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Schwann Cell Development and Pathology

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Chapter 4
Schwann Cell–Axon Interactions: The Molecular and Metabolic Link Between Schwann Cells and Axons

Nobuhiko Ohno, Takashi Sakoh, Yurika Saitoh, Nobuo Terada, and Shinichi Ohno

Abstract Schwann cells and axons have close and complex interactions that determine Schwann cell behavior and fate and support or impair axonal integrity. The interactions are mediated by molecules that are responsible for physical junctions between Schwann cells and axons and also soluble mediators which are generated and bidirectionally transported in the interface. Multiple types of axonal signals are critical for regulating Schwann cell proliferation, differentiation, myelination, and myelin maintenance. At the same time, Schwann cells regulate axonal development and play essential roles for survival of axons. Current evidence suggests that the trophic support of Schwann cells is associated with modulation of axonal metabolism, which is involved in functional maintenance of axonal mitochondria. Further advancement in genetic techniques, transgenic models, and myelinating cultures will elucidate the molecular and cellular mechanisms of Schwann cell–axon interactions that could lead to new therapies of peripheral nervous system diseases.

Keywords Axonal survival • Demyelination • Dysmyelination • Glycolysis • Lactate • Mitochondria • Myelination • Na^+/K^+-ATPase • Neuregulin • Trophic support

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4.1 Introduction

Schwann cells, the glial cells in the peripheral nervous system (PNS), are among the largest and most ultrastructurally sophisticated cells in the body, and can undergo rapid and dynamic transformation during development as well as after injury. The complex structures and dynamic behavior of Schwann cells determine the way of interaction with axons, neuronal processes that confer nerve impulses to the target cells in the PNS (Hoke et al. 2006; Jessen and Mirsky 2005; Meyer et al. 1992; Mirsky et al. 2008; Webster Hde 1971). Initially in development, Schwann cells surround the external margins of the axonal bundles, and support axonal outgrowth by providing growth factors, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (Fig. 4.1a). Thereafter, Schwann cells segregate the axons into successively smaller bundles. Finally, individual axons are covered by Schwann cell cytoplasm and separated from one another near the Schwann cell surface. Many PNS axons including small sensory and autonomic axons are kept in this state, and these units composed of small-diameter axons and their ensheathing Schwann cells are called unmyelinated or "Remak" fibers (Fig. 4.1b). On the other hand, other Schwann cells spirally wrap single axons, and form multilamellar membranes called myelin, which is an essential structure for rapid salutatory conduction (Fig. 4.1c, d).

Development of myelin appears later after evolution of primitive members of the vertebrate line, whereas glial ensheathment around axons itself is an early feature of nervous system evolution (Hartline and Colman 2007). Indeed, glial cells in the invertebrate nervous system engulf multiple axons without myelinating them and appear similar to the non-myelin-forming Schwann cells in vertebrates (Klambt et al. 2001). By contrast, the PNS and central nervous system (CNS) of vertebrates have many myelinated axons with clustering of membrane-associated proteins including

