

Glial Cells: The Other Cells of the Nervous System

3. Oligodendrocytes – Ensheathers of the CNS

Yasmin Khan and Medha S Rajadhyaksha



Yasmin Khan did post doctoral work at TIFR and then joined the Life Science Department, Sophia College, Mumbai and specializes in conducting courses in cell and developmental neurobiology.



Medha S Rajadhyaksha is a reader in life sciences at Sophia College, Mumbai. She is involved in teaching undergraduate and postgraduate courses in life sciences with specialization in neurobiology.

Neuroscientists have believed for a long time that glial cells are supportive elements of the nervous system and have little role in neuronal function. Despite outnumbering neurons tenfold in the Central Nervous System (CNS), and contributing to more than half the brain volume, not much attention was paid to these cells. Recently, glial cells have been found to be far more active participants in CNS function. A set of glial cells, the oligodendrocytes, has attracted attention as their precursors have been found to be extremely plastic. Though these precursor cells are initially committed to form oligodendrocytes alone, they can also be induced to form astrocytes and neurons. Such examples of transdetermination are opening up new lines of research with immense clinical implications. In this part of the series we review some aspects of oligodendrocyte structure and function.

Structure of Oligodendrocytes

Oligodendrocytes are small non-neuronal cells which myelinate the axons in the CNS (*Figure 1*). These cells have cytoplasmic extensions emanating from the cell body similar to astrocytes, another type of glial cell in the brain. As the name indicates, oligodendrocytes have fewer processes than astrocytes, and the cell body is much smaller (approximately 5 μm in diameter). Each oligodendrocyte can myelinate up to 50 different axonal internodes. The internodes are interrupted at the nodes of Ranvier, where an astrocytic process makes contact with the axon. The spacing of the nodes and the appropriate distribution of the Na^+ and K^+ channels on the axon also appear to be controlled by the oligodendrocytes. Like astrocytes, oligodendrocytes, too, have Ca^{2+} channels, but no Na^+ or K^+ channels

Part 1. An Introduction to Glial Cells, *Resonance*, Vol.7, No.1, pp.4-10, 2002.

Part 2. Astrocytes – Star Performers in the Neural Tissues, *Resonance*, Vol.7, No.4, pp.20-26.



have as yet been detected. Oligodendrocytes express certain molecules, such as myelin basic protein (MBP), myelin associated glycoprotein (MAG) and myelin oligodendrocyte specific protein (MOSP) which can be used as markers to identify them (Table 1).

Oligodendrocytes have been classified into four types based on the nature of their association with the axon.

Type I oligodendrocytes are small cells with branching processes which ensheath multiple segments; the segments are the shortest and with thinnest myelin sheaths.

Type II oligodendrocytes have fewer, stouter processes, which engage larger axons and make thicker myelin sheaths.

Type III oligodendrocytes are larger cells with two or more processes ensheathing the axon.

Type IV oligodendrocytes are the largest, with 1 or 2 processes supporting large diameter internodal myelin sheaths.



Figure 1. Electronmicrograph showing a neuron (*) with a pale nucleus and thin rim of cytoplasm containing rough endoplasmic reticulum, mitochondria and ribosomes, capped by a dark oligodendroglial cell (x 5,300).

(Courtesy: DMangani, Bombay Hospital, Mumbai)

Myelin specific proteins	Enzymes
Myelin basic protein (MBP)	Carbonic anhydrase II (CAII)
Proteolipid protein (PLP)	2', 3'-cyclic nucleotide 3'-phosphodiesterase (CNPase)
Myelin associated glycoprotein (MAG)	
Myelin oligodendrocyte associated glycoprotein (MOG)	Others
Myelin oligodendrocyte specific protein (MOSP)	Leu-7 (HNK-1, a carbohydrate epitope, first identified in lymphocytes)
Transferrin	Rip (monoclonal antibody recognizing unidentified oligodendrocyte-specific cytosolic epitope)
Myelin specific lipids	
Galactocerebroside	

Keywords

Glia, myelin, central nervous system.

Table 1. Some important markers (molecules) found in mature oligodendrocytes.



Myelination is carried out by the oligodendrocytes by sending large extensions of their plasma membrane (sometimes 10 times the diameter of their cell bodies) to wrap around neighbouring axons, thus forming the myelin sheath. Each oligodendrocyte can synthesize up to 3 times its own weight of myelin each day.

