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Excerpt

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Introduction to the Schwann cell

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THEODOR SCHWANN 1810–1882

The Schwann cell is named in honour of the German physiologist Theodor Schwann (1810–1882, Figure 1.1) who is now acknowledged as the founder of modern histology. In addition to describing the Schwann cell, he made numerous contributions to the fields of biology, physiology and histology – not least as one of the instigators and main advocates of cell theory. The cell theory defined the cell as the base unit of all living organisms, and had great influence on the study of both plants and animals. The cell theory was radical for the time and irrevocably discredited Vitalism, the mainstream belief that life was attributed to a vital force. Among other things, Schwann is known for recognising that the crystals seen during fermentation, first reported by Leeuwenhoek in 1680, were in fact living organisms; although it was not until Pasteur in 1878 wrote to Schwann acknowledging this observation that Schwann's finding was accepted. In fact, Pasteur's germ theory stems from Schwann's work in which he showed that microorganisms were required for the putrefaction of meat.

Schwann spent his undergraduate years at the University of Bonn and then the equivalent of postgraduate study in Wuerzburg and Berlin. Schwann was appointed Professor of Anatomy at Louvain in 1839. In 1848 he moved to the Chair of Anatomy in Liege. In a biography of Schwann (Causey 1960), Causey reported that he avoided the strife of scientific controversy and appears to have risen above petty jealousies.

During his time in Louvain, Schwann described the nucleus in animal cells and defined the nucleus as being important in animal development. His studies were made in the dorsal horn cells. Schwann did not differentiate between the Schwann cell plasma membrane

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Figure 1.1 Theodor Schwann.

and the Schwann cell itself. This has led to the interchangeable and confusing nomenclature of neurilemma and Schwann cell membrane. He worked at a time when microscopy was in its infancy, but with foresight recognised that his observations would in the future be verified or discounted. His contribution to neurohistology continued with his observations that nerve cells were ensheathed by cells he considered to be secondary nerve cells. Nevertheless, to this day they bear his name – the Schwann cell.

THE SCHWANN CELL – MORE THAN MEETS THE EYE

Throughout most of the history of neuroscience, neuroglial cells in both the peripheral (PNS) and the central (CNS) nervous systems have been regarded merely as the ‘glue’ that physically and metabolically holds the nervous system together. Neuroglia have historically been presented as passive bystanders; however, it is now clear that they are major players alongside the neurons of the PNS and the CNS. Ironically, it is the efficiency and blatancy with which the Schwann cell can produce the specialised unique and complex spirals of myelin membrane that has resulted in it being perceived as an axonal comfort blanket, with little regard for its more subtle but essential roles in the operation of the PNS. Such a biased view of the Schwann cell meant that for a long time our knowledge of its other equally

important functions remained rudimentary. However, the interdependence between the Schwann cell and the neuron underpins the functioning of the entire PNS, and the fates of these two cell types are inextricably entwined (like star-crossed lovers) so that it is no longer valid to consider Schwann cells as passive support cells. This book challenges many of the preconceived ideas about the Schwann cell and highlights the importance of this cell to the functioning of the PNS in health, in disease and in repair following damage. In addition, as described in Chapter 7, current data suggest that Schwann cells can perform the entire spectrum of an immune response.

All neurons in the PNS are in intimate physical contact with Schwann and satellite cells, regardless of whether they are myelinated or unmyelinated, sensory or autonomic. All axons of the peripheral nerves are ensheathed by rows of Schwann cells, in the form of either one Schwann cell to each axonal length, or in Remak bundles, formed when an individual Schwann cell envelopes lengths of multiple unmyelinated axons (Figures 1.2, 1.3 and 1.4b).

There is now a large body of evidence that defines a multitude of Schwann cell functions that are not related to myelination (Lemke 2001). This uncoupling of myelin-associated functions from other Schwann cell roles emphasises the essentially symbiotic relationship between nerve cells and Schwann cells, where each is dependent on the other for normal development, function and maintenance. For example, it is the axon that controls the initiation of myelination, the number of myelin lamellae and the maintenance of the complex Schwann cell organisation (Michailov *et al.* 2004). However, it is the

