Glial Cells: The Other Cells of the Nervous System

4. Schwann Cells – Regulators of the Periphery

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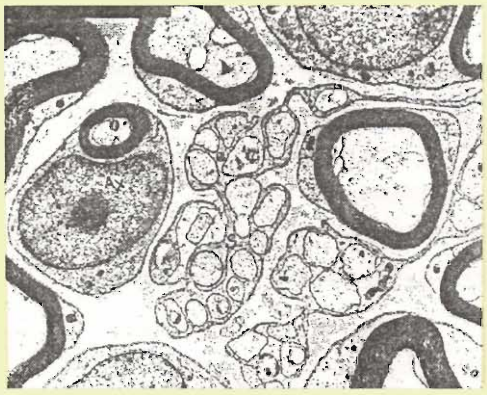
Theodor Schwann, the German physiologist who first propounded the cell theory with M Schleiden, had diverse interests. He was not only the first to isolate the enzyme pepsin, but also investigated muscle contraction and nerve structure. In the mid nineteenth century Schwann discovered that a sheath made up of myelin covered the axons of neurons in the peripheral nervous system (PNS). The cells that form the myelin are today called Schwann cells after him. Today, we know that the Schwann cells not only form the myelin sheath around neurons, but also regulate several neuronal functions and are an indispensable part of the PNS.

The organization of the PNS is very different from the central nervous system (CNS). Unlike in the CNS, the neuron cell bodies in the PNS are clustered into ganglia and the cell bodies and axons are completely insulated from their surroundings by the processes of glial cells. Two types of glial cells are involved – the satellite cells and Schwann cells. Satellite cells (sometimes called amphicytes) surround the neuron cell bodies in the ganglia, whereas Schwann cells (or neurolemmocytes) form a sheath around the peripheral axons.

Structure of Schwann Cells

Schwann cells as seen in an eletronmicrograph have a small cell body with little cytoplasm, and an extended membrane that winds around an axon to form a sheath (*Figure* 1). All axons of peripheral nerves, both myelinated and unmyelinated, are ensheathed by Schwann cells. Occasionally, the term Remak cells is used to describe the cells enclosing unmyelinated axons to distinguish them from Schwann cells, which ensheath myelinated axons. The Schwann cells, which have a bipolar spindle-



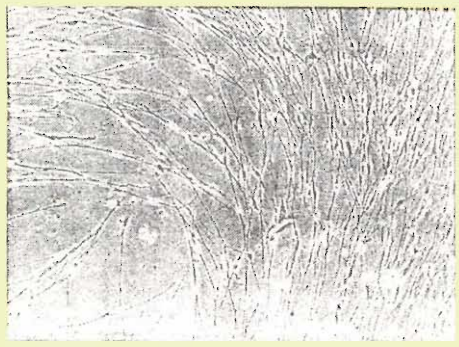


Figure 1 (left). An electronmicrograph of a transverse section through the sciatic nerve of an adult mouse . Bundles of non-myelinated axons are enwrapped by the processes of adjacent Schwann cell, (S) and larger diameter axons (Ax) are ensheathed by myelin within individual Schwann cell sheaths. (x 12,000).

(Courtesy: Dr. Vanaja Shetty, The Foundation for Medical Research, Mumbai)

Figure 2 (right). Purified Schwann cells from monkey sciatic nerve grown in culture. Note the typical bipolar spindle shaped appearance of the cells (x 200).

shaped appearance when grown in isolation in tissue culture (*Figure* 2), stretch in cords around the axons. While one Schwann cell can enclose several small unmyelinated axons, one Schwann cell myelinates only one axon. This is in contrast to the CNS, where one oligodendrocyte can myelinate several axons (see Part 3 of this series). Moreover, the expression of myelin genes in Schwann cells is regulated by contact with axons, while in oligodendrocytes the expression of these genes depends on the presence of astrocytes.

