The Biology of Schwann Cells

Development, Differentiation and Immunomodulation

Edited by
Patricia J. Armati

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Schwann cells are a diverse group of cells formed from neural crest cells. They are essential components of the peripheral nerves of both vertebrate and invertebrate nervous systems. The diversity of Schwann cell subsets and function is seen in those Schwann cells that form myelin – that uniquely specialised part of the plasma membrane that spirals around axonal lengths to myelinate the peripheral nerves. *The Biology of Schwann Cells* concentrates on Schwann cells of mammals and in particular humans. It covers the distinction between compact and non-compact myelin in depth, along with the perisynaptic cells which form the partnership between nerve terminals and muscle fibre. Developmental aspects are discussed alongside differentiation, together with the genetics of Schwann cells in health and disease. With chapters from world-renowned experts, this book is aimed at postgraduates and researchers in neuroscience and neurology, and anyone involved in the study of peripheral nerves.

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Dedication

This book is dedicated to all the 'Friends of the Schwann cell': Theodore Schwann who first named the cell; Richard and Mary Bunge and the unsung Patrick Wood; and also John Pollard my husband, whose ever-enquiring mind, excellence in research and dedication to all those with peripheral nerve diseases inspired my interest in the extraordinary tale of the Schwann cell.

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Preface

It is now over 200 years since Theodore Schwann first described the cell which bears his name. Such early descriptions of nervous system components were done without the powerful microscopes we have today, yet Schwann and Ramon Y. Cajal made foundation observations which still stand. Cajal's papers, especially, show the power of careful observation, an essential element of good science.

The Schwann cell has been historically underrated and poorly understood. In particular, the myelin-forming Schwann cells or their myelin are still often referred to as a simple 'sheath' for the neuron. However, Schwann cells in all their complexity form essential partnerships with neurons, and muscles. This is of particular relevance in the case of the myelin-forming Schwann cell, an enormous cell that expresses unique molecules and complex relationships related to maintenance of the compact and non-compact myelin regions of its plasma membrane. Schwann cells have other complex interactions, not least of which are found where nerve terminals and muscle fibres form the tripartite synapse in association with the perisynaptic Schwann cells. There are also the poorly understood satellite cells that surround the dorsal root ganglion nerve cell bodies, and of course the complexity of non-myelinated Schwann cells and their axonal associations.

It may be that the histopathological prominence of abnormalities of compact myelin has focussed research on this region of the Schwann cell. This is shown by the historical concentration on disturbance of compact myelin in diseases of the peripheral nervous system such as Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP) and Charcot–Marie–Tooth disease. The study of the basic biology of this cell is therefore increasingly recognised as

an essential element in understanding the development, function and potential for repair of the nervous system, including the central nervous system.

With the development of electron microscopy, molecular biology and genetic techniques, proteomics and other technologies pushing the boundaries of our knowledge, the unravelling of the astounding complexity of all cells including the Schwann cell is well underway. It is therefore timely that the current understanding of this cell be gathered into a book such as *The Biology of Schwann Cells*.

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Patricia Armati
October 2006

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Introduction to the Schwann cell

EMILY MATHEY AND PATRICIA J. ARMATI

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

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

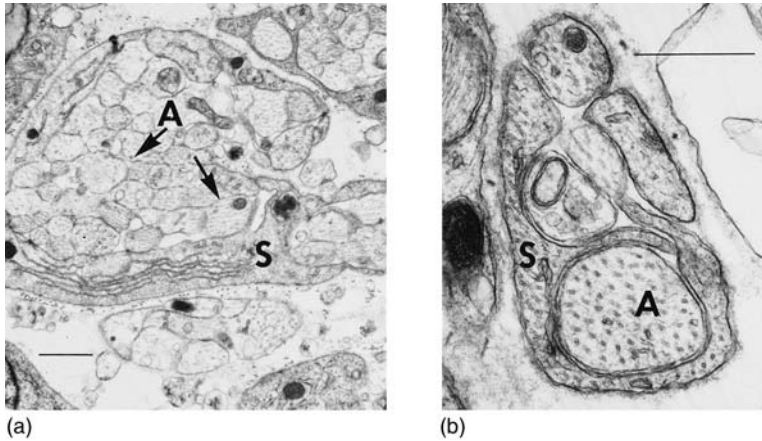

Figure 1.2 Ensheathed axonal bundles (Crawford and Armati, 1982).

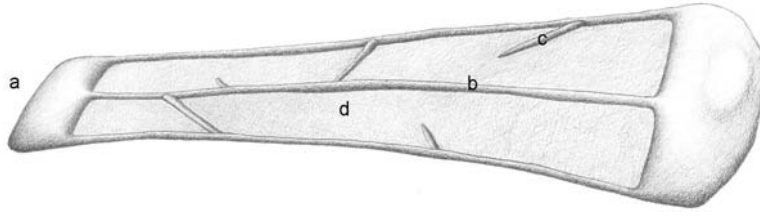

Figure 1.3 A diagrammatic representation of an unrolled Schwann cell showing (a) the inner mesaxon which ensheathes the axolemma, (b) the Schmidt Lanterman incisures, (c) The transverse processes, (d) the compacted regions of myelin, and (e) the outer mesaxon which rolls and ensheathes the whole Schwann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

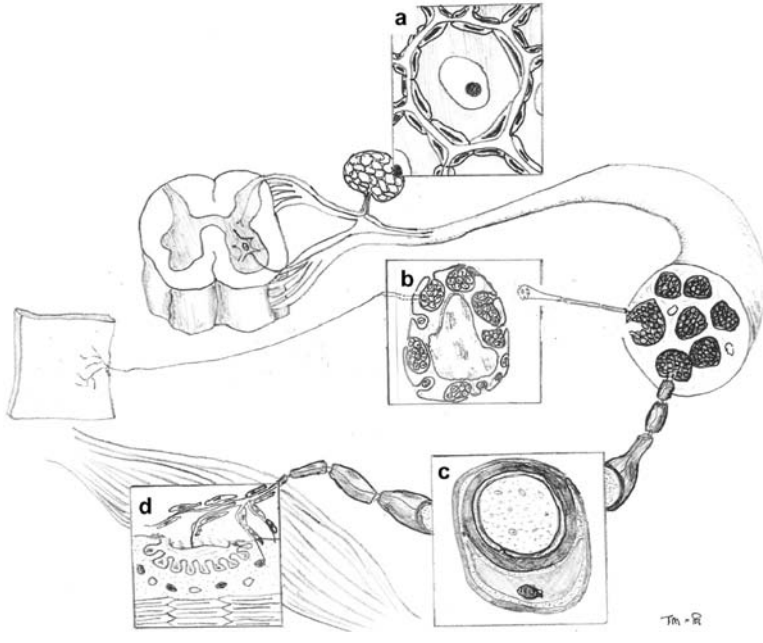

Figure 1.4 Locations of the Schwann cell subsets in the PNS. (a) Satellite Schwann cells are found in the dorsal root ganglia where they associate with the neuronal cell bodies of sensory neurons. (b) Non-myelin-forming Schwann cells are found in mixed peripheral nerve fibres and can ensheath up to ten 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,