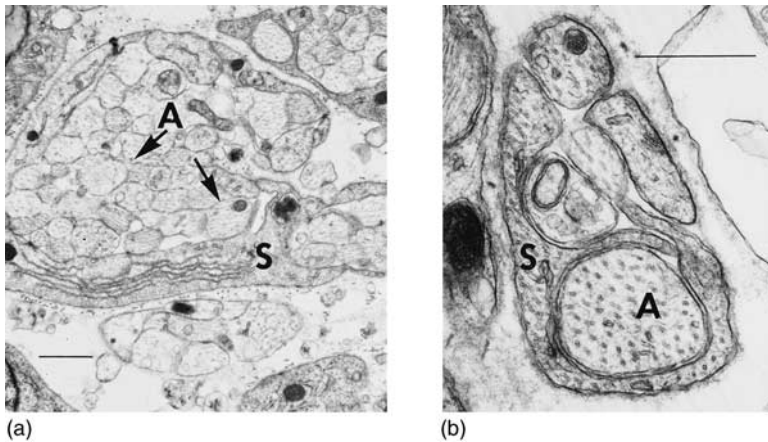


Figure 1.2 Ensheathed axonal bundles (Crawford and Armati, 1982).

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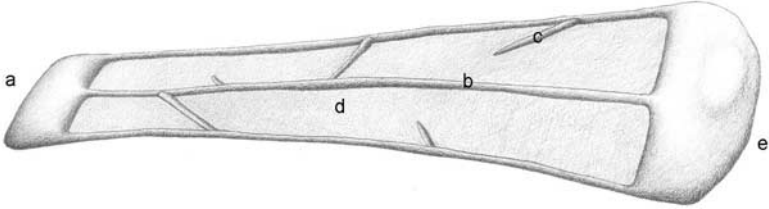


Figure 1.3 A diagrammatic representation of an unrolled Schwann cell showing (a) the inner mesaxon which ensheathes the axolemma, (b) the Schmidt Lanterman incisures, (c) The transverse processes, (d) the compacted regions of myelin, and (e) the outer mesaxon which rolls and ensheathes the whole Schwann cell/myelin complex and around which is the Schwann cell secreted basal lamina.

Schwann cell that regulates axonal diameter, neurofilament spacing and phosphorylation (Hsieh *et al.* 1994), and the clustering of ion channels at the node of Ranvier in myelinated axons (Poliak and Peles 2003). The Schwann cell and its extracellular basal lamina are also involved in axonal regeneration and the guidance of axons to their target destinations (Nguyen *et al.* 2002; Son and Thompson 1995b). Furthermore, Schwann cells have the capacity to interact with cells from outside the nervous systems, as evidenced by their well-established ability to communicate with cells of the immune system through the expression of MHC class II molecules (Armati *et al.* 1990; Armati and Pollard 1996).

Even though all Schwann cells are of neural crest lineage, Schwann cells in the mature PNS can be further categorised for convenience by their morphology, antigenic phenotype, biochemistry and anatomical location. These categories are (i) myelinating (MSCs), (ii) nonmyelinating (NMSCs), (iii) perisynaptic Schwann cells (PSCs) of the neuromuscular junction (Corfas *et al.* 2004) and (iv) satellite cells that ensheath the cell bodies of sensory neurons (Hanani 2005). These different types of Schwann cells and their anatomical location are shown schematically in Figure 1.4.

Myelinating Schwann cells

Myelinating Schwann cells are the best-characterised cells of all Schwann cell categories, as there has been extensive research on myelination during development, and in demyelinating diseases where disruption of the specialised Schwann cell myelin membrane has been the defining characteristic. To some extent this concentration