Several molecular markers help identify Schwann cells, both *in vivo* and *in vitro*. Most are myelin-related proteins such as peripheral myelin protein Po, myelin basic protein (MBP), proteolipid protein (PLP) or lipids like galactosyl ceramides (eg. Galactocerebroside – GalC) and sulfatides. These molecules get expressed on Schwann cells on initiation of myelination and can be detected as long as the Schwann cells remain in contact with neurons. Disruption of neuron-glial interaction reduces the expression of these proteins to basal levels. There are other molecules like an antigen detected by monoclonal antibody

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, 2002.
Part 3. Oligodendrocytes Ensheathers of the CNS, *Resonance*, Vol.7, No.6, pp.6-13, 2002.

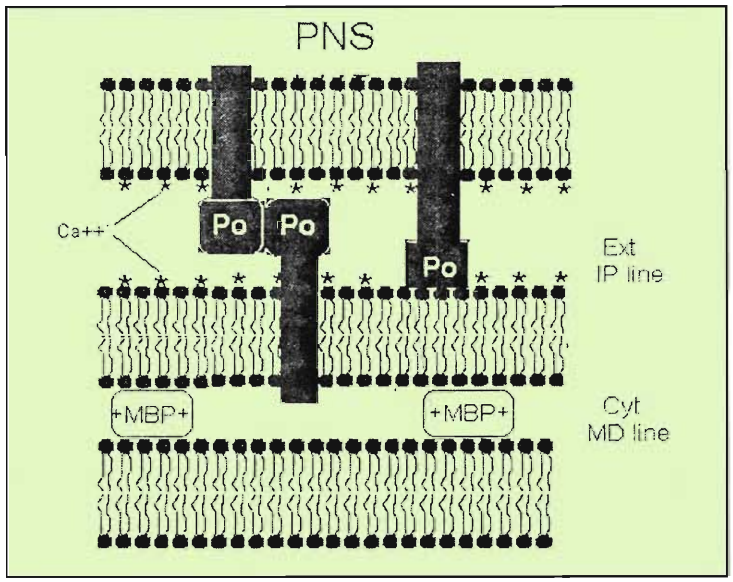


Figure 3. A diagrammatic representation of the model for PNS myelin, where Po protein bridges the extracellular faces of the sheath. MBP interacts with the cytoplasmic faces at the phospolipid bilayer to form the MD line.

Cyt – cytoplasmic face; Ext – extracellular face; IP – intraperiod line; MBP – myelin basic protein; MD – major dense line.

23E9, which is expressed developmentally on initiation of myelination and becomes down regulated in adults, suggesting a role in induction of myelination.

Role of Schwann Cells in Myelination

The myelin sheath around PNS axons is basically a proteophospholipid spiral formed by compacted membrane of the Schwann cell around the axon (*Figure* 3). As each axon is ensheathed by a chain of several Schwann cells with their separate myelin sheaths, there are intervals at the junctions of two cells called the nodes of Ranvier (*Box* 1). The myelin sheath around an axon not only physically protects it, but also increases the speed of transmission of impulses along the fiber. The factors leading to myelination of some axons and not others, are still largely unknown, though the diameter of the axon seems to play some role in determining myelination. Experimental studies have shown that all Schwann cells, even those around unmyelinated axons, have the capability to myelinate an axon given the necessary stimulus. Myelinated axons have large diameters (may occasionally exceed 20 μm) compared to unmyelinated axons whose diameters range from 0.2 to 3.0 μm in humans. Experiments using nerve grafts, or those with mutant mice, have

Box 1. Schwann Cell Myelin: The Sheath of the Peripheral Nerves

The Schwann cells that ensheath the peripheral axons have two distinct portions because of the myelin spiral in their cytoplasm The myelin spiral forms the internodal segment of length ranging from 200-250 μm to 1500 μm in mammalian nerves. The internode is interrupted at the 'node of Ranvier' In large diameter fibers the compact internodal myelin has oblique clefts at an angle of 90° to the long axis of the sheath called the 'incisures of Schmidt–Lanterman'. Myelin in these incisures is less compact and they are labile structures that change due to trauma or toxicity, and during regeneration. These regions are the protoplasmic pathways that connect the outer and inner compartments of the Schwann cells.

