Neuron-glia communication in the control of oligodendrocyte function and myelin biogenesis

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Summary

During the development of the central nervous system the reciprocal communication between neurons and oligodendrocytes is essential for the generation of myelin, a multilamellar insulating membrane that ensheathes the axons. Neuron-derived signalling molecules regulate the proliferation, differentiation and survival of oligodendrocytes. Furthermore, neurons control the onset and timing of myelin membrane growth. In turn, signals from oligodendrocytes to neurons direct the assembly of specific subdomains in neurons at the node of Ranvier. Recent work has begun to shed light on the molecules and signaling systems used to coordinate the interaction of neurons and oligodendrocytes. For example, the neuronal signals seem to control the membrane trafficking machinery in oligodendrocytes that leads to myelination. These interconnections at multiple levels show how neurons and glia cooperate to build a complex network during development.

Key words: Neurons, Oligodendrocytes, Myelin

Introduction

All complex nervous systems consist of two main cell types, neurons and glia. The evolution of increasing complexity in the nervous system is accompanied by a steady rise in glial cell number. In the mammalian nervous system, glia outnumber neurons by far. During evolution vertebrates not only expanded the numbers of their glial cells but have also developed the myelin sheath. This is one of the most abundant membrane structures in the vertebrate nervous system. It is produced by two types of specialized glial cells, oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS). The myelin sheath is formed by the spiral wrapping of glial plasma membrane extensions around the axon, followed by the extrusion of cytoplasm and the compaction of the stacked membrane bilayers (Fig. 1A). These tightly packed membrane stacks provide electrical insulation around the axons and maximizes their conduction velocity.

The structure and molecular composition of myelin are unique. In contrast to most plasma membranes, myelin is a lipid-rich membrane (lipids constitute 70% of dry myelin weight) that is highly enriched in glycosphingolipids and cholesterol. The major glycosphingolipids in myelin are galactosylceramide and its sulfated derivative sulfatide (20% of lipid dry weight). There is also an unusually high proportion of ethanolamine phosphoglycerides in the plasmalogen form, which accounts for one-third of the phospholipids. Myelin contains a relatively simple array of proteins, myelin basic protein (MBP) and the proteolipid proteins (PLP/DM20) being the two major CNS myelin proteins. During the active phase of myelination, each oligodendrocyte must produce as much as ~5-50×10^3 μm^2 of myelin membrane surface area per day (Pfeiffer et al., 1993).

Since the ensheathment of the axons must occur at the appropriate time of neuronal development, reciprocal communication between neurons and oligodendrocytes is essential to coordinate myelin biogenesis (Boiko and Winckler, 2006). Neurons control the development of oligodendrocytes by regulating the proliferation, differentiation and survival of oligodendrocytes (Barres and Raff, 1999). The signals are important to match the number of oligodendrocytes to the axonal surface requiring myelination. Furthermore, the timing of myelination is crucial because the ensheathment of axons must not occur before neurons signal to oligodendrocytes. In turn, signals from oligodendrocytes to neurons are necessary to cluster multiprotein complexes in the axonal membrane into distinct subdomains at the nodes of Ranvier – the gaps beween myelinated segments of neurons (Pedraza et al., 2001; Scherer and Arroyo, 2002; Poliak and Peles, 2003; Salzer, 2003). Moreover, the axonal cytoskeleton and the rate of vesicular transport along the axons are modified by oligodendrocytes (de Waegh et al., 1992; Hsieh et al., 1994; Edgar et al., 2004). The reciprocal communication between neurons and oligodendrocytes is thus important for the development of the nervous system. Here, we discuss the cellular and molecular mechanisms of myelin biogenesis focusing on the role of neuron-oligodendrocyte communication in this process.

Neuronal control of oligodendrocyte development

Myelination of the axonal tracts of the CNS by oligodendrocytes takes place primarily in early postnatal life when oligodendrocytes have differentiated from oligodendrocyte precursor cells (OPCs). OPCs arise from the neuroepithelium of the ventricular/subventricular zone of the brain and migrate from this region into the developing white matter until they reach the appropriate axons. After OPCs have

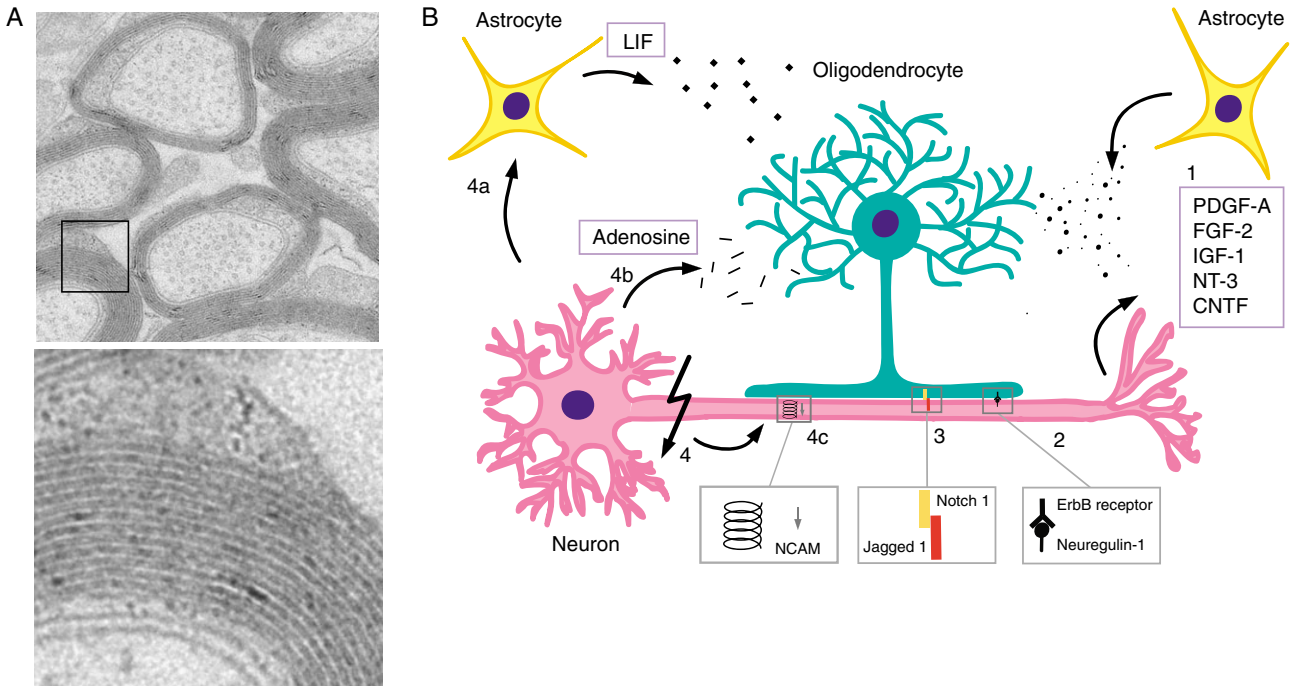

Fig. 1. Neuronal and glial signals in the regulation of myelin biogenesis. (A) An electron micrograph of myelinated nerve fibers within the optic nerve. (B) (1) Astrocytes and/or neurons release several growth/trophic factors factors, such as PDGF, FGF-2, IGF-1, NT-3 and CNTF that regulate oligodendrocyte proliferation and/or survival. (2) Membrane-associated or soluble neuregulin binds the ErbB receptor on oligodendrocytes to promote survival and maturation of oligodendrocytes. (3) Interaction of the Notch 1 receptor with Jagged 1 inhibits the differentiation of oligodendrocytes. (4) An increase in electrical activity causes the release of promyelinating factors such as LIF from astrocytes (4a), adenosine from neurons (4b) and changes the expression level of axonal cell adhesion molecules (4c).

arrived at their final target, they exit the cell cycle, become non-migratory and differentiate into myelin-forming oligodendrocytes (Baumann and Pham-Dinh, 2001). To ensure full and timely myelination of all axonal tracts, the timing of OPC differentiation must be tightly controlled by their target cells. This was not initially evident because the differentiation of oligodendrocytes in cell culture occurs normally in the absence of neurons (Mirsky et al., 1980; Dubois-Dalcq et al., 1986). The differentiation of oligodendrocytes seems to follow a default pathway in which intrinsic signals define the number of cell divisions before the cells exit the cell cycle and undergo their characteristic sequence of developmental steps (Temple and Raff, 1986).

