

Molecular biology of myelin

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SUMMARY: Myelin is one of the most essential component of the nervous system. It forms myelin sheets that envelop the axons of both central and peripheral nervous system and its main function is to speed up the signal that travels down the axon. Myelin sheet consists mainly of lipids and proteins; some are myelin specific, whereas other are found in all animal cells. Portions and ratios of myelin components are also different when compared to other cells, as well as when comparing CNS and PNS myelin. The process of formation of myelin sheets is called myelination, and the opposite process is called demyelination. Remyelination is another important process, that occurs around axons that were previously demyelinated, and a deeper insight in that process could help combat diseases such as multiple sclerosis.

KEYWORDS: myelin, myelin lipids, myelin proteins, myelin sheet

Myelin is one of the most integral part of the nervous system. It forms a myelin sheet which is found wrapped around an axon of a neuron and it is essential for the proper functioning of the nervous system. Importance of myelin can be easily followed up and down the evolutionary ladder, as vertebrates have fully developed myelin sheets, while invertebrates only possess myelin-like sheets (and those are found only in some families) that share structural similarities with the myelin sheets of vertebrates. Even so, it is important to notice that the record for the fastest conduction speed of a signal is actually held by a member of invertebrate taxa.

The sole purpose of myelin and its sheet is to increase the speed of an impulse that travels along the axon. The process of producing and developing of the myelin sheets is called myelination. In humans it occurs around 14th week of fetal development, and it continues all the way through infancy, childhood and adolescence. Compositional parts of myelin sheets are Schwann cells, which are found in the peripheral nervous system, and oligodendrocytes, found in the central nervous system. Furthermore, the term “white matter” derives from the fact that myelinated neurons appear white in colour. Demyelination, on the other hand, is a marker of many autoimmune diseases, such as Guillain–Barré syndrome and multiple sclerosis.

It is important to stress that myelination differs from species to species, as well as its progress differ in the central nervous system (CNS) and the peripheral nervous system (PNS). First to myelinate are parts of the PNS, then the spinal cord, followed by the brain.¹ Some axons remain unmyelinated.¹ Myelin sheet consists mostly of lipids and proteins; those parts are synthesized in different organelles, and must be sorted and transported to the target molecules (in this instance myelin sheets).¹

Composition of myelin: lipids

The main difference between myelin sheet and any other cell membrane is the different percentage of lipids and proteins. While in the most of common membranes proteins prevail in numbers, in myelin sheet numbers are quite the opposite; lipids can occupy up to 85% of the content, while protein numbers can go only as high as 30%.¹ Those numbers refer to dry mass of myelin of both peripheral nervous system and central nervous system. Naturally, another essential component is water.¹ It is important to mention that there are no lipids that are exclusive for myelin sheet; in other words, every lipid molecule that appears in the sheet is also present in some other part of the brain.¹ Nevertheless, cerebroside is the most common of all myelin lipids and its concentration in the tissue is directly dependant on the quantity of myelin.¹ Cerebroside is in fact a group of glycosphingolipids; they consist of ceramide (sphingosine and a fatty acid) and a single sugar, which can be either glucose or galactose. It's precisely galactocerebroside that are usually found in nervous tissue, while glucocerebroside are found in the membranes of the muscles. It is also significant to mention, that in myelin sheets, one fifth of all galactolipids is sulfatide¹, otherwise known as sulfated galactocerebroside or even 3-O-sulfogalactosylceramide, which are essentially glycolipids that contain a sulfate group. Glycolipids are in myelin, along being in all other cell membranes, localized on the extracellular part of the membrane.¹ Because of the amount of cerebroside present, it was long thought they are essential in formation of myelin, but recent experiment in mice showed that their role isn't so crucial.^{1,2} Other lipids that are present in a great amount in the myelin are cholesterol and phospholipids.¹ Cholesterol is an essential sterol molecule found in all human and animal cells, and its main purpose is maintaining fluidity of the membrane. Phospholipids are lipid molecules that contain a phosphate

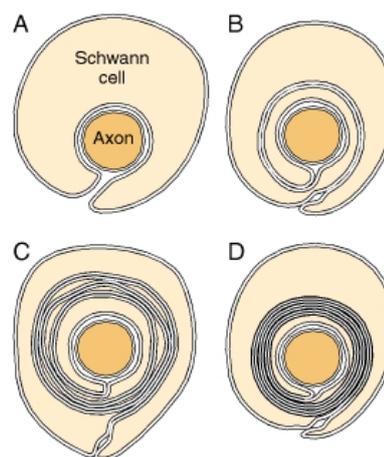


Fig 1. Formation of a myelin sheet in the PNS
From: *The Myelin Sheet, Basic Neurochemistry: Molecular, Cellular and Medical Aspects, 6th edition.*

group and form lipid bilayers; their structure can be roughly distinguished on hydrophobic tails (two fatty acids) and hydrophilic head (phosphate group and alcohol glycerol). Other important lipids are plasmalogen, lecithin, sphingomyelin, and gangliosides such as monosialoganglioside (GM1).¹ Moreover, there are differences in composition between myelin located in the CNS and PNS; in the peripheral nervous system there is apparent increase in sphingomyelin, while cerebroside and sulfatide are present in lesser extent.¹ When compared interspecific (between all the mammals studied), the structure of myelin sheet is, more or less, the same, even though some species (e.g. rats) exhibit certain differences (lower levels of sphingomyelin).¹