Towards the end of the internode, the myelin sheath increases in diameter and is characterized by longitudinal grooves and ridges that extend back 20-40 μm from the nodal margin. At the node of Ranvier, the ridges become shallow and the myelin lamella turns inwards to the axolemma. At the node a short stretch of axon is free of myelin sheath. However, this part is not exposed to tissue fluids. A complex arrangement of microvilli extending from the Schwann cell embedded in the gap matrix covers this region. This arrangement, along with modifications of the axolemma in nodal regions, ensures that the ionic milieu and energy rich environment necessary for saltatory conduction is maintained.

demonstrated that deficiency in myelin formation is usually a result of defective Schwann cells and not the axons. A mutant mouse called *Trembler* has an inherited disorder which leads to gross abnormality in myelin formation. Grafts of normal nerves into this mouse exhibited normal myelination, whereas in the opposite scenario, the *Trembler* Schwann cells were unable to myelinate axons when grafted into normal mice.

Schwann cells Regulate Nerve Development

Earlier, Schwann cells were considered as only accessory cells that were totally dependent for their survival and differentiation on the neurons. Myelination and protection of the neuron were considered their only functions. Recent evidence, however, shows that Schwann cell signals may regulate the development of not only the axons, but also of the connective tissue cells and Schwann cells themselves. For several years it has been known that axonal/neuronal survival is dependent on neurotrophic factors secreted by their target cells. However, studies on knock-out mice which lack Schwann cell precursors and Schwann cells have shown that most of their sensory and motor neurons are

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lost during embryonic development, suggesting that the neurons are dependent on signals from Schwann cell precursors for their survival. The survival factors emanating from Schwann cells responsible for survival of neurons have not been identified yet. Neuronal loss seen in Schwann cell lacking mice is more severe than in mice lacking a single neurotrophic factor or receptor. This suggests that several factors may be involved. These survival cues may be different for sensory and motor neurons. A likely candidate suggested for motor neuron survival is the glial cell line derived neurotrophic factor (GDNF) and its relatives which include neurorturin, while neurotrophin-3 (NT-3) may be involved in the survival of sensory neurons.

Several studies have also shown that besides their role in regulating the survival of neurons, Schwann cells also provide autocrine signals for their own survival. Schwann cell precursors are entirely dependent for survival on axonal signals through β-neuregulins. However, mature Schwann cell survival appears to be axon-independent. In fact, following nerve transection, the Schwann cells in the distal stump survive for long periods in the absence of axons and this is important for regeneration of the axons to their targets. Certain growth factors, including insulin-like growth factor 2 (IGF2), platelet-derived growth factor – BB (PDGF-BB) and NT-3, probably act together as autocrine signals to prevent Schwann cell death.

Role of Schwann Cells in Regulating Ionic Milieu

Voltage-gated Na^+ and K^+ currents have been recorded on cultured Schwann cells, leading to the identification of different voltage-gated ion channels. K^+ currents, both outward rectifying (K_{or}) and inward rectifying (K_{in}), can be detected in freshly dissociated Schwann cells, but experiments have shown that the K_{in} are detected only when Schwann cells are in contact with functional axons. The possible role of these K^+ channels in Schwann cells could be to take up surplus K^+ that would otherwise accumulate in periaxonal spaces during neuronal activity. The Schwann cells could later release the K^+ which

would be taken up by the neuronal Na^+/K^+ pump. Thus, Schwann cells may not only play a role in removing excess K^+ from the microenvironment of neurons, but also in returning K^+ to the neurons.

Similar to their expression in astrocytes (see Part 2), voltage-gated Na^+ channels have also been identified on Schwann cells, both in tissue culture and *in vivo*. These channels are found concentrated on the Schwann cell processes that are in intimate contact with the axon at the nodes of Ranvier, suggesting that preformed channels may be supplied to the axon when required. The observation that these channels are structurally, physiologically and pharmacologically identical to neuronal Na^+ channels strengthens this idea. Several types of Ca^{2+} channels also have been identified in Schwann cells, both voltage-gated and receptor mediated. Ca^{2+}-signalling may mediate interactions between neurons and glia, since neuronal activity can trigger Ca^{2+} signals in glial cells and in turn glial Ca^{2+} signals are shown to elicit neuronal responses.