Many studies now point to the importance of extrinsic neuron-derived signalling molecules at multiple stages of oligodendrocyte development (Fig. 1B) (Barres and Raff, 1999). These extrinsic signals serve two major purposes. They help to control the proper timing of OPC differentiation to ensure myelination at the appropriate time and place, and they control and match the number of oligodendrocytes to the axonal surface area requiring myelination. Several growth factors and trophic factors, such as PDGF-A, FGF-2, IGF-1, NT-3 and CNTF, have been shown to regulate oligodendrocyte development (Barres and Raff, 1994; Miller, 2002; Baron et al., 2005). PDGF-A is produced by both astrocytes and neurons and regulates the proliferation and survival of OPCs (Noble et al., 1988; Raff et al., 1988; Richardson et al., 1988). Overexpression of PDGF-A in transgenic mice results in a dramatic increase in the number of OPCs in the embryonic mouse spinal cord and ectopic production of oligodendrocytes (Calver et al., 1998). However, the excess oligodendrocytes die at an immature stage of differentiation and the final result is a normal number of myelin-forming oligodendrocytes.

This is a nice example of how increased proliferation can be balanced by increased apoptosis. Even during normal development, oligodendrocytes are greatly overproduced and the cell number is adjusted to the number and length of the axons requiring myelination. Only oligodendrocytes that manage to ensheath the axon survive, whereas those that fail degenerate (Barres et al., 1992; Trapp et al., 1997). One mechanism that may determine the final number of oligodendrocytes is competition for limiting amounts of target-derived molecules, such as FGF-2, IGF-1, NT-3 and CNTF. Because most of these factors are also produced by astrocytes, the role of neurons was not initially apparent. An important clue to the requirement for axonal factors came from experiments on transected optic nerves. Removal of axons reduces the number of oligodendrocytes significantly (Barres et al., 1993). By contrast, transgenic optic nerves that display an increased number of axons have more oligodendrocytes (Burne et al., 1996).

Which are the neuron-derived molecules that control oligodendrocyte survival? One such a factor is neuregulin (NRG). The NRGs constitute a family of proteins containing an epidermal growth factor (EGF)-like motif that activates the membrane-associated ErbB2, ErbB3 and ErbB4 receptor tyrosine kinases. In the developing CNS, NRGs activate ErbB on oligodendrocytes. In the absence of ErbB2,

oligodendrocytes fail to undergo terminal differentiation and to ensheath axons (Park et al., 2001). In culture, NRG-1 supports the survival of maturing oligodendrocytes (Fernandez et al., 2000; Flores et al., 2000; Carteron et al., 2006) and the addition of NRG decreases the amount of cell death that occurs during normal development or optic nerve transection experiments (Fernandez et al., 2000). However, NRGs not only promote the survival and maturation of oligodendrocytes but also act as powerful mitogens and strongly enhance OPC proliferation (Canoll et al., 1996). Surprisingly, NRGs can also prevent or even reverse oligodendrocyte maturation in OPC cultures (Canoll et al., 1996; Canoll et al., 1999). Furthermore, recent data from ErbB4-knockout mice indicate that ErbB4 inhibits oligodendrocyte lineage maturation and is not required for oligodendrocyte differentiation (Sussman et al., 2005).

How can the same growth factors have such opposite effects? Multiple factors may be responsible for the variable response to NRG at distinct stages of oligodendrocyte development. These include different levels of the ligand, the repertoire of receptors expressed and the presence of co-factors. Recently, an integrin-mediated switch has been implicated in the NRG signalling pathway (Colognato et al., 2002; Colognato et al., 2004). Without neuronal contact, NRG activates a PI(3)K-dependent proliferation pathway, whereas adhesion of axons to $\alpha6\beta1$ integrin on the surface of oligodendrocytes leads to NRG-dependent survival through MAPK signalling (Colognato et al., 2002; Colognato et al., 2004). In this model, the integrin-mediated signalling defines the action of NRG. The interaction of integrin with the axonal surface depends on contact with laminin located there. This is consistent with a study of laminin-2-deficient mice that demonstrated a crucial role for laminin-2 in CNS myelination (Chun et al., 2003).

Another example of an axonally derived signalling pathway that influences oligodendrocyte development is the Notch signalling pathway. OPCs express the Notch 1 receptor and interaction with Jagged 1 located at the axonal surface results in the activation of the Notch pathway in OPCs, which inhibits their differentiation into oligodendrocytes (Wang et al., 1998). Because the expression of Jagged 1 is developmentally regulated in neurons, decreasing with a time course that parallels myelination, it is likely that neurons help to regulate the timing of myelination by preventing oligodendrocyte differentiation. This view is supported by in vivo experiments using a conditional knockout approach to selectively eliminate Notch signalling from oligodendrocytes. This results in premature oligodendrocyte differentiation in the CNS (Genoud et al., 2002). In addition, the axonal cell adhesion molecule contactin was shown to act as an alternative Notch ligand, promoting rather than inhibiting oligodendrocyte differentiation (Hu et al., 2003) and thereby adding another level of regulation to the Notch signalling pathway in oligodendrocytes.

Neuronal factors in myelination

The next event after differentiation of OPCs is the formation of myelin. Myelination is a multi-step process requiring precise coordination of several different signals. The following steps can be distinguished: (1) recognition of and adhesion of the oligodendrocytes to the appropriate axon; (2) synthesis and transport of myelin components to the axon; (3) the wrapping of the myelin membrane around the axons; and (4) the compaction of the myelin sheath. Here, we restrict ourselves to recent findings that shed light on those poorly understood processes, examining how myelin-forming glia recognize their targets and how neurons regulate the synthesis and transport of myelin components.

Oligodendrocytes do not wrap their plasma membrane randomly around neuronal processes but carefully select axons that have a diameter of >0.2 μm; they also exclude dendrites. A recent study shows that NRG1 type III on the axonal surface is required for the myelination by Schwann cells in the PNS (Taveggia et al., 2005). In fact, the levels of NRG1 type III define not only whether or not an axon will be myelinated but also the thickness of the sheath: transgenic mice with reduced NRG-1 expression display hypomyelination, whereas overexpression of NRG-1 induces increased myelin thickness (Michailov et al., 2004). Myelin-forming Schwann cells thus appear to use NRG-1 signals to know whether and to what extent axons require myelination. The signalling pathways involved in the CNS are not known. Whether oligodendrocytes have the ability to read NRG-1 levels and thereby signals from CNS axons in a similar way to that used by Schwann cells is still an open issue.

After oligodendrocytes have established proper contact with the axonal membrane, they start to extend their membrane by spirally wrapping it around the axon. Because each oligodendrocyte is able to produce up to 40 myelinated segments on multiple axons, they have to synthesize a tremendous amount of membrane in a short time (Pfeiffer et al., 1993). Intuitively, one would assume that the production of these myelin components is strictly under neuronal control because they are required at the time oligodendrocytes begin wrapping their membrane around axons. However, this is only partially true. Although neurons seem to regulate myelin gene expression to some extent (Macklin et al., 1986; Goto et al., 1990; Scherer et al., 1992), the production of myelin components is initiated and also continues at a high rate in primary cultures of oligodendrocytes in the absence of neurons (Mirsky et al., 1980; Dubois-Dalcq et al., 1986). Because the uncoordinated production of myelin membrane by oligodendrocytes in the absence of axons may have deleterious consequences (e.g. formation of intracellular myelin), it is likely that control mechanisms exist in vivo. Thus an intrinsic program within oligodendrocytes lays out the timing of their development (Temple and Raff, 1986), which can be influenced by external factors.

One signal that seems to be required to trigger myelination is the electrical activity of neurons (Demerens et al., 1996). Note however, that a recent study in the zebrafish demonstrated that neither neuronal activity nor synaptic function is required for myelination in the larval nervous system (Woods et al., 2006). There are numerous studies that address the mechanism of how electrical activity in axons after target innervation may influence myelination. There is evidence that it leads to the secretion of promyelinating factors such as adenosine from neurons (Stevens et al., 2002). In the PNS, by contrast, impulses in premyelinated axons trigger the release of adenosine triphosphate, which inhibits proliferation and differentiation of Schwann cells (Stevens and Fields, 2000). Recent work reveals a role for astrocytes in initiation of myelination in response to electrical impulses: they appear to

release leukemia inhibitory factor (LIF), which then stimulates the oligodendrocytes (Ishibashi et al., 2006).