Functions of Oligodendrocytes

Oligodendrocytes Synthesize Myelin and Ensheath Axons

Myelination is carried out by the oligodendrocytes by sending large extensions of their plasma membrane (sometimes 10 times the diameter of their cell bodies) to wrap around neighbouring axons, thus forming the myelin sheath. Each oligodendrocyte can synthesize up to 3 times its own weight of myelin each day. The advantage of one oligodendrocyte myelinating several axons is that it allows more myelinated axons to be packed in a small volume.

During development, in a pre-myelination stage, the newly formed oligodendrocytes express a characteristic 'Rip antigen' and are called the pro-oligodendrocytes. At this stage, the cells engage an axon, which has a minimum diameter of 0.2 μm , and begin myelination. Usually the first axons to be myelinated grow into fibers with large diameters.

Myelin formed by oligodendrocytes is made up of lipid bilayers assembled with proteins (*Figure 2*). The lipid composition of myelin differs from that of the glial cell membrane and is richer in cholesterol and phosphatidylcholine (*Box 1*). Its protein composition is also specific and has 2 major proteins, proteo-lipid protein (PLP) and myelin basic protein (MBP) and other minor proteins, including myelin-associated glycoprotein (MAG). The major proteins help to maintain the structure of myelin. MBP is rich in positively charged lysine and arginine and interacts with the negatively charged proteins of the cell membrane. This is thought to bring the myelin lamellae together to form a compact structure. PLP, the other major protein, is a transmembrane protein with a large extracellular domain that interacts with a similar extracellular domain of the adjacent whorl to provide stability. MAG, a minor protein, is a member of the immunoglobulin superfamily and has strong homology to N-CAM. Its concentration peaks at 3 weeks in the mouse suggesting that it recognizes and binds to axonal mem-



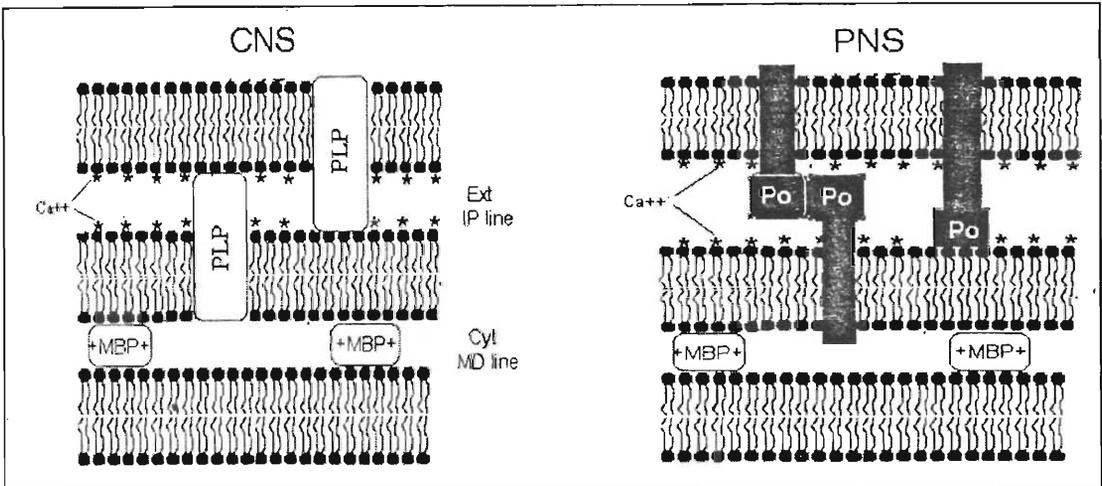


Figure 2. A diagrammatic representation of the model for CNS and PNS myelin, where Po protein and PLP bridge the extracellular faces of the sheath. MBP interacts with the cytoplasmic faces at the phospholipid bilayer to form the MD line. Cyt – cytoplasmic face; Ext – extracellular face; IP – intraperiod line; MBP – myelin basic protein; MD – major dense line; PLP – proteolipid protein.

brane to initiate myelinogenesis. The myelin formed by oligodendrocytes is different from the myelin formed by Schwann cells in the peripheral nerves, which has less cholesterol, galactolipid and plasmalogen and more sphingomyelin than the former.