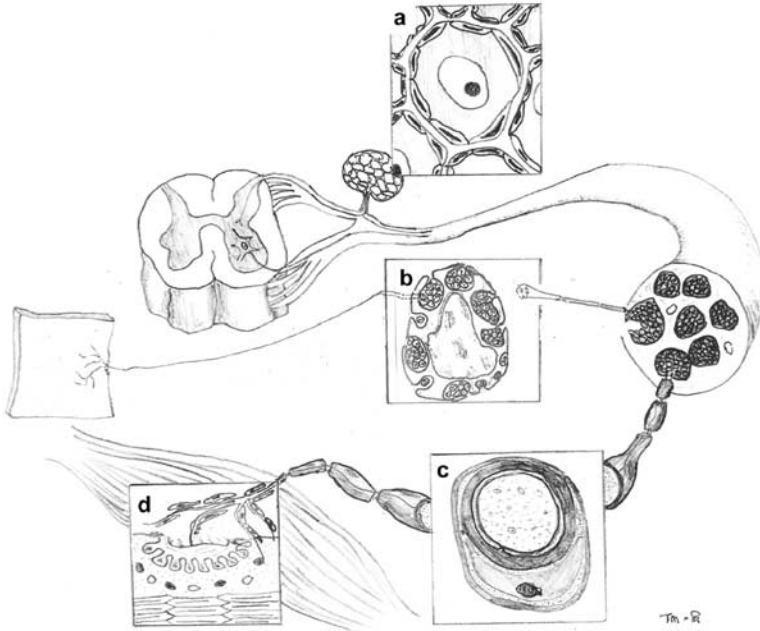


Figure 1.4 Locations of the Schwann cell subsets in the PNS. (a) Satellite Schwann cells are found in the dorsal root ganglia where they associate with the neuronal cell bodies of sensory neurons. (b) Non-myelin-forming Schwann cells are found in mixed peripheral nerve fibres and can ensheath up to ten axonal lengths. (c) Myelinating Schwann cells are also found in mixed peripheral nerve fibres but only myelinate one axonal length. (d) Perisynaptic Schwann cells are located at the neuromuscular junction where they not only enwrap the axonal length but also extend processes to encompass the synapse.

on myelin has diverted us from understanding this huge cell. Myelin-forming Schwann cells have a profound impact in both the healthy and diseased nervous system, not only on axonal conduction but also on many properties of the axons themselves. While Chapters 2 and 3 discuss in detail myelin-forming cells, it is salutary to consider the size and complexity of these Schwann cells.

Schwann cells in the human sciatic nerve can make as many as 100 spiral turns around an axonal length, so that their longitudinal length far exceeds the diameter of their associated axonal length (Webster 1971). To put this in perspective, if one unwrapped Schwann cell with 100 spirals of compact myelin membrane from a hypothetical axonal length (diameter 6 mm), the Schwann cell would be trapezoid and approximately 39 m in length. An axon of the leg, for example,

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could be 1 m in length and have as many as 100 000 Schwann cells associated with it. Clearly, the formation of so much myelin requires the synthesis of a vast amount of specialised membrane, the expression of a new array of genes, and complex cytoskeletal reorganisation, as discussed in Chapter 3.

With the advent of high throughput technologies, such as neuroproteomics (Kim *et al.* 2004), functional genomics (Bult *et al.* 2004), siRNA (Holen and Mobbs 2004) and improved methods for culturing neural cells, the workings of the molecular machinery required to achieve this intricate remodelling are only now beginning to be understood. Questions such as what determines whether an axon becomes myelinated by a Schwann cell (Taveggia *et al.* 2005) and how the number of myelin spiral lamellae is regulated (Michailov *et al.* 2004) are now being answered. Chan *et al.* (2006) have found that Par-3 (a member of the Par family of adaptor proteins) is localised within the myelin-forming Schwann-cell–axolemmal interface prior to the unidirectional spiralling of the Schwann cell around the axon. Inhibition of the asymmetrically expressed Par-3 inhibits myelination.

As well as the compacted myelin membranes of the Schwann cell, there are Schmidt–Lanterman incisures, cytoplasm-containing channels spiralling within the myelin membranes (Hall and Williams 1970). They contain the complete range of cytoplasmic components and are in continuity with the Schwann cell cytoplasm of the outer and inner mesaxonal regions (Fannon *et al.* 1995; Ghabriel and Allt 1981; Arroyo and Scherer 2000). These components of the myelin-forming Schwann cells are considered to be essential for development, growth, maintenance and turnover of myelin. They contain adherens junctions, including E-cadherin, catenins and F-actin. Tricaud *et al.* have further explored the role of adherens junctions, myelin architecture and their morphogenetic role in Schwann cells (Tricaud *et al.* 2005). They report that disturbance of the adherens junctions in mouse Schwann cells has a direct effect on the interface between compact and non-compact myelin, as discussed by Scherer and Arroyo in Chapter 3. These important but to date neglected components of the Schwann cell are also discussed in Chapter 8.