Electrical activity of neurons not only controls the secretion of promyelinating factors but also leads to a change in the expression pattern of axonal proteins (Coman et al., 2005). The removal of some of these proteins, such as the polysialated adhesion molecule NCAM, is essential and allows the myelination process to proceed (Charles et al., 2000). The molecular mechanisms by which these factors influence myelin membrane generation are not clear. One pathway recently shown to coordinate myelination is the regulation of RhoA activity by LINGO-1 in oligodendrocytes (Mi et al., 2005). Activation of RhoA by LINGO-1 negatively regulates myelination (Liang et al., 2004; Mi et al., 2005). It will now be important to find out how these different signaling cascades act on the cellular machinery that generates myelin membrane in oligodendrocytes.

Myelin assembly and trafficking

Myelin assembly and trafficking is much more than the expression of myelin genes and involves the assembly of particular components in a temporally and spatially regulated manner. This requires specific sorting and transport mechanisms for delivering myelin membrane components from the site of synthesis to the newly forming myelin membrane (Kramer et al., 2001; Pfeiffer et al., 1993). A level of complexity is added by the division of myelin into distinct specialized regions: PLP/DM20 and MBP are found in compact internodal myelin; the immunoglobulin-like cell adhesion molecule neurofascin-155 is localized to paranodes; and myelin-associated glycoprotein (MAG) is concentrated in periaxonal lamellae. What is known about the machinery that sorts out myelin proteins and lipids, and is the transport regulated by neurons? Below we discuss how the internodal region, which comprises nearly 99% of total myelin, is formed, before going into the mechanisms that organize the membrane at the nodes.

Individual myelin components are synthesized in oligodendrocytes at several subcellular localizations and transported by different mechanisms to the growing myelin membrane. For example, targeting of MBP to myelin depends on transport of the respective MBP mRNAs. The MBP mRNA is assembled into granules in the perikaryon of oligodendrocytes, transported along processes and localized to the myelin membrane (Ainger et al., 1993). The transport of the RNA to the plasma membrane depends on a 21-nucleotide sequence, the RNA transport signal (RTS), in the 3′UTR of the MBP mRNA (Ainger et al., 1997). Whether the transport and/or final localization of the mRNA or protein are regulated by extrinsic signals is not known. However, the finding that MBP is initially synthesized in the cell body and is found within processes and the myelin sheath later during development suggests that its transport may be under developmental control (Shiota et al., 1989). The mechanistic function of MBP in the formation of myelin is not understood. The binding of the positively charged MBP to the negatively charged inner leaflet of the plasma membrane suggests that it can function as a lipid coupler by bringing the layers of myelin close together. Recent data indicate that neurons increase the lipid packing of the myelin-forming bilayer in oligodendrocytes and that MBP is involved in this process of plasma membrane rearrangement (Fitzner et al. 2006).

The other major myelin protein, the integral-membrane protein PLP/DM20, is transported by vesicular transport through the biosynthetic pathway to myelin (Colman et al., 1982). On its way to the plasma membrane, PLP/DM20 associates with cholesterol and galactosylceramide in the Golgi complex, which might assist the targeting of PLP/DM20 to myelin (Simons et al., 2000). The first hint of the signal determining the selective targeting of PLP/DM20 to myelin came from work on transgenic mice showing that the N-terminal 13 amino acids of PLP are sufficient to target a cytoplasmic fusion protein (lacZ) to the myelin membrane (Wight et al., 1993). Recent work indicates that the palmitoylation of this sequence is required for the selective sorting to myelin (Schneider et al., 2005). These studies, together with others, suggest the involvement of lipid rafts in the transport of proteins to myelin (Kim et al., 1995; Kramer et al., 1997; Simons et al., 2002; Taylor et al., 2002; Marta et al., 2003).

The PLP-delivery pathway might be under the control of neuronal signals (Fig. 2) (Trajkovic et al., 2006). In the absence of neurons, PLP/DM20 is internalized and stored in late endosomes/lysosomes (LE/L), entering a cholesterol-dependent endocytosis pathway. After receiving an unknown soluble signal from neurons, oligodendrocytes reduce the rate of endocytosis and trigger transport from LE/L to the plasma membrane. This regulation of PLP trafficking might represent a mechanism to store superfluous membrane produced before the onset of myelination and release it on demand in a regulated

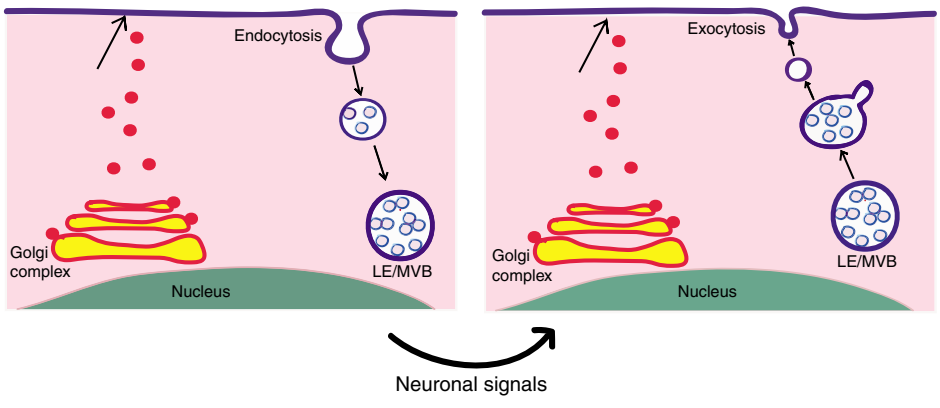

Fig. 2. Neurons organize the membrane-trafficking machinery in oligodendrocytes. In the absence of neurons, PLP is internalized and stored in late endosomes/lysosomes (LE/L) via a cholesterol-dependent endocytosis pathway. After receiving signals from neurons, the rate of endocytosis is reduced and transport from LE/L to the plasma membrane is triggered.

fashion. Because MBP does not localize to LE/L, it may also be an important mechanism for differentially compartmentalizing myelin components to prevent premature and inappropriate assembly of myelin.

It is interesting to compare the regulation of PLP trafficking in oligodendrocytes by neuronal signals with the changes in membrane trafficking during the development of polarized tissue (Mostov et al., 2003). For example, during tubulogenesis, cells depolarize and develop intracellular compartments containing components that are normally found at the surface. Polarization, by contrast, often involves the redirection of membrane from intracellular reservoirs to the plasma membrane. These are only a few examples of how membrane trafficking can undergo profound changes during development. The regulation of membrane trafficking in oligodendrocytes during development makes these cells an interesting model system to study the influence of cell-to-cell signaling on membrane trafficking.

Little is yet known about the trafficking machinery in oligodendrocytes. The upregulation of specific Rab proteins (Rab-3, Rab-5, Rab-8 and Rab-40) and SNARE proteins (VAMP-2 and syntaxin-4) during oligodendrocyte development gives some clue as to the players that might be involved (Rodriguez-Gabin et al., 2004). A recent genetic screen in zebrafish showed that N-ethylmaleimide-sensitive factor (NSF), a protein involved in membrane fusion, is required for the expression of MBP and the proper formation of the myelin membrane (Woods et al., 2006). This finding points to an interesting link between intracellular transport and myelin biogenesis. NSF may have a previously unidentified role in the targeting of essential signaling molecules. In addition, the exocyst, a multimeric protein complex involved in the recruitment of transport vesicles during the formation of polarized cells, has recently been implicated in vesicle transport in oligodendrocytes (Anitei et al., 2006). The challenge will now be to integrate the signaling and trafficking pathways to attain a comprehensive view of how myelination is regulated. The cellular trafficking and signaling machinery are interconnected more then previously thought (Dudu et al., 2004; Polo and Di Fiore, 2006). This connection is likely to be particularly pronounced in oligodendrocytes, which must produce and sort membrane upon neuronal request.