Box 1. The Composition of Myelin in the Human Central Nervous System

Protein % dry weight	21
Lipid % dry weight	79

	Molar ratio
Cholesterol	1.0
Galactolipids	0.5
Plasmalogen	0.4
Sphingomyelin	0.1
Phosphatidyl ethanolamine	0.3
Phosphatidyl choline	0.3
Serine inositols	0.3



The oligodendrocytes do not permit regeneration of denervated axons in the CNS. In fact, it appears that oligodendrocytes may inhibit axonal regrowth and lateral sprouting. These inhibitory influences are important during normal development as they may help to delineate boundaries between bundles of axonal fibers.

Oligodendrocytes Modulate CNS Neuronal Regeneration

In adult mammals, unlike invertebrates, cut CNS axons do not regenerate. However, regeneration of axons with reinnervation of appropriate targets is a common feature of the peripheral nervous system (PNS) axons where Schwann cells act as a conduit, providing positional cues and growth factors to the regenerating axon. Unlike Schwann cells in the PNS, the oligodendrocytes do not permit regeneration of denervated axons in the CNS. In fact, it appears that oligodendrocytes may inhibit axonal regrowth and lateral sprouting. These inhibitory influences are important during normal development as they may help to delineate boundaries between bundles of axonal fibers. Though the inhibitory molecules remain largely unknown, two proteins NI 35 and NI 250 have been shown to strongly inhibit growth of neurites.

The inhibitory role of oligodendrocytes in regeneration has been studied in neonatal as well as in adult, as tissue regeneration of CNS has immense clinical importance. Some important findings are mentioned here.

1. When the spinal cord is lesioned in the immature CNS, conduction is restored within a few days. This is probably because at this stage the spinal cord lacks myelin and has few glial cells. Thus the inhibitory signals are absent and the regeneration is possible.
2. Transplantation of Schwann cells (either a graft of sciatic nerve or cultured Schwann cells) into the lesioned area of the adult CNS permits axons to regrow through the bridge formed by the Schwann cells. On the other hand, if a graft of the optic nerve (which is part of the CNS) is grafted into a peripheral nerve lesion, it prevents regeneration of severed axons. This brings out the contrasting roles of the two myelin forming glia, Schwann cells and oligodendrocytes in regeneration.
3. If crushed nerves of the CNS are allowed to grow in the



presence of antibodies against myelin proteins, damaged fibres regrow across a crush site. In addition to the inhibitory effects of oligodendrocytes and CNS myelin, the formation of a glial scar, mainly due to reactive astrocytes, and presence of inhibitory proteoglycans in the extracellular matrix following injury to the CNS, also prevents regeneration of axons.

However, some observations provide hope for restoration of some of the functional deficits of neurodegenerative diseases. During development, neural stem cells give rise to neuronal and glial cell progenitors (see Part 1). From glial progenitors, oligodendrocyte precursor cells are formed which can give rise to oligodendrocytes *in vivo*. *In vitro* these cells can also form astrocytes. It has been recently shown that oligodendrocyte precursors from fetal as well as adult tissue can be induced to revert back to stem cells and give rise to neurons and astrocytes, as well as oligodendrocytes. These findings are interesting as such reverted cells can be used in cell replacement therapy in cases of neurodegenerative diseases. Oligodendrocyte precursors are attractive candidates for cell replacement therapy specially because they are one of the best studied precursors of CNS, abundant and easier to isolate than other stem cells.

Oligodendrocyte precursors are attractive candidates for cell replacement therapy specially because they are one of the best studied precursors of CNS, abundant and easier to isolate than other stem cells.

Oligodendrocytes and Oligodendrocyte Precursor Cells During Injury and Diseases

Central nervous system demyelinating diseases, whether of genetic, autoimmune or viral origin, cause degenerative changes in the oligodendrocyte-myelin sheath complex, and are often associated with an adverse response in neurons, astrocytes and microglia. The oligodendrocyte cell damage and death is due to a series of event, often beginning with a breakdown of the blood brain barrier. (see Part 2 on astrocytes and microglia). Inflammatory blood macrophages and local activated microglia in the brain along with astrocytes, launch a cytokine mediated immune attack on the oligodendrocytes as a result of which activation of proteins of the complement system, generation of free radicals and eventually phagocytosis of myelin occurs. The

Multiple sclerosis is an inherited disorder where the myelin producing genes are not affected but demyelination occurs because of attack on self tissue by macrophages/microglia leading to disruption of the myelin sheath and damage to the oligodendrocytes.