Composition of myelin: proteins

Myelin proteins, on the other hand, are more myelin specific. The most significant ones are myelin proteolipid protein (PLP) and myelin basic protein (MBP), as they both play a substan-

tial role in the process of myelination. Other protein, such as glycoproteins, are also present, but in lesser quantities.¹ PLP is an integral protein that shows hydrophobic properties.³ It is assumed that its main role is the stabilization of an intraperiod line of myelin located in the CNS.¹ In support of that hypothesis are conclusions drawn from a study in mice, where the CNS intraperiod line is abnormally condensed both in the PLP knockout mice and in spontaneously occurring PLP mutants⁴ confirming a structural role for PLP in determining the membrane spacing at the intraperiod line.¹ DM20, a proteolipid protein that is actually alternatively spliced isoform of PLP¹, is also of a significant value, as it seems that both PLP and DM20 are needed in the process of maturation of oligodendrocytes.⁵ It is also worth mentioning that DM20 doesn't appear in the same state in the CNS and PNS; in the central nervous system it's part of a membrane, while in the peripheral system it's found in cytoplasm of the cell.⁶ In addition, even though PLP and DM20 are major players in stabilizing of myelin sheet, they are actually not essential

Substance ^a	Myelin			White matter		Gray matter (human)	Whole brain (rat)
	Human	Bovine	Rat	Human	Bovine		
Protein	30.0	24.7	29.5	39.0	39.5	55.3	56.9
Lipid	70.0	75.3	70.5	54.9	55.0	32.7	37.0
Cholesterol	27.7	28.1	27.3	27.5	23.6	22.0	23.0
Cerebroside	22.7	24.0	23.7	19.8	22.5	5.4	14.6
Sulfatide	3.8	3.6	7.1	5.4	5.0	1.7	4.8
Total galactolipid	27.5	29.3	31.5	26.4	28.6	7.3	21.3
Ethanolamine phosphatides	15.6	17.4	16.7	14.9	13.6	22.7	19.8
Lecithin	11.2	10.9	11.3	12.8	12.9	26.7	22.0
Sphingomyelin	7.9	7.1	3.2	7.7	6.7	6.9	3.8
Phosphatidylserine	4.8	6.5	7.0	7.9	11.4	8.7	7.2
Phosphatidylinositol	0.6	0.8	1.2	0.9	0.9	2.7	2.4
Plasmalogens ^b	12.3	14.1	14.1	11.2	12.2	8.8	11.6
Total phospholipid	43.1	43.0	44.0	45.9	46.3	69.5	57.6

Table 1. Components of myelin quantitatively compared to those of a brain with interspecific comparison. From: *Characteristic Composition of Myelin, Basic Neurochemistry: Molecular, Cellular and Medical Aspects, 6th edition.*

Table notes: : a) Protein and lipid figures in percent dry weight; all others in percent total lipid weight.; b) Plasmalogens are primarily ethanolamine phosphatides.

proteins in the whole process of myelination.¹ Myelin basic protein (MBP) could be regarded as one of the most prolific protein, as it has many functions; it can interact with many other proteins (e.g. tubulin, clathrin), act as a membrane actin-binding protein, play a role in signalling, but its main function is “adhesion of the cytosolic surfaces of multi-layered compact myelin”.⁷ MBP is localized on the inner side or the membrane, i.e. to the cytoplasmic surface,^{1,8} and it's thought to have a major role in stabilization of a major dense line of a myelin found in the CNS.¹ In the PNS, myelin basic protein is present in lesser extent, and studies with mutant mice have shown that its role in the PNS is not as crucial as it is in the CNS.¹ This difference is attributed to the protein P0, which is present in the peripheral nervous system, and whose features will be discussed later.¹

Another important group of proteins are 2',3'-cyclic-nucleotide 3'-phosphodiesterase, otherwise known as CNPase; a CNS myelin enzyme that is found in highly specific regions of oligodendrocytes, such as “oligodendroglial processes, inner and outer tongue processes, and lateral loops.”¹ It is found in the cytoplasm of the cell, and some evidence support the theory that it could act as a regulator in the differentiation of the oligodendrocytes.¹ However, further studies in CNP-null mice have shown that its role could be compensated with other proteins.¹

Myelin-associated glycoprotein (MAG) comes in relatively lesser extent when compared to other myelin proteins, but its role is all but that.¹ It is located next to axon, as it seems to be involved in signalling between glial cells and axons (in both directions).¹ It is not essential to the myelination process, but MAG-null mice did experience a delay in myelination and numerous structural abnormalities in the CNS myelin.¹ MAG is naturally present in both the CNS and PNS, the difference being exactly in the direction of the conduction of the signal; in the CNS it transfers the signal from axons to Schwann cells, whilst the direction is the opposite in the PNS.¹