Neuron and glia interaction in domain organization of myelinated axons

Myelinated axons are organized into several distinct longitudinal domains centered around the nodes of Ranvier. These are gaps between each myelin segment and are required for efficient and rapid propagation of action potentials. The nodes are flanked on either side by lateral loops formed by the myelinating glia. These paranodal loops form septate-like junctions with the axonal membrane. The juxtaparanodal domain lies just under the compact myelin sheath next to the paranodes. Each of these domains consists of distinct multiprotein complexes, containing different cell-adhesion molecules, cytoplasmic adaptor proteins and ion channels (Fig. 3). Below we discuss briefly how these domains are generated, focusing on the intercellular interactions that direct their assembly. For a more comprehensive coverage, we refer readers to previous reviews of this topic (Pedraza et al., 2001;

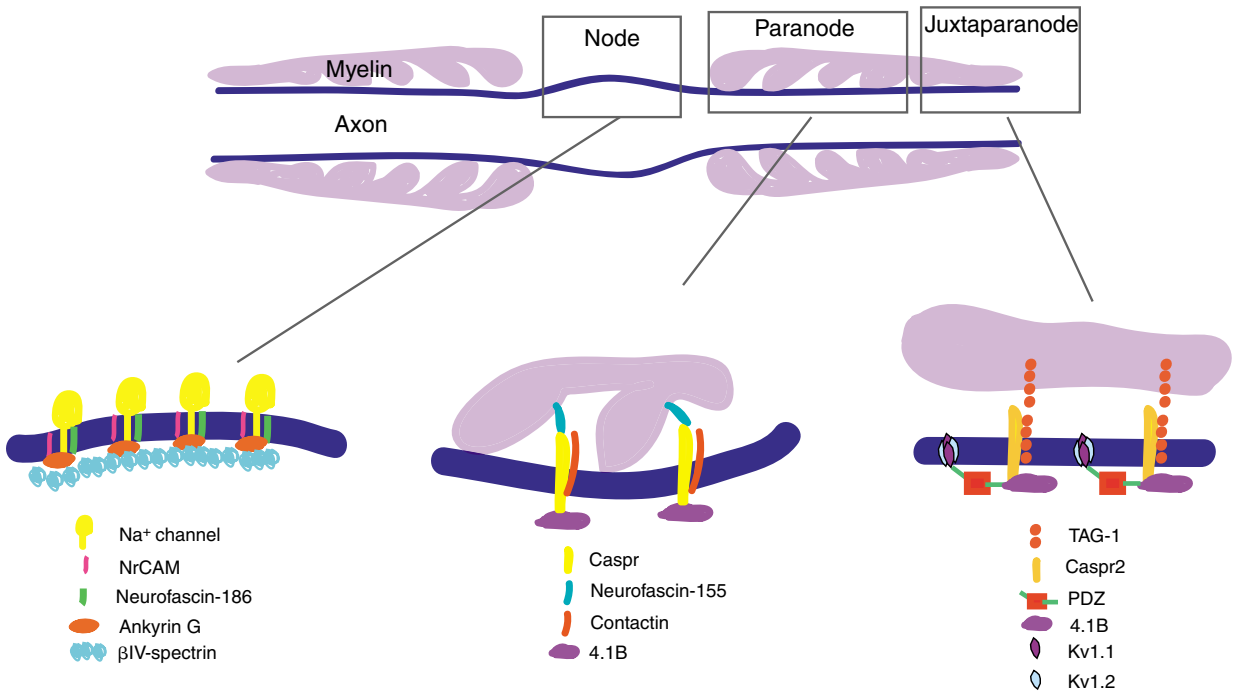

Fig. 3. Molecular composition of domains at the node of Ranvier. Components of the nodes include neurofascin-186, NrCAM and voltage-gated Na^+ channels, which are tethered to a complex containing ankyrin G and βIV-spectrin. The paranodes contain a complex of Caspr, contactin and 4.1B at the axonal membrane, which binds to neurofascin-155 on the paranodal loop. The multiprotein complex in the juxtaparanode contains a *cis* complex of Caspr2 and TAG-1, which interact with 4.1B and a PDZ-domain-containing protein associated with the two shaker-type K^+ channels, $K_v1.1$ and 1.2. This complex is linked through a *trans* interaction with TAG-1 to the glial membrane.

Scherer and Arroyo, 2002; Poliak and Peles, 2003; Salzer, 2003).

Nodes

The domains are formed sequentially by reciprocal interactions between glia and neurons. This assembly starts at the nodes and progresses to the paranodes and the juxtaparanodes. Before glial cells have approached the axons, voltage-gated Na^+ channels are diffusely distributed over the axonal membrane. In the PNS, the clustering of the channels does not occur before the Schwann cells have extended longitudinally and established close contact with the axon. Clustering starts at sites adjacent to glial processes that contain dynamic protrusions enriched in the ezrin-radixin-moesin (ERM) family of actin-binding proteins (Melendez-Vasquez et al., 2001; Gatto et al., 2003). The glial molecule required for axonal Na^+-channel clustering has long been elusive. A recent paper, however, identified gliomedin, a novel ligand for the neuronal adhesion molecules neurofascin and NrCAM, as the mediator responsible at the nodes of Ranvier (Eshed et al., 2005). This finding fills an important gap in our understanding of the molecular assembly at the node of Ranvier and supports a model in which sequential protein interactions initiate Na^+-channel clustering. Gliomedin accumulates in processes at the edges of Schwann cells, where it is presented to axons. There the interaction with neurofascin and NrCAM occurs and this complex in turn recruits ankyrin G, a cytoskeletal/scaffolding protein, which contains binding sites for Na^+ channels (Zhou et al., 1998; Jenkins and Bennett, 2002; Garrido et al., 2003). Recruitment of stabilizing components such as βIV spectrin further enhances the clustering by anchoring the complex more firmly to the axonal cytoskeleton (Berghs et al., 2000; Komada and Soriano, 2002; Lacas-Gervais et al., 2004). This specialized cytoskeleton not only confers the specific localization and retention of nodal proteins but also functions as a matrix by creating sites for Na^+ channel clustering.

Specific targeting and sorting mechanisms may also contribute to the segregation of nodal components. For example, the trapping of individual components at the nodal multiprotein complex may prevent their elimination by endocytosis and thereby reinforce their accumulation at the node (Fache et al., 2004). The specific targeting of proteins by vesicular carriers to the node is another potential mechanism that remains to be investigated. Moreover, the attachment of the lateral edges of the glial cells to the axonal membrane creates a diffusion barrier that might help to concentrate the nodal protein complex by restricting its lateral diffusion (Pedraza et al., 2001). The interaction of the glial ligand with the axonal adhesion molecule thus appears to initiate domain formation by generating a seed for the growth of a multiprotein complex, which is expanded by recruitment of further components, tethered to both the axonal cytoskeleton and the glial membrane and has limited capacity for diffusion. In the CNS, there seems to be at least one exception to this model. Initiation of complex formation does not depend on direct contact between oligodendrocytes and axons, but rather on an unknown soluble factor (Kaplan et al., 1997; Kaplan et al., 2001).

Paranodes

Both in the PNS and the CNS, the formation of the paranodes is dependent on axon-glia interactions. The interaction of glial loops with the axonal membrane is mediated by neurofascin-155 and contactin (Tait et al., 2000; Boyle et al., 2001; Charles et al., 2002; Sherman et al., 2005). The interaction of neurofascin-155 in glia to a complex of contactin and contactin-associated protein (Caspr) in axons initiates the assembly of the paranodal complex, which is then stabilized by interactions with a specialized axonal cytoskeleton consisting of proteins such as the membrane skeleton component protein 4.1B, ankyrin B and α/βII spectrin (Denisenko-Nehrbass et al., 2003; Ogawa et al., 2006). The binding of neurofascin-155 to the Caspr-contactin complex may not be direct and other components are probably required to bridge these proteins (Gollan et al., 2003).

The paranodes seem to be particularly vulnerable to disruptions of the myelin membrane – for example, in multiple sclerosis (Wolswijk and Balesar, 2003; Coman et al., 2006). In addition, a surprisingly high number of mouse myelin mutants display specific abnormalities in the paranodes and not in compact myelin. These include mice lacking the myelin glycolipids, galactosylceramide and sulfatide (Coetzee et al., 1996; Dupree et al., 1999; Honke et al., 2002), the myelin and lymphocyte protein (MAL) (Schaeren-Wiemers et al., 2004) or 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNPase) (Rasband et al., 2005). Interestingly, all these molecules play a role in the transport of vesicular membrane carriers by regulating sorting (Cheong et al., 1999; Puertollano et al., 1999; Degroote et al., 2004) or cytoskeleton dynamics (Lee et al., 2005). This suggests that they might be required for appropriate trafficking of glial molecules to the paranode (Schafer et al., 2004).

