by Waehneldt indicated that there were two shark MPZ isoforms, but it was found only until later by using specific antibodies to different epitopes of MPZ, that there were in fact three, not two MPZ glycosylated isoforms: 32, 27 and 25kD (Rotenstein et al., 2008). Interestingly, shark PNS expressed only the two glycosylated 32 and 27kD protein isoforms.

What is puzzling from this study is that the 27 and 25kD isoforms are most likely not fully functional since they lack the cytoplasmic domain necessary for Po homophilic adhesion (Wong and Filbin, 1994). This finding strongly supports the hypothesis of a “takeover of PLP/DM20 proteins” in the amphibians/reptile transition upon its appearance in CNS in these taxa (Schliess and Stoffel, 1991). Past hypothesis had suggested a “silent drop” of MPZ, however, if this were the case it is puzzling that MPZ can substitute PLP in generating CNS compact myelin, but not the reverse (Yin et al., 2015; Yoshida and Colman, 1996). Given that we still do not know the adhesive capabilities of elasmobranch DMα, it is premature to tell what their true functionality is in myelin compared with MPZ adhesiveness beyond stating that it is expressed by elasmobranch oligodendrocytes.

Myelin Proteolipid Proteins

PLP, DM20, and M6 tetraspan proteins belong to the lipophilin family proteins (Gow et al., 1997). The PLP proteins are the most abundant proteins in tetrapod compact myelin (Inouye and Kirschner, 1994). The existence of PLP/DM20 proteins in elasmobranchs was not firmly established until Colman’s group cloned a family of novel proteolipid proteins (DMα, DMβ and DMγ), related but not identical to the tetrapod DM20 in the CNS of sharks and rays (Kitagawa et al., 1993). The hypothesis since then has been that these ancient PLP/DM20 isoforms, which appeared first 400 million years ago in cartilaginous fish myelin and neurons, where at the transition of sarcopterygian’s to tetrapods and was coopted by duplication of an ancestral gene (DMα family) as the main CNS myelin protein (Schweitzer et al., 2006; Yoshida and Colman, 1996). However, a more ancestral origin of this family has been supported by the identification of smaller DM20 and related M6 proteins in earlier chordates like the sea squirt *Ciona intestinalis* (Gould et al., 2005).

The elasmobranch DMα and the tetrapod DM20 proteins are 62% identical, and the difference between DM20 and PLP is the addition of 35 amino acids (Macklin et al., 1987; Nave et al., 1987). Despite these highly similar sequences, it has been shown that while MPZ can replace temporarily PLP in mammalian CNS, PLP cannot replace MPZ in mammalian PNS (Yin et al., 2006; Yin et al., 2015). Findings like these show that they are not fully interchangeable in tetrapod myelin and leaves open the question for elasmobranchs. Furthermore, we cannot forget that DM isoforms were found to co-localize with MPZ in myelinated dorsal funiculus of dogfish as well as zebrafish (Kitagawa et al., 1993;

Schweitzer et al., 2006). Altogether, these findings raise many interesting questions, some raised quite few years ago by Colman, still remain: what are the functions of these DMs in elasmobranch oligodendrocytes? Do they play some adhesive role in their CNS?

Myelin Basic Proteins

The myelin basic proteins (MBP) are a family of alternatively spliced proteins (Campagnoni et al., 1993), that are responsible for the cytoplasmic adhesion of myelin as well as interacting with actin, tubulin, clathrin and negatively charged lipids (Boggs, 2006; Dyer et al., 1994; Nawaz et al., 2013). MBPs are so crucial that they are considered indispensable for CNS myelination: all MBP mutant mouse lines suffer severe hypomyelination in contrast to PLP mutants (Popko et al., 1987; Readhead et al., 1987).

Saavedra et al. were the first ones to clone elasmobranchs MBPs and determine that it is well conserved (44% amino acid similarity) (Fors et al., 1993; Saavedra et al., 1989). Given its similar proportion in elasmobranch myelin extracts and its similarity to mammalian MBP, it has been understood that elasmobranchs' MBP plays the same cytoplasmic function in myelin compaction as mammalian MBP.