Another protein worth mentioning is myelin-oligodendrocyte glycoprotein (MOG), which stands out because it is located on the outer surface of the myelin sheet.¹ Its role is not fully explored yet, but it is strongly suspected that it is an antigen in multiple sclerosis.¹

Myelin protein zero, more known as P0 glycoprotein, is characteristic for the peripheral nervous system, as it's a major contributor to PNS myelin sheet.¹ As a matter of fact, it is regarded as a myelin proteolipid protein (PLP) equivalent, as they share similar roles in the process of myelination, despite being rather different in structure and post-translational

modifications.¹ P0 contributes to stabilization of both intraperiod and major dense lines of a myelin sheet, as well as it participates in different homophilic binding interactions.¹ The importance of P0 was established in a study with double null animals (for MBP and P0) where major dense line was severely more damaged, thus proving its already mentioned role in the stabilization of the line.¹

Another PNS protein compared to PLP is peripheral myelin protein-22 (PMP-22), which, surprisingly, is not specific for neuronal tissue, but is found in many other cells as well.¹ Given that it is present in both myelinated and non-myelinated cell tissue, it has been suggested that it could play some kind of a maintenance role.¹ A study conducted in Germany in 1999 proved that PMP-22, in fact, interacts with P0.⁹

Myelin protein P2 is interesting because its quantity varies from species to species (15% of total bovine proteins, but only 5% of human PNS proteins).¹ It belongs to a family of cytoplasmic proteins that bind lipid ligands¹⁰ and fatty acids.¹ P2 has a similar structural role as myelin basic protein in major dense lines.¹

There are, of course, other proteins present in the myelin sheets that in some way differ from compact myelin itself.¹ Those proteins include tetraspan proteins, paranodal proteins, and different enzymes associated with myelin.¹ Among the tetraspan proteins, the most famous is myelin and lymphocyte tetraspan protein (MAL).¹ MAL belongs to the family of proteins that includes plasmalogen, another myelin tetraspan protein.¹ It seems that their role may be in signal conduction (through lipid rafts) or maybe protein sorting.¹ Claudins are other family of proteins that belong to tetraspan group; they form tight junctions (area where membranes of two cells are joint together and form a fluid barrier).¹ CD9 protein, present in higher amount in the PNS myelin, is found in paranodal junctions and its expression occurs during late myelination.¹ Connexin-32 and connexin-29 are found mainly in paranodal regions, at gap junctions (intercellular that directly connect cytoplasm of two cells).¹ When it comes to enzymes, CNPase were already mentioned and briefly described. Other enzymes found in myelin include: cholesterol ester hydrolase, cAMP-stimulated kinase, calcium/calmodulin-dependent kinase, protein kinase C, and phosphoprotein phosphatases, just to name a few, as well as enzymes of glycerophospholipid metabolism, and enzymes of phosphoinositide metabolism.¹

Another protein of some importance is surely myelin-associated oligodendrocytic basic protein located in major dense line of a myelin sheet.¹ Between all the other proteins present in the myelin, it's substantial to mention neurotransmitters united

with it; muscarinic acetylcholine (mACh) receptors, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, N-methyl-d-aspartate (NMDA) receptors, and kainate receptors.¹

Conclusion

Despite all the components of the myelin sheets being known to us, the studies and experiments are still conducted every day, but with the different objective; to learn the exact nature of all proteins and lipids and roles they play in the process of (de)myelination, and also focusing in what ways to use

that knowledge to help those suffering from demyelinating diseases. The main purpose of those researches could easily be the remyelination, process in which myelin sheets in the CNS are newly formed around previously demyelinated axons. Remyelination is a process that naturally occurs in the body, but in the advanced stages of multiple sclerosis ceases completely, for unknown reasons. A deeper understanding and even new discoveries about the mechanisms of demyelination and remyelination, and all the factors that partake in them could prove valuable in the battle against, not only MS, but all the other diseases caused by the abnormal or defected myelin proteins.

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Mijelin- molekularna biologija

SAŽETAK: Mijelin je jedna od najvažnijih komponenti živčanog sustava. Formira ovojnicu koja obavlja aksonne središnjeg i perifernog živčanog sustava, a njegova glavna funkcija je ubrzavanje živčanih signala koji putuju aksonima. Kao i druge stanične membrane, mijelinska ovojnica se sastoji od lipida i proteina; neki su specifični za mijelin, dok se drugi nalaze u svim animalnim stanicama. Udjeli i omjeri mijelinskih komponentata se razlikuju u usporedbi s drugim stanicama, kao i kad uspoređujemo mijelin SŽŠ i PŽŠ. Proces formiranja mijelinskih ovojnica naziva se mijelinizacija, a suprotan proces se zove demijelinizacija. Remijelinizacija je važan proces koji se javlja kod prethodno demijeliniziranih aksona, te bi dublje razumijevanje tog procesa pomoglo u borbi protiv bolesti kao što je primjerice multipla skleroza.

KLJUČNE RIJEČI: mijelin, mijelinski lipidi, mijelinski proteini, mijelinska ovojnica