On the axonal side, the localization of contactin to the paranodes not only depends on the interaction with glial neurofascin but also on the association with Caspr (Faivre-Sarrailh et al., 2000; Bhat et al., 2001; Gollan et al., 2002; Gollan et al., 2003). Caspr associates with contactin in the ER and this interaction is required for the transport to the cell surface (Faivre-Sarrailh et al., 2000). In addition, the interaction modulates the intracellular processing of sugar moieties and this affects its ability to interact with neurofascin (Gollan et al., 2003).

Juxtaparanodes

The process of domain assembly next progresses to the juxtaparanodes. Caspr2 and K^+ channels, the juxtaparanodal components, first transiently appear in the nodes and paranodes and are later gradually displaced into the juxtaparanodes. Like the assembly of nodes and paranodes, the formation of the juxtaparanodes critically depends on axon-glia contacts. The GPI-anchored cell adhesion molecule TAG-1 plays a crucial role in this process (Poliak et al., 2003; Traka et al., 2003). It is expressed in both glia and neurons and associates in *cis* with Caspr2 and in *trans* with itself. Caspr2, in turn, associates with the K^+ channels $K_v1.1$ and 1.2 (Poliak et al., 1999) through an unidentified PDZ-containing protein (Rasband et al., 2002) and through protein 4.1B with the cytoskeleton (Denisenko-Nehrbass et al., 2003). Again, axon-glia interactions, attachment of the complex to the axonal cytoskeleton and lateral diffusion barriers within the axonal membrane are all mechanisms that contribute to the segregation of the plasma membrane.

Concluding remarks

The reciprocal communication between neurons and oligodendrocytes plays an essential role during the development of the nervous system. These signals not only control the development of oligodendrocytes but also regulate the generation of the myelin membrane sheath. Many aspects of myelin biogenesis are, however, still unresolved. For example, the machinery required to drive the membrane around the axon and to remove the cytoplasm between the different layers to achieve compaction is completely unknown. Since axons define the thickness of the myelin sheath, it is likely that neuronal signals also regulate the myelin membrane-wrapping machinery in oligodendrocytes. Furthermore, there is mounting evidence that neuron-glia communication has a role in the pathogenesis of many neurological diseases. Oligodendrocyte dysfunction, for example, leads to massive axonal degeneration (Griffiths et al., 1998; Lappe-Siefke et al., 2003; Yin et al., 2006). Moreover, axonal outgrowth in the CNS is limited by growth inhibitors provided by oligodendrocytes (Sandvig et al., 2004; Schwab, 2004; Huang et al., 2005). Therefore, more research into neuron and glia communication will not only provide new exciting insights into the development of the nervous system but also help us to find new treatment strategies for various neurological diseases.

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References

Ainger, K., Avossa, D., Morgan, F., Hill, S. J., Barry, C., Barbarese, E. and Carson, J. H. (1993). Transport and localization of exogenous myelin basic protein mRNA microinjected into oligodendrocytes. *J. Cell Biol.* **123**, 431-441.

Ainger, K., Avossa, D., Diana, A. S., Barry, C., Barbarese, E. and Carson, J. H. (1997). Transport and localization elements in myelin basic protein mRNA. *J. Cell Biol.* **138**, 1077-1087.

Anitei, M., Ifrim, M., Ewart, M. A., Cowan, A. E., Carson, J. H., Bansal, R. and Pfeiffer, S. E. (2006). A role for Sec8 in oligodendrocyte morphological differentiation. *J. Cell Sci.* **119**, 807-818.

Baron, W., Colognato, H. and ffrench-Constant, C. (2005). Integrin-growth factor interactions as regulators of oligodendroglial development and function. *Glia* **49**, 467-479.

Barres, B. A. and Raff, M. C. (1994). Control of oligodendrocyte number in the developing rat optic nerve. *Neuron* **12**, 935-942.

Barres, B. A. and Raff, M. C. (1999). Axonal control of oligodendrocyte development. *J. Cell Biol.* **147**, 1123-1128.

Barres, B. A., Hart, I. K., Coles, H. S., Burne, J. F., Voyvodic, J. T., Richardson, W. D. and Raff, M. C. (1992). Cell death and control of cell survival in the oligodendrocyte lineage. *Cell* **70**, 31-46.

Barres, B. A., Jacobson, M. D., Schmid, R., Sendtner, M. and Raff, M. C. (1993). Does oligodendrocyte survival depend on axons? *Curr. Biol.* **3**, 489-497.

Baumann, N. and Pham-Dinh, D. (2001). Biology of oligodendrocyte and myelin in the mammalian central nervous system. *Physiol. Rev.* **81**, 871-927.

Berghs, S., Aggujaro, D., Dirkx, R., Jr, Maksimova, E., Stabach, P., Hermel, J. M., Zhang, J. P., Philbrick, W., Slepnev, V., Ort, T. et al. (2000). betaIV spectrin, a new spectrin localized at axon initial segments and nodes of ranvier in the central and peripheral nervous system. *J. Cell Biol.* **151**, 985-1002.

Bhat, M. A., Rios, J. C., Lu, Y., Garcia-Fresco, G. P., Ching, W., St Martin, M., Li, J., Einheber, S., Chesler, M., Rosenbluth, J. et al. (2001). Axon-glia interactions and the domain organization of myelinated axons requires neurexin IV/Caspr/Paranodin. *Neuron* **30**, 369-383.

Boiko, T. and Winckler, B. (2006). Myelin under construction – teamwork required. *J. Cell Biol.* **172**, 799-801.

Boyle, M. E., Berglund, E. O., Murai, K. K., Weber, L., Peles, E. and Ranscht, B. (2001). Contactin orchestrates assembly of the septate-like junctions at the paranode in myelinated peripheral nerve. *Neuron* **30**, 385-397.

Burne, J. F., Staple, J. K. and Raff, M. C. (1996). Glial cells are increased proportionally in transgenic optic nerves with increased numbers of axons. *J. Neurosci.* **16**, 2064-2073.

Calver, A. R., Hall, A. C., Yu, W. P., Walsh, F. S., Heath, J. K., Betsholtz, C. and Richardson, W. D. (1998). Oligodendrocyte population dynamics and the role of PDGF in vivo. *Neuron* **20**, 869-882.

Canoll, P. D., Musacchio, J. M., Hardy, R., Reynolds, R., Marchionni, M. A. and Salzer, J. L. (1996). GGF/neuregulin is a neuronal signal that promotes the proliferation and survival and inhibits the differentiation of oligodendrocyte progenitors. *Neuron* **17**, 229-243.

Canoll, P. D., Kraemer, R., Teng, K. K., Marchionni, M. A. and Salzer, J. L. (1999). GGF/neuregulin induces a phenotypic reversion of oligodendrocytes. *Mol. Cell. Neurosci.* **13**, 79-94.

Carteron, C., Ferrer-Montiel, A. and Cabedo, H. (2006). Characterization of a neural-specific splicing form of the human neuregulin 3 gene involved in oligodendrocyte survival. *J. Cell Sci.* **119**, 898-909.

Charles, P., Hernandez, M. P., Stankoff, B., Aigrot, M. S., Colin, C., Rougon, G., Zalc, B. and Lubetzki, C. (2000). Negative regulation of central nervous system myelination by polysialylated-neural cell adhesion molecule. *Proc. Natl. Acad. Sci. USA* **97**, 7585-7590.

Charles, P., Tait, S., Faivre-Sarrailh, C., Barbin, G., Gunn-Moore, F., Denisenko-Nehrbass, N., Guennoc, A. M., Girault, J. A., Brophy, P. J. and Lubetzki, C. (2002). Neurofascin is a glial receptor for the paranodin/Caspr-contactin axonal complex at the axoglial junction. *Curr. Biol.* **12**, 217-220.

Cheong, K. H., Zacchetti, D., Schneeberger, E. E. and Simons, K. (1999). VIP17/MAL, a lipid raft-associated protein, is involved in apical transport in MDCK cells. *Proc. Natl. Acad. Sci. USA* **96**, 6241-6248.