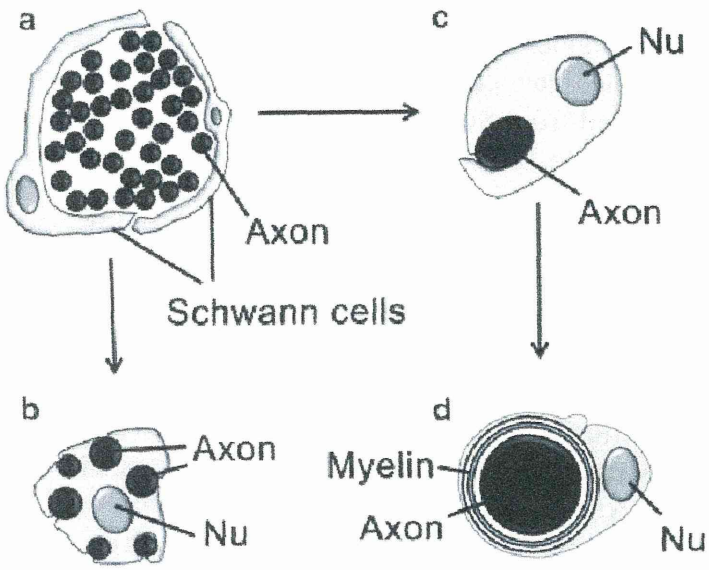

Fig. 4.1 Schematic drawing of developmental changes in Schwann cell morphology. Immature Schwann cells engulf the bulk of axons (**a**). Schwann cells ensheath small-diameter axons and differentiate to make unmyelinated Remak bundles (**b**), whereas those ensheathing the large-diameter axons produce myelin (**c**, **d**). *Nu* Schwann cell nuclei

adhesion molecules and ion channels in differential axonal segments divided by distinct myelin domains (Salzer 2003). A large part of Schwann cell development and fate determination in the vertebral nervous system including myelin formation is controlled by interactions between Schwann cells and axons. For example, the initiation of myelin formation by Schwann cells is strictly dependent on axonal signals, in contrast to myelin-forming cells in the CNS, the oligodendrocytes (Birchmeier and Nave 2008). At the same time, recent studies elucidated the metabolic relationship between Schwann cells and axons, which regulates the axonal microenvironment and affects axonal survival (Nave 2010b). Interestingly, certain aspects of glial support for axonal integrity and survival appear to be common in PNS and CNS, indicating that different sets of glial cells have similar roles for ensheathed axons. The principal goal of this chapter is to provide an overview of recent findings regarding the molecular and metabolic link between Schwann cells and axons, which significantly affect Schwann cell behavior as well as axonal integrity.

4.2 Structural Interactions Between Schwann Cells and Axons

Myelination of Schwann cells is extreme cellular specialization of the vertebrate nervous system. Myelination requires the generation of large amounts of extended cell membranes to ensheath around axons many times. The compacted and insulating sheath of myelin leaves gaps for the highly specialized nodes of Ranvier (Fig. 4.2a). At the nodes, voltage-dependent Na^+ channels are clustered on the axolemma, and focal depolarization of these Na^+ channels is responsible for saltatory conduction. During development, heminodes are first formed at the longitudinally expanding edges of single Schwann cells. Na^+ channels and nodal proteins are localized in the adjacent regions of the outermost edges of Schwann cells. Thereafter, the nodal components are moved ahead together with the edges of Schwann cells, and finally form mature nodes with nodal components of adjacent Schwann cells. Nodal regions are formed and maintained by scaffolding and adhesion molecules. For example, interaction between a membrane-bound extracellular matrix, gliomedin, produced from Schwann cells and axolemmal cell adhesion molecules, including neurofascin 186 (NF186) and NrCAM, is an early event in nodal formation (Salzer et al. 2008). When these molecules are genetically disrupted, the formation of the nodes such as Na^+-channel clustering is significantly impaired or delayed (Eshed et al. 2007; Feinberg et al. 2010; Sherman et al. 2005).

In the PNS, axonal regions between two adjacent nodes are covered with myelin sheath and composed of different types of segments with specialized functions. The nodes of Ranvier are flanked by paranodes that have axo–glial junctions which limit the diffusion of small molecules (Fig. 4.2b) (Perkins et al. 2008; Rosenbluth 2009). In paranodes, Schwann cell membranes are closely juxtaposed to axolemma and form a "paranodal loop". Paranodal loops and axolemma are separated by a distance of 2.5–3.0 nm and connected by high electron densities that represent septate-like