Role of Schwann Cells in Reinnervation at the Neuromuscular Junction

Schwann cells are required for reinnervation of neuromuscular junctions, and guide the sprouting of new axons. Schwann cells of both myelinating and non-myelinating type, on loss of contact with their axons, dedifferentiate and exhibit surface markers characteristic of earlier developmental stages. These Schwann cells are called 'reactive' Schwann cells. In adult vertebrates, experimental transection of motor neurons has shown that the terminal reactive Schwann cells extend processes over the muscle end plate and form a network by fasciculating with similar processes from neighboring Schwann cells. These processes then guide the reinnervating axons as they arrive at the end plate. These axons in fact do not terminate at the end plate but continue along these adjoining processes, so that muscle fibres become polyneuronally innervated after regeneration. It is, however, unclear whether Schwann cells play any role during devel-

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opment in the peripheral axonal projections. This is because neonatal Schwann cells are dependent for their survival on trophic signals (mainly glial growth factor – GGF) from their associated axons. Denervation of neonatal peripheral nerves causes apoptotic death of the associated Schwann cells.

Role of Schwann Cells in Synaptic Transmission

Experiments have shown that perisynaptic Schwann cells modulate neurotransmitter release at frog neuromuscular junctions. It is well-known that a high frequency stimulation of a nerve leads to decreased synaptic transmission. This phenomenon was earlier attributed solely to the depletion of vesicles carrying the neurotransmitters in the presynaptic neurons. Recently, Schwann cells have been implicated in the synaptic depression. There appears to be a feedback signal from the Schwann cells causing inhibition of synaptic transmission in high frequency stimulated neurons. This cross talk between neurons and Schwann cells is apparent at neuromuscular junctions. Terminal Schwann cells at a neuromuscular junction respond to synaptic stimulation by an increase in their intracellular Ca^{2+} levels. The increase is partly due to opening of channels and partly to release of Ca^{2+} from internal stores.

Role of Schwann Cells in Regeneration of Nerves

In the invertebrate CNS, axons regenerate after injury or transection with complete precision. Lower vertebrates such as fish and amphibians also show considerable regenerative powers of neurons in their CNS. However, regeneration in the adult mammalian CNS is very restricted. This is unlike the situation in peripheral nerves where neurons after crush injury as well as transection regenerate and reinnervate their original targets, often quite precisely. The Schwann cells are the prominent players that permit the regeneration of peripheral axons. The precise mechanism by which they do so is not yet known, but the several possibilities suggested include 1) formation of a cellular bridge spanning the gap between the severed ends, 2) secretion

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of essential tropic and trophic factors, and 3) generation of a basal lamina which is required at the synaptic region.

The importance of Schwann cells is shown by an experiment where the rate of regeneration was measured following a complete transection, where both axons and Schwann cells migrate and grow towards the target, and after a crush injury where only axons grow out through an existing Schwann cell tube. The former rate of growth is much slower, approximately 0.2 mm/day, whereas axons growing through a preexisting bridge of Schwann cells grow at 1 mm/day. Interestingly, experiments in the 1980's had demonstrated that axons in the CNS could grow several centimeters through a graft of peripheral nerve tissue consisting of Schwann cells and its basal lamina. This disproved the notion that neurons of the CNS were incapable of regeneration. Several other studies have shown that the failure of CNS to regenerate is due to several factors (see Part 3 of this series). The CNS glia may inhibit regrowing axons or may be unable to provide the necessary trophic support. The capacity of Schwann cells to permit regeneration of CNS neurons holds great promise in ameliorating some of the deficits following injury to the CNS or in demyelinating diseases. The multifactorial functions of Schwann cells clearly indicate that these cells play a role far more important than just being supportive or accessory cells to the neurons in the PNS.

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Suggested Reading

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