Chun, S. J., Rasband, M. N., Sidman, R. L., Habib, A. A. and Vartanian, T. (2003). Integrin-linked kinase is required for laminin-2-induced oligodendrocyte cell spreading and CNS myelination. *J. Cell Biol.* **163**, 397-408.

Coetzee, T., Fujita, N., Dupree, J., Shi, R., Blight, A., Suzuki, K. and Popko, B. (1996). Myelination in the absence of galactocerebroside and sulfatide: normal structure with abnormal function and regional instability. *Cell* **86**, 209-219.

Colman, D. R., Kreibich, G., Frey, A. B. and Sabatini, D. D. (1982). Synthesis and incorporation of myelin polypeptides into CNS myelin. *J. Cell Biol.* **95**, 598-608.

Colognato, H., Baron, W., Avellana-Adalid, V., Relvas, J. B., Baron-Van Evercooren, A., Georges-Labouesse, E. and ffrench-Constant, C. (2002). CNS integrins switch growth factor signalling to promote target-dependent survival. *Nat. Cell Biol.* **4**, 833-841.

Colognato, H., Ramachandrappa, S., Olsen, I. M. and ffrench-Constant, C. (2004). Integrins direct Src family kinases to regulate distinct phases of oligodendrocyte development. *J. Cell Biol.* **167**, 365-375.

Coman, I., Barbin, G., Charles, P., Zalc, B. and Lubetzki, C. (2005). Axonal signals in central nervous system myelination, demyelination and remyelination. *J. Neurol. Sci.* **233**, 67-71.

Coman, I., Aigrot, M. S., Seilhean, D., Reynolds, R., Girault, J. A., Zalc, B. and Lubetzki, C. (2006). Nodal, paranodal and juxtaparanodal axonal proteins during demyelination and remyelination in multiple sclerosis. *Brain* 10.1093/brain/awl144.

de Waegh, S. M., Lee, V. M. and Brady, S. T. (1992). Local modulation of neurofilament phosphorylation, axonal caliber, and slow axonal transport by myelinating Schwann cells. *Cell* **68**, 451-463.

Degroote, S., Wolthoorn, J. and van Meer, G. (2004). The cell biology of glycosphingolipids. *Semin. Cell Dev. Biol.* **15**, 375-387.

Demerens, C., Stankoff, B., Logak, M., Anglade, P., Allinquant, B., Couraud, F., Zalc, B. and Lubetzki, C. (1996). Induction of myelination in the central nervous system by electrical activity. *Proc. Natl. Acad. Sci. USA* **93**, 9887-9892.

Denisenko-Nehrbass, N., Oguievetskaia, K., Goutebroze, L., Galvez, T., Yamakawa, H., Ohara, O., Carnaud, M. and Girault, J. A. (2003). Protein 4.1B associates with both Caspr/paranodin and Caspr2 at paranodes and juxtaparanodes of myelinated fibres. *Eur. J. Neurosci.* **17**, 411-416.

Dubois-Dalcq, M., Behar, T., Hudson, L. and Lazzarini, R. A. (1986). Emergence of three myelin proteins in oligodendrocytes cultured without neurons. *J. Cell Biol.* **102**, 384-392.

Dudu, V., Pantazis, P. and Gonzalez-Gaitan, M. (2004). Membrane traffic during embryonic development: epithelial formation, cell fate decisions and differentiation. *Curr. Opin. Cell Biol.* **16**, 407-414.

Dupree, J. L., Girault, J. A. and Popko, B. (1999). Axo-glial interactions regulate the localization of axonal paranodal proteins. *J. Cell Biol.* **147**, 1145-1152.

Edgar, J. M., McLaughlin, M., Yool, D., Zhang, S. C., Fowler, J. H., Montague, P., Barrie, J. A., McCulloch, M. C., Duncan, I. D., Garbern, J. et al. (2004). Oligodendroglial modulation of fast axonal transport in a mouse model of hereditary spastic paraplegia. *J. Cell Biol.* **166**, 121-131.

Eshed, Y., Feinberg, K., Poliak, S., Sabanay, H., Sarig-Nadir, O., Spiegel, I., Bermingham, J. R., Jr and Peles, E. (2005). Gliomedin mediates Schwann cell-axon interaction and the molecular assembly of the nodes of Ranvier. *Neuron* **47**, 215-229.

Fache, M. P., Moussif, A., Fernandes, F., Giraud, P., Garrido, J. J. and Dargent, B. (2004). Endocytotic elimination and domain-selective tethering constitute a potential mechanism of protein segregation at the axonal initial segment. *J. Cell Biol.* **166**, 571-578.

Faivre-Sarrailh, C., Gauthier, F., Denisenko-Nehrbass, N., Le Bivic, A., Rougon, G. and Girault, J. A. (2000). The glycosylphosphatidyl inositol-anchored adhesion molecule F3/contactin is required for surface transport of paranodin/contactin-associated protein (caspr). *J. Cell Biol.* **149**, 491-502.

Fernandez, P. A., Tang, D. G., Cheng, L., Prochiantz, A., Mudge, A. W. and Raff, M. C. (2000). Evidence that axon-derived neuregulin promotes oligodendrocyte survival in the developing rat optic nerve. *Neuron* **28**, 81-90.

Fitzner, D., Schneider, A., Kippert, A., Möbius, W., Willig, K. I., Hell, S. W., Bunt, G., Gaus, K. and Simons, M. (2006). Myelin basic protein-dependent plasma membrane reorganization in the formation of myelin. *EMBO J.* (in press).

Flores, A. I., Mallon, B. S., Matsui, T., Ogawa, W., Rosenzweig, A., Okamoto, T. and Macklin, W. B. (2000). Akt-mediated survival of oligodendrocytes induced by neuregulins. *J. Neurosci.* **20**, 7622-7630.

Garrido, J. J., Giraud, P., Carlier, E., Fernandes, F., Moussif, A., Fache, M. P., Debanne, D. and Dargent, B. (2003). A targeting motif involved in sodium channel clustering at the axonal initial segment. *Science* **300**, 2091-2094.

Gatto, C. L., Walker, B. J. and Lambert, S. (2003). Local ERM activation and dynamic growth cones at Schwann cell tips implicated in efficient formation of nodes of Ranvier. *J. Cell Biol.* **162**, 489-498.

Genoud, S., Lappe-Siefke, C., Goebbels, S., Radtke, F., Aguet, M., Scherer, S. S., Suter, U., Nave, K. A. and Mantei, N. (2002). Notch1 control of oligodendrocyte differentiation in the spinal cord. *J. Cell Biol.* **158**, 709-718.

Gollan, L., Sabanay, H., Poliak, S., Berglund, E. O., Ranscht, B. and Peles, E. (2002). Retention of a cell adhesion complex at the paranodal junction requires the cytoplasmic region of Caspr. *J. Cell Biol.* **157**, 1247-1256.

Gollan, L., Salomon, D., Salzer, J. L. and Peles, E. (2003). Caspr regulates the processing of contactin and inhibits its binding to neurofascin. *J. Cell Biol.* **163**, 1213-1218.

Goto, K., Kurihara, T., Takahashi, Y. and Kondo, H. (1990). Expression of genes for the myelin-specific proteins in oligodendrocytes in vivo demands the presence of axons. *Neurosci. Lett.* **117**, 269-274.

Griffiths, I., Klugmann, M., Anderson, T., Yool, D., Thomson, C., Schwab, M. H., Schneider, A., Zimmermann, F., McCulloch, M., Nadon, N. et al. (1998). Axonal swellings and degeneration in mice lacking the major proteolipid of myelin. *Science* **280**, 1610-1613.

Honke, K., Hirahara, Y., Dupree, J., Suzuki, K., Popko, B., Fukushima, K., Fukushima, J., Nagasawa, T., Yoshida, N., Wada, Y. et al. (2002). Paranodal junction formation and spermatogenesis require sulfoglycolipids. *Proc. Natl. Acad. Sci. USA* **99**, 4227-4232.

Hsieh, S. T., Kidd, G. J., Crawford, T. O., Xu, Z., Lin, W. M., Trapp, B. D., Cleveland, D. W. and Griffin, J. W. (1994). Regional modulation of neurofilament organization by myelination in normal axons. *J. Neurosci.* **14**, 6392-6401.

Hu, Q. D., Ang, B. T., Karsak, M., Hu, W. P., Cui, X. Y., Duka, T., Takeda, Y., Chia, W., Sankar, N., Ng, Y. K. et al. (2003). F3/contactin acts as a functional ligand for Notch during oligodendrocyte maturation. *Cell* **115**, 163-175.