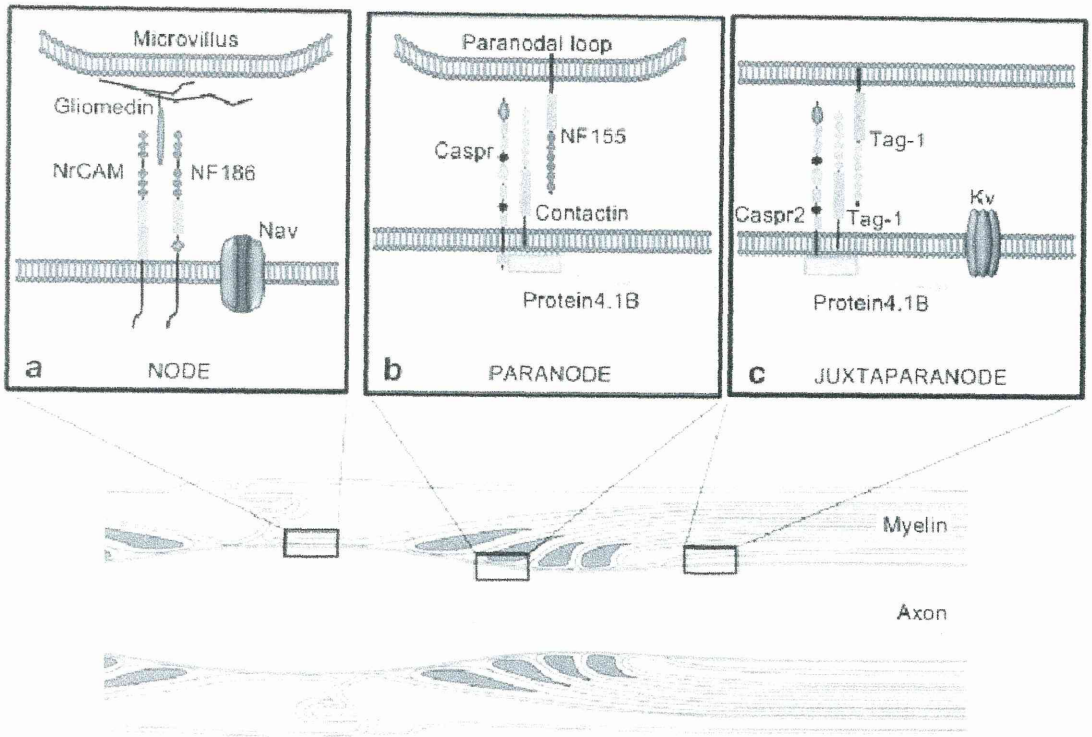

Fig. 4.2 Schematic drawing shows junctional complexes between Schwann cells and axons in different segments of myelinated axons. Nodal axolemma with voltage-gated Na^+ channels (*Nav*) has NrCAM and NF186, which interact with gliomedin (**a**). Paranodal axolemma contains Caspr and contactin, which interact with NF155 on paranodal loops of Schwann cells and are tethered to axonal actin cytoskeletons via protein 4.1B (**b**). Juxtaparanodal axolemma with enriched K^+ channels is associated with Schwann cell membranes via Tag-1 and Caspr2, which are connected to axonal actin cytoskeletons via protein 4.1B (**c**)

junctions (Peters et al. 1991). The septate-like junctions are the adhesive apparatus between myelin and axons, composed of contactin and contactin-associated protein (Caspr), the axonal membrane proteins enriched in paranodal regions (Einheber et al. 1997; Menegoz et al. 1997; Rios et al. 2000). These contactin–Caspr complexes are tethered to membrane-associated actin cytoskeletons via protein 4.1B (Buttermore et al. 2011; Denisenko-Nehrbass et al. 2003). Paranodal membranes of Schwann cells contain neurofascin 155 (NF155), which interacts with contactin and Caspr (Charles et al. 2002; Tait et al. 2000). The critical roles of paranodal septate-like junctions have been well documented through analyses of mice lacking components of the septate-like junctions (Bhat et al. 2001; Boyle et al. 2001; Sherman et al. 2005). Paranodal septate-like junctions are absent or abnormal in mice lacking Caspr and contactin. Nerve conduction in those mice is significantly slowed with accumulation of intracellular organelles in nodal/paranodal axoplasm. Although clustering of nodal Na^+ channels appears to be unchanged in contactin-null mice, voltage-gated K^+ channels normally excluded from paranodal axolemma in wild-type mice are diffused into paranodal axolemma in Caspr- or contactin-knockout mice (Bhat et al. 2001; Boyle et al. 2001). The paranodal axo–glial junction therefore functions as a "diffusion barrier" and spatially separates Na^+ and K^+ channel