Non-myelin-forming Schwann cells

In a mixed peripheral nerve unmyelinated fibres outnumber myelinated fibres by a ratio of three or four to one (Jacobs and Love 1985). For example, a transverse section of a human sural nerve contains

approximately 8000 myelinated fibres per mm^2 , whereas the unmyelinated axons number 30 000 per mm^2 . Most of these unmyelinated fibres are small-diameter axons of C fibres originating from sensory ganglia and axons from sympathetic neurons. Little attention has been given to the associated non-myelin-forming Schwann cells (Kennedy 2004). However, all of these unmyelinated fibres are in close contact with non-myelin-forming Schwann cells, which envelope a number of axonal lengths to form Remak bundles. The number of axons within a Remak bundle ranges from one to more than 10, and each axon is encircled by thin extensions of the Schwann cell (Berthold *et al.* 2005). Although the physiological roles of non-myelin-forming Schwann cells are poorly defined, it is becoming apparent that they are vital for the function and maintenance of unmyelinated axons and also necessary for pain sensation. This has been demonstrated in transgenic mice that have disrupted communication between unmyelinated axons and their non-myelin-forming Schwann cell partners. When communication between axons and adult non-myelinating Schwann cells was specifically disrupted, the mice began to lose their sensory perception and could no longer respond appropriately to hot and cold stimuli. Moreover, there was aberrant proliferation of non-myelinating Schwann cells as well as loss of unmyelinated C fibres (Chen *et al.* 2003). This study emphasises the fundamental need for communication between Schwann cells of all types and the axons they associate with. Although studies directed specifically towards non-myelin-forming Schwann cells are rare, they are becoming more frequent and important in uncoupling essential roles of the Schwann cell that are distinct from myelination.

Satellite cells

Satellite cells are of the same neural crest lineage as Schwann cells and the sensory neurons in the dorsal root ganglia (DRG), and have a distinct partnership with the neuronal cell they ensheath when compared to other neuroglial interactions. Satellite Schwann cells associate directly with the cell body rather than the axon of a neuron, so that each neuronal cell body in the DRG is completely surrounded by a cap of several satellite Schwann cells to form a discrete anatomical unit. Although little is known about the physiology of satellite Schwann cells, they are likely to share many functions in common with the other classes of Schwann cells. Current information suggests that they have specific roles given their location and unique interaction

with the sensory neuronal cell bodies they envelope. The proximal and distal arms of the peripheral nerves have a blood/nerve barrier (BNB) where the endothelial cells form tight junctions similar to that of the central nervous system blood/brain barrier (BBB). These barriers shield the nervous system from noxious blood-borne cells and molecules. However, the dorsal roots, the dorsal root ganglia and the neuromuscular junction (or tripartite synapse discussed in the next section) have an incomplete BNB. This lack of a BNB is in part compensated for by the satellite cells, which have the ability to regulate the neuronal environment by acting as a partial diffusion barrier. On the whole, satellite cells have barely been examined in terms of their specialisations and unique interactions with the neurons they support.

Schwann cells of the neuromuscular junction – the perisynaptic Schwann cells

The Schwann cell as an independent and essential player in the PNS is further exemplified at the neuromuscular junction (NMJ). The NMJ had long been considered as a synapse with two active components: the presynaptic nerve terminal and the postsynaptic muscle membrane. However, in recent years the perisynaptic Schwann cell (PSC) has gained recognition as the third component of what is now termed a tripartite synapse (Koirala *et al.* 2003). Although it is well established that Schwann cells regulate the extracellular neuronal environment by buffering ions and taking up neurotransmitters, it now appears that they can also contribute to the formerly archetypal neuronal function of neurotransmission (Robitaille 1998; Auld and Robitaille 2003a). PSCs encapsulate the motor end-plate (where the motor neurons synapse on the muscle and form an integral part of the neuromuscular synapse (Hughes *et al.* 2005a)), and not only are located in an ideal position to monitor synaptic activity but are also fully equipped to receive and respond to signals at this tripartite synapse (Araque *et al.* 1999; Auld and Robitaille 2003a). Although these specialised PSCs express many proteins in common with myelinating Schwann cells, they can be distinguished by their increased expression of neurotransmitter receptors and ion channels. Since PSCs are not directly connected to other synaptic elements their mode of action appears to be via a synapse–PSC–synapse regulatory loop (Auld and Robitaille 2003a), whereby PSCs are activated by synaptic activity to provide an inhibitory or excitatory feedback signal (Rochon *et al.* 2001). It is

now accepted that PSCs make a substantial contribution to the NMJ, resulting in a more stable and efficient synapse. In addition to modulating NMJ function, PSCs are also essential for its formation and maintenance both during development and during repair following injury. Furthermore, denervated neurons can only reencounter the muscle end-plate when physically guided by Schwann cells.