Huang, J. K., Phillips, G. R., Roth, A. D., Pedraza, L., Shan, W., Belkaid, W., Mi, S., Fex-Svenningsen, A., Florens, L., Yates, J. R., 3rd et al. (2005). Glial membranes at the node of Ranvier prevent neurite outgrowth. *Science* **310**, 1813-1817.

Ishibashi, T., Dakin, K. A., Stevens, B., Lee, P. R., Kozlov, S. V., Stewart, C. L. and Fields, R. D. (2006). Astrocytes promote myelination in response to electrical impulses. *Neuron* **49**, 823-832.

Jenkins, S. M. and Bennett, V. (2002). Developing nodes of Ranvier are defined by ankyrin-G clustering and are independent of paranodal axoglial adhesion. *Proc. Natl. Acad. Sci. USA* **99**, 2303-2308.

Kaplan, M. R., Meyer-Franke, A., Lambert, S., Bennett, V., Duncan, I. D., Levinson, S. R. and Barres, B. A. (1997). Induction of sodium channel clustering by oligodendrocytes. *Nature* **386**, 724-728.

Kaplan, M. R., Cho, M. H., Ullian, E. M., Isom, L. L., Levinson, S. R. and Barres, B. A. (2001). Differential control of clustering of the sodium channels Na(v)1.2 and Na(v)1.6 at developing CNS nodes of Ranvier. *Neuron* **30**, 105-119.

Kim, T., Fiedler, K., Madison, D. L., Krueger, W. H. and Pfeiffer, S. E. (1995). Cloning and characterization of MVP17: a developmentally regulated myelin protein in oligodendrocytes. *J. Neurosci. Res.* **42**, 413-422.

Komada, M. and Soriano, P. (2002). [Beta]IV-spectrin regulates sodium channel clustering through ankyrin-G at axon initial segments and nodes of Ranvier. *J. Cell Biol.* **156**, 337-348.

Kramer, E. M., Koch, T., Niehaus, A. and Trotter, J. (1997). Oligodendrocytes direct glycosyl phosphatidylinositol-anchored proteins to the myelin sheath in glycosphingolipid-rich complexes. *J. Biol. Chem.* **272**, 8937-8945.

Kramer, E. M., Schardt, A. and Nave, K. A. (2001). Membrane traffic in myelinating oligodendrocytes. *Microsc. Res. Tech.* **52**, 656-671.

Lacas-Gervais, S., Guo, J., Strenzke, N., Scarfone, E., Kolpe, M., Jahkel, M., De Camilli, P., Moser, T., Rasband, M. N. and Solimena, M. (2004). BetaIVSigma1 spectrin stabilizes the nodes of Ranvier and axon initial segments. *J. Cell Biol.* **166**, 983-990.

Lappe-Siefke, C., Goebbels, S., Gravel, M., Nicksch, E., Lee, J., Braun, P. E., Griffiths, I. R. and Nave, K. A. (2003). Disruption of Cnp1 uncouples oligodendroglial functions in axonal support and myelination. *Nat. Genet.* **33**, 366-374.

Lee, J., Gravel, M., Zhang, R., Thibault, P. and Braun, P. E. (2005). Process outgrowth in oligodendrocytes is mediated by CNP, a novel microtubule assembly myelin protein. *J. Cell Biol.* **170**, 661-673.

Liang, X., Draghi, N. A. and Resh, M. D. (2004). Signaling from integrins to Fyn to Rho family GTPases regulates morphologic differentiation of oligodendrocytes. *J. Neurosci.* **24**, 7140-7149.

Macklin, W. B., Weill, C. L. and Deininger, P. L. (1986). Expression of myelin proteolipid and basic protein mRNAs in cultured cells. *J. Neurosci. Res.* **16**, 203-217.

Marta, C. B., Taylor, C. M., Coetzee, T., Kim, T., Winkler, S., Bansal, R. and Pfeiffer, S. E. (2003). Antibody cross-linking of myelin oligodendrocyte glycoprotein leads to its rapid repartitioning into detergent-insoluble fractions, and altered protein phosphorylation and cell morphology. *J. Neurosci.* **23**, 5461-5471.

Melendez-Vasquez, C. V., Rios, J. C., Zanazzi, G., Lambert, S., Bretscher, A. and Salzer, J. L. (2001). Nodes of Ranvier form in association with ezrin-radixin-moesin (ERM)-positive Schwann cell processes. *Proc. Natl. Acad. Sci. USA* **98**, 1235-1240.

Mi, S., Miller, R. H., Lee, X., Scott, M. L., Shulag-Morskaya, S., Shao, Z., Chang, J., Thill, G., Levesque, M., Zhang, M. et al. (2005). LINGO-1 negatively regulates myelination by oligodendrocytes. *Nat. Neurosci.* **8**, 745-751.

Michailov, G. V., Sereda, M. W., Brinkmann, B. G., Fischer, T. M., Haug, B., Birchmeier, C., Role, L., Lai, C., Schwab, M. H. and Nave, K. A. (2004). Axonal neuregulin-1 regulates myelin sheath thickness. *Science* **304**, 700-703.

Miller, R. H. (2002). Regulation of oligodendrocyte development in the vertebrate CNS. *Prog. Neurobiol.* **67**, 451-467.

Mirsky, R., Winter, J., Abney, E. R., Pruss, R. M., Gavrilovic, J. and Raff, M. C. (1980). Myelin-specific proteins and glycolipids in rat Schwann cells and oligodendrocytes in culture. *J. Cell Biol.* **84**, 483-494.

Mostov, K., Su, T. and ter Beest, M. (2003). Polarized epithelial membrane traffic: conservation and plasticity. *Nat. Cell Biol.* **5**, 287-293.

Noble, M., Murray, K., Stroobant, P., Waterfield, M. D. and Riddle, P. (1988). Platelet-derived growth factor promotes division and motility and inhibits premature differentiation of the oligodendrocyte/type-2 astrocyte progenitor cell. *Nature* **333**, 560-562.

Ogawa, Y., Schafer, D. P., Horresh, I., Bar, V., Hales, K., Yang, Y., Susuki, K., Peles, E., Stankewich, M. C. and Rasband, M. N. (2006). Spectrins and ankyrinB constitute a specialized paranodal cytoskeleton. *J. Neurosci.* **26**, 5230-5239.

Park, S. K., Miller, R., Krane, I. and Vartanian, T. (2001). The erbB2 gene is required for the development of terminally differentiated spinal cord oligodendrocytes. *J. Cell Biol.* **154**, 1245-1258.

Pedraza, L., Huang, J. K. and Colman, D. R. (2001). Organizing principles of the axoglial apparatus. *Neuron* **30**, 335-344.

Pfeiffer, S. E., Warrington, A. E. and Bansal, R. (1993). The oligodendrocyte and its many cellular processes. *Trends Cell Biol.* **3**, 191-197.

Poliak, S. and Peles, E. (2003). The local differentiation of myelinated axons at nodes of Ranvier. *Nat. Rev. Neurosci.* **4**, 968-980.

Poliak, S., Gollan, L., Martinez, R., Custer, A., Einheber, S., Salzer, J. L., Trimmer, J. S., Shrager, P. and Peles, E. (1999). Caspr2, a new member of the neurexin superfamily, is localized at the juxtaparanodes of myelinated axons and associates with K+ channels. *Neuron* **24**, 1037-1047.

Poliak, S., Salomon, D., Elhanany, H., Sabanay, H., Kiernan, B., Pevny, L., Stewart, C. L., Xu, X., Chiu, S. Y., Shrager, P. et al. (2003). Juxtaparanodal clustering of Shaker-like K+ channels in myelinated axons depends on Caspr2 and TAG-1. *J. Cell Biol.* **162**, 1149-1160.

Polo, S. and Di Fiore, P. P. (2006). Endocytosis conducts the cell signaling orchestra. *Cell* **124**, 897-900.

Puertollano, R., Martin-Belmonte, F., Millan, J., de Marco, M. C., Albar, J. P., Kremer, L. and Alonso, M. A. (1999). The MAL proteolipid is necessary for normal apical transport and accurate sorting of the influenza virus hemagglutinin in Madin-Darby canine kidney cells. *J. Cell Biol.* **145**, 141-151.