Regarding its appearance in evolution there are some opposing views that brings the need to address it in more detail in the future. The recent sequencing of the lamprey genome brought into light the presence of MBP-like sequences (Smith et al., 2013). However, we and others had searched within the fully sequenced genomes of lamprey and amphioxus and had not found any true MBP (Nawaz et al., 2013; Werner, 2013). Werner's explanation is that those MBP sequences are just Golli-MBP, which is not involved in myelin formation (Givogri et al., 2001; Paez et al., 2009). Thus it looks like the same scenario for MPZ: true MBPs likely evolved in the group before chondrichthyans, the placoderms. With the sequencing of small genome of the chimera (*Callorhinchus milii*) (Venkatesh et al., 2007) we were able to search for MBP sequences and aligned the one EST with known MBPs from other elasmobranchs (Fig. 2). The results follow the phylogenetic origin of chondrichthyans: sequences from *Squalus* and *Leucoraja* were closer to one another than either is to the Galeomorph sharks, while Holocephali placed separate from the rest (Spivack et al., 1993). Past phylogenetic studies have demonstrated these same findings for cartilaginous fish MBP sequences; as well as that tetrapod MBP sequences are closer to elasmobranchs than to any of the two teleost MBP clusters (Nawaz et al., 2013).

The mammalian MBPs for reasons still unknown undergo extensive posttranslational modifications. Likewise, dogfish MBP polypeptide has phosphorylation sites, although it was found to be less cationic than mammalian MBP, with ~50% lower mobility (Saavedra et al., 1993; Zand et al., 2001). These observations strengthen the hypothesis for a common ancestor to chondrichthyans and osteichthyans MBP gene complex (Saavedra et al., 1993).

Conclusions

Chondrichthyans form a large group of vertebrates, with more than 400 of shark-like fishes and 530 of skates and rays (Helfman et al., 1997). In light of being the largest, oldest extant jawed group among living vertebrates, with extreme variation in their nervous system

structure and organization, they are a challenging group for the study of brain/myelin evolution. Much more work is required regarding understanding myelin evolution. For example, we do not have myelin morphology or composition studies on the recently sequenced chimera. Myelin lipids composition in cartilaginous fishes is waiting for more thorough studies, which under the light that lipids are more critical for stabilizing its ultrastructure, suggests a venue for understanding its appearance in these taxa,

More importantly, if we take into consideration the conclusion by Thomas Waehneldt that MAG and MBP, MPZ and PLP/DM20, seem to be irreplaceable constituents of CNS myelin, while CNP and 36K appear to serve some special purposes then the study of cartilaginous fish (positioned at the root of the successful appearance of compact myelin and these adhesive proteins in vertebrates) is a worthy one (Fig. 3 and Fig. 4) (Waehneldt, 1990).

In summary, the observation that myelin formation and composition across elasmobranchs has been conserved demonstrates that myelin appearance in this group marked a successful step in evolution in comparison with its appearance/disappearance in earlier taxa.

METHODS

MBP and MPZ Multiple Sequence Alignment and Construction of Phylogenetic Trees

We performed a multiple sequence alignment (MSA) of known MBP and MPZ sequences. We used the chicken and mouse as the MSA outgroup. The MSA was performed using MUSCLE with its default parameters (Edgar, 2004). The distance matrix, FastTree was carried out on the MSA, which uses the Maximum-Likelihood (ML) method and Nearest-Neighborhood Interchanges (NNIs) (Price et al., 2010). FastTree creates trees using 1,000 replicates and utilizes the Jones-Taylor-Thorton (JTT) and/or the Whelan Goldman (WAG) models to determine amino acid evolution as well as uses the unbiased Shimodaira-Hasegawa test (SH) (Shimodaira, 2002). Both phylogenetic trees were viewed using FigTree (http://tree.bio.ed.ac.uk/software/figtree).

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Highlights

- Myelin is made by glia plasma membrane tightly wrapped around an axon.
- Cartilaginous fish are positioned at the root myelin appearance
- The ultrastructure of myelin across evolution in vertebrates is indistinguishable
- MBP and MPZ first appear in cartilaginous fish or its ancestor, the placoderms.