milieu produced can cause membrane and DNA damage in the oligodendrocytes and disruption of metabolic processes. Myelin formation and genes involved in myelination are inhibited. Functional devastation in the brain in injury is often not due to neuronal death alone but due to uncontrolled demyelination due to such reactions. Under these conditions of demyelination, a certain population of glial cells – named adult oligodendrocyte precursor cells or OPCs (to differentiate them from the perinatal OPCs or O-2A cells) undergo repeated mitosis and differentiate into myelinating oligodendrocytes to replenish the damaged ones. These adult OPCs make up 5 to 8% of the glial cell population of the CNS. These cells are characterized by the presence of NG2 chondroitin sulphate, O4 glycolipid antigen, platelet derived growth factor- α receptor and receptor for basic fibroblast growth factor. Several similarities between the perinatal OPCs and adult OPCs suggest that the adult cells may have originated from the perinatal precursors. The role of these cells in the healthy adult brain is still under investigation.

Extensive and progressive CNS demyelination is seen in multiple sclerosis, an autoimmune disease. Multiple sclerosis is an inherited disorder where the myelin producing genes are not affected but demyelination occurs because of attack on self tissue by macrophages/microglia leading to disruption of the myelin sheath and damage to the oligodendrocytes. Pathology is due to activation of phagocytosis by macrophages against particulate myelin or via Fc receptor binding of immune complexes. Moreover, in multiple sclerosis patients, remyelination with the aid of adult OPCs fails to occur. The reasons are not known, but could be a result of depletion or destruction of the adult OPCs or their inability to migrate to the lesion sites due to the presence of glial scar or damage to the axons.

A host of neurodegenerative diseases other than multiple sclerosis are also associated with defective myelination or demyelination.

A host of neurodegenerative diseases other than multiple sclerosis are also associated with defective myelination or demyelination. Molecular neurogenetic studies have led to



the identification and cloning of several genes whose mutations are the cause of neurodegenerative diseases and good animal models are now available to study myelin producing genes. In mice, mutation in the MBP gene causes the *shiverer* (*shi*) and *myelin-deficient* (*mld*) phenotype, where animals show uncontrollable shivering and convulsions leading to death between 50 to 100 days of age. Mutations in the other major myelin protein PLP, causes *jumpy* (*jp*) in mice. In humans, an X-linked disease, called Pelizaeus-Merzbacher disease (PMD), is due to faulty splicing of mRNA transcript of PLP. Genetic studies of X-linked adrenoleukodystrophy (ALD) have identified a mutation in a peroxisomal protein, which is important for normal β -oxidation of long chain fatty acids. Mutations in this gene lead to accumulation of the fatty acids and hence abnormal myelination.

Certain recent developments have raised the possibility of using gene transfer in such diseases. First, is the production of recombinant forms of growth factors which allow glial cells to be grown and maintained *in vitro*. Initial studies have used Schwann cells, but such strategies can be used for oligodendrocytes too. The other important advance has been in purifying oligodendrocyte-progenitor cells and maintaining them *in vitro*, (in the presence of the growth factor – brain derived neurotrophic factor) without loss of their myelinating capabilities. These cells could, therefore, be used for gene transfer and subsequent transplantation into diseased regions of the nervous system.

Conclusions

It is increasingly being realized that oligodendrocytes are versatile cells performing a number of seemingly simple functions that nevertheless have far reaching effects on health of the neural tissue. The fact that the precursors of oligodendrocytes are labile has added a new dimension to research in neural transplantation.

Suggested Reading

- [1] *Elements of Molecular Neurobiology*, Ed CUM Smith, John Wiley & Sons, 1996.
- [2] J M Levine, R Reynolds and J W Fawcett The oligodendrocyte precursor cell in health and disease, *Trends Neurosci*, Vol. 24, pp. 39-47, 2001.
- [3] Dubois-Dalcq, Regeneration of oligodendrocytes and myelin, *Trends Neurosci*, Vol. 18, pp. 289-291, 1995.
- [4] P S Sastry, Biochemistry of myelin, *In Lectures in Neurobiology*, Ed P N Tandon, V Bijlani and S Wadhwa, Wiley Eastern Ltd, New Delhi 1989.

Address for Correspondence

Medha S Rajadhyaksha
Reader
Life Sciences Department
Sophia College
B Desai Road
Mumbai 400 026, India.

Yasmin Khan
Reader
Sophia College
Mumbai, India.