Raff, M. C., Lillien, L. E., Richardson, W. D., Burne, J. F. and Noble, M. D. (1988). Platelet-derived growth factor from astrocytes drives the clock that times oligodendrocyte development in culture. *Nature* **333**, 562-565.

Rasband, M. N., Park, E. W., Zhen, D., Arbuckle, M. I., Poliak, S., Peles, E., Grant, S. G. and Trimmer, J. S. (2002). Clustering of neuronal potassium channels is independent of their interaction with PSD-95. *J. Cell Biol.* **159**, 663-672.

Rasband, M. N., Tayler, J., Kaga, Y., Yang, Y., Lappe-Siefke, C., Nave, K. A. and Bansal, R. (2005). CNP is required for maintenance of axon-glia interactions at nodes of Ranvier in the CNS. *Glia* **50**, 86-90.

Richardson, W. D., Pringle, N., Mosley, M. J., Westermark, B. and Dubois-Dalcq, M. (1988). A role for platelet-derived growth factor in normal gliogenesis in the central nervous system. *Cell* **53**, 309-319.

Rodriguez-Gabin, A. G., Almazan, G. and Larocca, J. N. (2004). Vesicle transport in oligodendrocytes: probable role of Rab40c protein. *J. Neurosci. Res.* **76**, 758-770.

Salzer, J. L. (2003). Polarized domains of myelinated axons. *Neuron* **40**, 297-318.

Sandvig, A., Berry, M., Barrett, L. B., Butt, A. and Logan, A. (2004). Myelin-, reactive glia-, and scar-derived CNS axon growth inhibitors: expression, receptor signaling, and correlation with axon regeneration. *Glia* **46**, 225-251.

Schaeren-Wiemers, N., Bonnet, A., Erb, M., Erne, B., Bartsch, U., Kern, F., Mantei, N., Sherman, D. and Suter, U. (2004). The raft-associated protein MAL is required for maintenance of proper axon–glia interactions in the central nervous system. *J. Cell Biol.* **166**, 731-742.

Schafer, D. P., Bansal, R., Hedstrom, K. L., Pfeiffer, S. E. and Rasband, M. N. (2004). Does paranode formation and maintenance require partitioning of neurofascin 155 into lipid rafts? *J. Neurosci.* **24**, 3176-3185.

Scherer, S. S. and Arroyo, E. J. (2002). Recent progress on the molecular organization of myelinated axons. *J. Peripher. Nerv. Syst.* **7**, 1-12.

Scherer, S. S., Vogelbacker, H. H. and Kamholz, J. (1992). Axons modulate the expression of proteolipid protein in the CNS. *J. Neurosci. Res.* **32**, 138-148.

Schneider, A., Lander, H., Schulz, G., Wolburg, H., Nave, K. A., Schulz, J. B. and Simons, M. (2005). Palmitoylation is a sorting determinant for transport to the myelin membrane. *J. Cell Sci.* **118**, 2415-2423.

Schwab, M. E. (2004). Nogo and axon regeneration. *Curr. Opin. Neurobiol.* **14**, 118-124.

Sherman, D. L., Tait, S., Melrose, S., Johnson, R., Zonta, B., Court, F. A., Macklin, W. B., Meek, S., Smith, A. J., Cottrell, D. F. et al. (2005). Neurofascins are required to establish axonal domains for saltatory conduction. *Neuron* **48**, 737-742.

Shiota, C., Miura, M. and Mikoshiba, K. (1989). Developmental profile and differential

localization of mRNAs of myelin proteins (MBP and PLP) in oligodendrocytes in the brain and in culture. *Brain Res. Dev. Brain Res.* **45**, 83-94.

Simons, M., Kramer, E. M., Thiele, C., Stoffel, W. and Trotter, J. (2000). Assembly of myelin by association of proteolipid protein with cholesterol- and galactosylceramide-rich membrane domains. *J. Cell Biol.* **151**, 143-154.

Simons, M., Kramer, E. M., Macchi, P., Rathke-Hartlieb, S., Trotter, J., Nave, K. A. and Schulz, J. B. (2002). Overexpression of the myelin proteolipid protein leads to accumulation of cholesterol and proteolipid protein in endosomes/lysosomes: implications for Pelizaeus-Merzbacher disease. *J. Cell Biol.* **157**, 327-336.

Stevens, B. and Fields, R. D. (2000). Response of Schwann cells to action potentials in development. *Science* **287**, 2267-2271.

Stevens, B., Porta, S., Haak, L. L., Gallo, V. and Fields, R. D. (2002). Adenosine: a neuron-glial transmitter promoting myelination in the CNS in response to action potentials. *Neuron* **36**, 855-868.

Sussman, C. R., Vartanian, T. and Miller, R. H. (2005). The ErbB4 neuregulin receptor mediates suppression of oligodendrocyte maturation. *J. Neurosci.* **25**, 5757-5762.

Tait, S., Gunn-Moore, F., Collinson, J. M., Huang, J., Lubetzki, C., Pedraza, L., Sherman, D. L., Colman, D. R. and Brophy, P. J. (2000). An oligodendrocyte cell adhesion molecule at the site of assembly of the paranodal axo-glial junction. *J. Cell Biol.* **150**, 657-666.

Taveggia, C., Zanazzi, G., Petrylak, A., Yano, H., Rosenbluth, J., Einheber, S., Xu, X., Esper, R. M., Loeb, J. A., Shrager, P. et al. (2005). Neuregulin-1 type III determines the ensheathment fate of axons. *Neuron* **47**, 681-694.

Taylor, C. M., Coetzee, T. and Pfeiffer, S. E. (2002). Detergent-insoluble glycosphingolipid/cholesterol microdomains of the myelin membrane. *J. Neurochem.* **81**, 993-1004.

Temple, S. and Raff, M. C. (1986). Clonal analysis of oligodendrocyte development in culture: evidence for a developmental clock that counts cell divisions. *Cell* **44**, 773-779.

Trajkovic, K., Dhaunchak, A. S., Goncalves, J. T., Wenzel, D., Schneider, A., Bunt, G., Nave, K. A. and Simons, M. (2006). Neuron to glia signaling triggers myelin membrane exocytosis from endosomal storage sites. *J. Cell Biol.* **172**, 937-948.

Traka, M., Goutebroze, L., Denisenko, N., Bessa, M., Nifli, A., Havaki, S., Iwakura, Y., Fukamauchi, F., Watanabe, K., Soliven, B. et al. (2003). Association of TAG-1 with Caspr2 is essential for the molecular organization of juxtaparanodal regions of myelinated fibers. *J. Cell Biol.* **162**, 1161-1172.

Trapp, B. D., Nishiyama, A., Cheng, D. and Macklin, W. (1997). Differentiation and death of premyelinating oligodendrocytes in developing rodent brain. *J. Cell Biol.* **137**, 459-468.

Wang, S., Sdrulla, A. D., diSibio, G., Bush, G., Nofziger, D., Hicks, C., Weinmaster, G. and Barres, B. A. (1998). Notch receptor activation inhibits oligodendrocyte differentiation. *Neuron* **21**, 63-75.

Wight, P. A., Duchala, C. S., Readhead, C. and Macklin, W. B. (1993). A myelin proteolipid protein-LacZ fusion protein is developmentally regulated and targeted to the myelin membrane in transgenic mice. *J. Cell Biol.* **123**, 443-454.

Wolswijk, G. and Balesar, R. (2003). Changes in the expression and localization of the paranodal protein Caspr on axons in chronic multiple sclerosis. *Brain* **126**, 1638-1649.

Woods, I. G., Lyons, D. A., Voas, M. G., Pogoda, H. M. and Talbot, W. S. (2006). nsf is essential for organization of myelinated axons in zebrafish. *Curr. Biol.* **16**, 636-648.

Yin, X., Baek, R. C., Kirschner, D. A., Peterson, A., Fujii, Y., Nave, K. A., Macklin, W. B. and Trapp, B. D. (2006). Evolution of a neuroprotective function of central nervous system myelin. *J. Cell Biol.* **172**, 469-478.

Zhou, D., Lambert, S., Malen, P. L., Carpenter, S., Boland, L. M. and Bennett, V. (1998). AnkyrinG is required for clustering of voltage-gated Na channels at axon initial segments and for normal action potential firing. *J. Cell Biol.* **143**, 1295-1304.