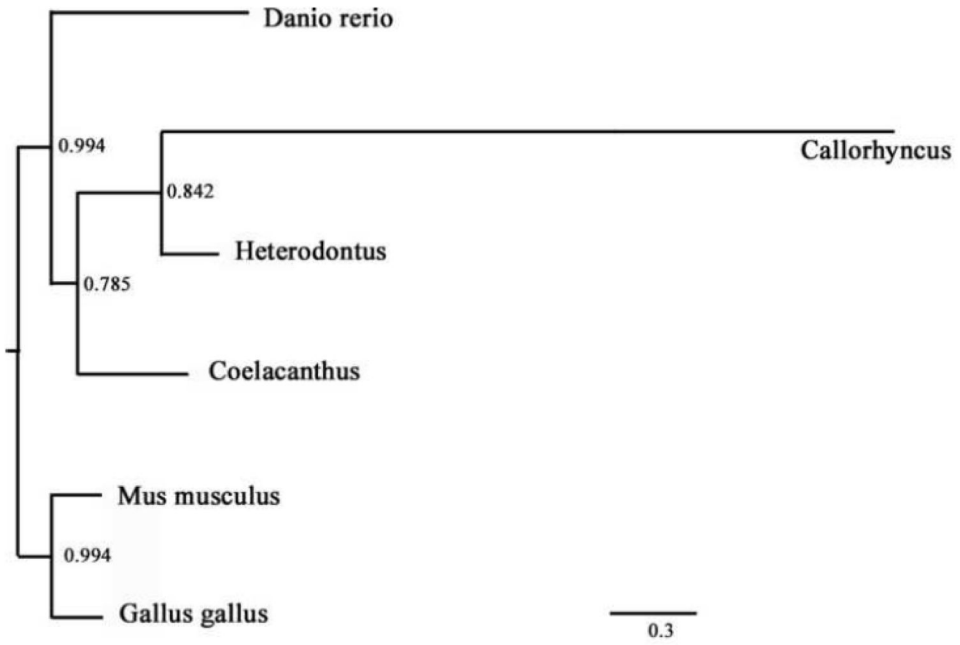

Figure 1. Phylogeny of Myelin from Chondrichthyes perspective

Sequence EST alignment for known MPZ from elasmobranchs (50% homology to mammalian MPZ) with coelacanths, zebrafish, chicken and mouse as outgroups. The results confirm what has been proposed for the phylogenetic origin of MPZ: sequences from chondrichthyans and actinopterygians aligned closer than tetrapod MPZ. The Holocephali MPZ had diverged far apart from the known Heterodontus sequence. The bar at the bottom provides a scale for the length of the tree arms (these indicate the amount of genetic change and represent evolutionary lineages changing over time). The vertical lines value corresponds to the confidence of that the sequences to the right of the node cluster together to the exclusion of any other.

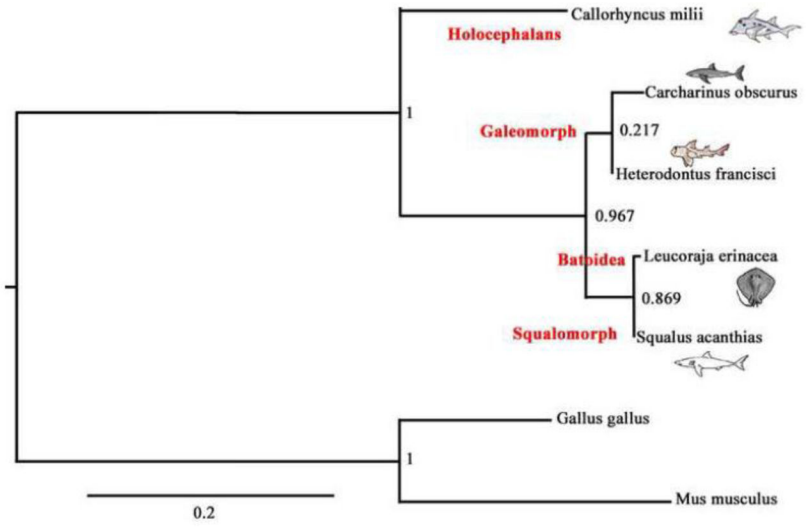

Figure 2. Phylogeny of Myelin Basic Protein

Sequence EST alignment for known MBPs from elasmobranchs with chicken and mouse as outgroups. The results confirm what has been proposed for the phylogenetic origin of chondrichthyans: sequences from *Squalus* and *Leucoraja* were closer to one another than either is to the Galeomorph sharks, while Holocephali placed separate from the rest. The bar at the bottom provides a scale for the length of the tree arms (these indicate the amount of genetic change and represent evolutionary lineages changing over time). The vertical lines value corresponds to the confidence of that the sequences to the right of the node cluster together to the exclusion of any other.