distribution in myelinated axons. Extracellularly, the spiral loops of paranodal segments provide a diffusion pathway to small soluble molecules, and their diffusion does not appear to be affected by lack of the paranodal junctions (Mackenzie et al. 1984; Mierzwa et al. 2011; Shroff et al. 2011).

The juxtaparanode is adjacent to the paranodal region and contains enriched voltage-gated fast K^+ channels. Although the adaxonal membranes of Schwann cells in internodes are usually smooth, juxtaparanodal membranes can form invaginations into the axons. In a variety of neuropathies, the invaginations of Schwann cell processes into the axoplasm become extensive (Griffin and Price 1981; Spencer and Thomas 1974). Tag-1 (transient axonal glycoprotein-1/contactin-2) on the juxtaparanodal membranes of Schwann cells and axons is considered to mediate Schwann cell–axon connection in the juxtaparanode and also to form complexes with Caspr2 (Fig. 4.2c) (Poliak et al. 1999; Traka et al. 2003). The Caspr2–Tag-1 complex is tethered to membrane-associated actin cytoskeletons via protein 4.1B (Denisenko-Nehrbass et al. 2003). These interactions in addition to paranodal septate-like junctions limit the diffusion of K^+ channels to the nodal region (Bhat et al. 2001; Traka et al. 2003).

Membrane-associated proteins are also localized at the interface between Schwann cells and axons and influence Schwann cell differentiation. Necl-4 (nectin-like protein-4) on Schwann cells binds to Necl-1 on axons and is considered to facilitate myelination, although mice lacking Necl-1 have little deficit in PNS myelination (Maurel et al. 2007; Park et al. 2008; Spiegel et al. 2007). Localization of Par3 and its interaction with p75NTR (neurotrophin receptor) at the axon–Schwann cell junction are crucial to start myelination during development, suggesting that neurotrophins play some modulatory roles in myelination of Schwann cells (Chan et al. 2006; Xiao et al. 2009). A cell adhesion molecule of Schwann cells, N-cadherin, colocalizes with Par3 at the axon–Schwann cell interface upon myelination and may mediate the recruitment of Par3 to the interface, as seen in epithelial cells (Lewallen et al. 2011). Because myelination is delayed in mice with Schwann cell-specific depletion of N-cadherin and its associated molecule, β-catenin, N-cadherin along with β-catenin may be involved in establishment of Schwann cell polarity and the timing of myelination. However, there are some redundant factors for both proteins in the formation and maturation of myelin (Lewallen et al. 2011).

Nonmyelinating Schwann cells forming Remak bundles lack myelin and myelin components but express cell adhesion molecules and cell-surface receptors that are less abundant in myelinating cells (Mirsky et al. 2008). The cell adhesion molecules, L1 and N-CAM, are abundant in Remak Schwann cells but are downregulated upon myelination. L1 expression by Schwann cells is essential for Schwann cell contact and survival of sensory axons (Haney et al. 1999). N-CAM is a 120- to 180-kDa glycoprotein that is related to axonal outgrowth (Martini 1994). The interaction between nonmyelinating Schwann cells and axons may also have specific functions to maintain and modulate the periaxonal ionic microenvironment, such as K^+ regulation (Robert and Jirounek 1994).

Schwann cells produce extracellular matrix molecules, such as collagens, laminins, fibronectin, and heparan-sulfated proteoglycans (Carey and Todd 1987;