SCHWANN CELLS RESPOND TO INJURY

Schwann cells have a pivotal role in response to PNS injury. The PNS regenerative powers are in part due to intrinsic properties of Schwann cells that encourage spontaneous regeneration and have been the focus of much investigation. PNS axonal regeneration occurs through the initiation of signalling cascades that activate Schwann cells to produce neurotrophic factors, cytokines, extracellular matrix and adhesion molecules, which aid in regrowth of the injured nerve. These abilities are in direct contrast to CNS neuroglia, particularly astrocytes, which produce a hostile environment for axonal regeneration in response to injury. In the CNS, damage results in extensive glial scarring, the production of inhibitory factors and the lack of axonal guidance, both physical and molecular. Due to these reparative qualities, Schwann cells are becoming candidates for use in cell transplantation to treat demyelinating diseases of the PNS and CNS and spinal cord injury. Schwann cells are considered a viable option for transplantation because they are not a target of immune attack in CNS autoimmune demyelinating disease, they can be cultured and expanded from adult biopsies for autologous engraftment (Rutkowski *et al.* 1995; Vroemen and Weidner 2003; Bachelin *et al.* 2005), and they can not only remyelinate but also promote nerve fibre regeneration. Moreover, because Schwann cells can be grown relatively easily in culture, they can be manipulated to enhance their regenerative properties or to act as vehicles for gene therapy. For example, non-human primate Schwann cells, genetically modified to overexpress the neurotrophic factors BDNF and NT-3 and transplanted into demyelinated spinal cord, promote not only axonal protection, Schwann cell differentiation and oligodendrocyte progenitor cell proliferation, but also clinical recovery (Girard *et al.* 2005).

However, if Schwann cells are to be used in spinal cord cell transplantation or genetic modification therapies, it becomes vital to recognise that PNS neuroglia are distinct from CNS neuroglia and cannot be used interchangeably. Although Schwann cells and

oligodendrocytes are both myelinating cells, they often have different responses to the same stimulus, as in the case of nerve growth factor (NGF) (Chan *et al.* 2004). It has long been assumed that myelination in the CNS and PNS is regulated by a common axonal signal. However, a recent study (Chan *et al.* 2004) has shown that NGF is a potent regulator of myelination but has inverse effects in the PNS and CNS. This finding highlights the importance of studying the basic biology of Schwann cells in their own right, and offers a caveat against the extrapolation of CNS data to the PNS and vice versa. Moreover, differential responses between neurons and neuroglia should also be considered; for example, although neurotrophins have a number of effects on developing or regenerating neurons, including the promotion of cell survival, neurite outgrowth, differentiation and synaptic plasticity and function, they also affect the responses of myelinating neuroglia.

SCHWANN CELLS ORCHESTRATE INFLAMMATION IN THE PERIPHERAL NERVOUS SYSTEM

It is imperative to consider how the PNS interacts with other systems of the body during development and maintenance, and in response to damage. This is particularly pertinent to the immune and endocrine systems, which can have considerable impact on the function of the PNS. A balanced interplay between the PNS and the immune system is necessary for healthy function, and again the Schwann cell plays a critical role in maintaining this delicate equilibrium with involvement in the initiation, perpetuation and termination of immune responses in the PNS (Chapters 6 and 7). In view of the fact that Schwann cells respond to and produce an extensive collection of immunomodulatory factors (including neurotrophins, cytokines and chemokines), it is increasingly apparent that they are key orchestrators of the immune response in the PNS (Maurer *et al.* 2002). Indeed, the expression of MHC class 1 and class 11 molecules (Armati *et al.* 1990; Gold *et al.* 1995; Lilje and Armati 1997) and T cell activation accessory molecules (Van Rhijn *et al.* 2000) on the Schwann cell has also raised the possibility of its direct participation in the initiation or exacerbation of T-cell-mediated responses, with clear evidence that Schwann cell can act as antigen presenting cells (Argall *et al.* 1992b; Armati and Pollard 1996; Lilje and Armati 1997). However, the full ramifications of the Schwann-cell-mediated neuro-immune interactions in the PNS are as yet far from fully realised.