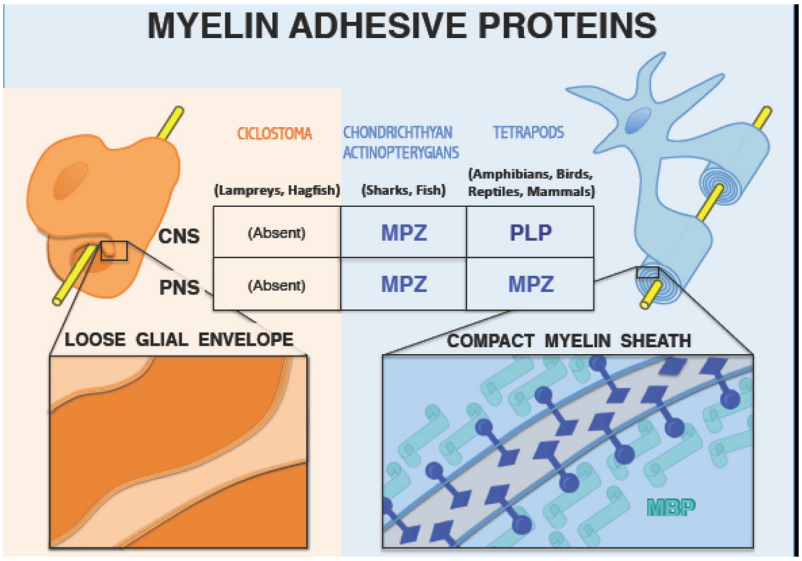

Figure 3. Comparison of Myelin morphology and composition across evolution

The cartoon shows the main differences between agnathans pseudo-myelin and gnathostomes true myelin. Although both have distinct PNS and CNS, agnathans axons are loosely wrapped by glial cells. Compact myelin appeared in chondrichthyans coinciding also with the appearance of MPZ and MBP. Later, tetrapods diverged their CNS myelin components from the original MPZ to PLP as main adhesive molecule.

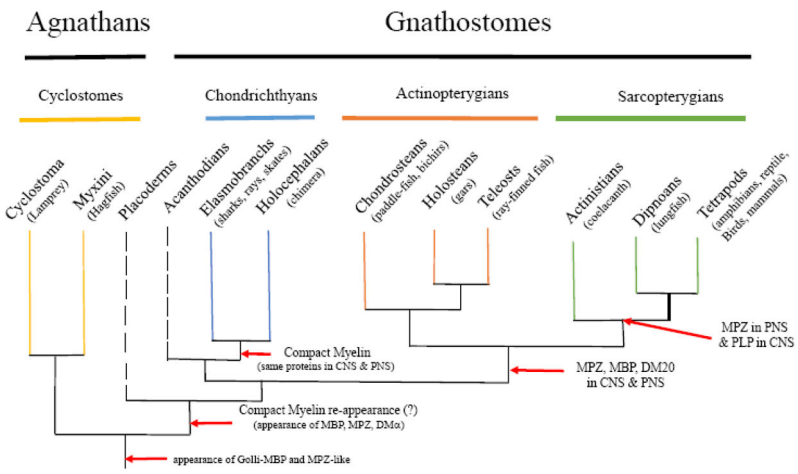

Figure 4. Phylogeny of Myelin from Chondrichthyes perspective

The phylogenetic tree summarizes the review on the evolution of main myelin proteins. Although compact myelin has been observed in non-chordates, upon the appearance of compact myelin in chondrichthyans, little has changed except for the transition of CNS myelin from MPZ to PLP/DM20 in tetrapods. The earliest MBP-like appeared in the ancestor to agnathans.