GLIA 56:1532–1540 (2008)

Molecular Domains of Myelinated Axons in the Peripheral Nervous System

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KEY WORDS
myelin; node of ranvier; paranodes; juxtaparanodes

ABSTRACT
Myelinated axons are organized into a series of specialized domains with distinct molecular compositions and functions. These domains, which include the node of Ranvier, the flanking paranodal junctions, the juxtaparanodes, and the internode, form as the result of interactions with myelinating Schwann cells. This domain organization is essential for action potential propagation by saltatory conduction and for the overall function and integrity of the axon.

INTRODUCTION

Myelinated axons in both the central and peripheral nervous system (PNS) are organized in a series of distinct subdomains, centered around the node of Ranvier. This organization is critical to the ability of these myelinated fibers to conduct impulses via saltatory conduction (Hille, 2001). Specifically, action potentials generated at the axon initial segment (AIS) regenerate at nodes of Ranvier, resulting in a much more rapid and energy efficient mechanism of impulse propagation than observed in nonmyelinated fibers (Salzer, 1997). Moreover, the extent of myelination, and the length of myelin internodes (Court et al., 2004), modulate conduction velocity and thus provide a mechanism to synchronize the presynaptic input to afferent targets (Waxman, 1997).

Along with these critical advantages, there are important vulnerabilities associated with myelination. Axon function, and its integrity, is dependent on this domain organization. Indeed, axon pathology and disrupted domain organization lead to conduction block and axonal degeneration—an important source of morbidity in disorders of myelination (see Scherer and Wrabetz, 2008, this issue) and may contribute to age-related changes in axon conduction (Hinman et al., 2006). Elucidation of the organization and function of the domains of myelinated axons and the mechanisms that govern their assembly therefore have significant clinical implications. In this review, we discuss our current understanding of the organization and mechanisms of assembly of the domains of myelinated axons in the PNS and potential implications for disorders of myelinated fibers. Other reviews (Poliak and Peles, 2003; Salzer, 2003; Susuki and Rasband, 2008) may be consulted for a discussion of the earlier literature and a comparison of the organization of CNS and PNS-myelinated fibers.

OVERVIEW OF THE DOMAIN ORGANIZATION OF MYELINATED FIBERS

Myelinating Schwann cells exhibit a striking radial and longitudinal polarity (Poliak and Peles, 2003; Salzer, 2003; Sherman and Brophy, 2005). This radial polarity is underscored and dictated by the fact that it has two distinct plasma membrane surfaces: an inner membrane in contact with the axon and an outer membrane in contact with the basal lamina (see Chernousov et al., 2008, this issue). The inner Schwann cell (adaxonal) membrane and the underlying axolemma are further organized into a series of distinct domains: node, paranode, juxtaparanode, and internode. Indeed, the entire axon, including its cytoskeleton, organelle content, and transport machinery, are differentially organized at these sites (Salzer, 2003). We focus here on the organization of the specialized membrane domains of myelinated fibers (see Fig. 1).

At the center of the function of myelinated axons are the nodes of Ranvier. Nodes are the gaps between myelinating Schwann cells. They are ~1 μm long and represent sites where the axon is exposed to and communicates with the extracellular environment. In the PNS, nodes are contacted by interdigitating microvilli that project from the end of the Schwann cell to closely appose the nodal axolemma. The microvilli, which are enriched in ERMs (ezrin, radixin, and moesin), express a unique perinodal matrix important in node formation and function (see below). The nodes are enormously enriched in voltage-gated sodium channels (~1500/sq

Grant sponsors: NIH, The National Multiple Sclerosis Society, The Wellcome Trust, MRC, MS Society, Israel Academy of Science, Dr. Miriam and Sheldon Adelson Medical Research Foundation.

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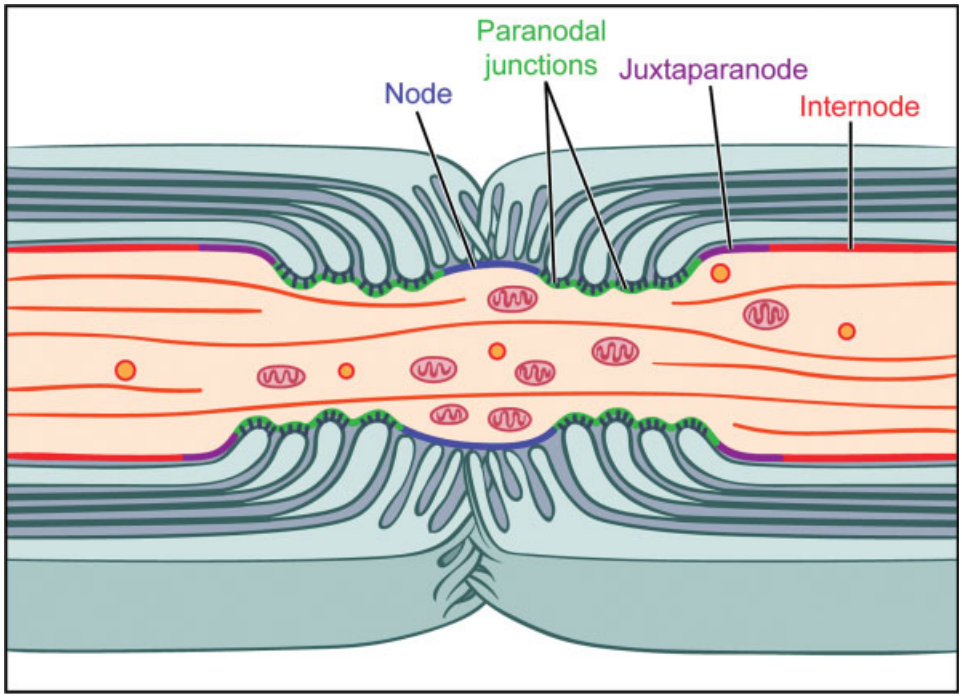
Received 11 June 2008; Accepted 3 July 2008

DOI 10.1002/glia.20750

Published online 19 September 2008 in Wiley InterScience (www.interscience.wiley.com).



	Node	Paranodes	Juxta-paranodes	Internode
Schwann Cell	ERMs Gliomedin Laminin HSPGs Collagen V	NF155	TAG1	Necl4, 2 MAG
Axonal CAMs	NF186 NrCAM	Contactin Caspr	TAG1 Caspr2	Necl1, 2
Axonal Channels	Nav1.6 KCNQ2,3		Kv1.1 Kv1.2	
Axonal Cytoskeleton	AnkG ßIV spectrin	4.1B AnkB αII/βII spectrin	4.1B αII/βII spectrin	

Fig. 1. Organization and composition of domains of myelinated PNS fibers. Longitudinal cross section through a myelinated axon in the PNS is schematically illustrated; the axon, with intracellular organelles concentrated in the nodal region, is in red and myelinating Schwann cells are in blue. The node of Ranvier, demarcated in purple, is contacted by numerous microvillar processes arising from the outer collar of the Schwann cells; the nodal gap substance and basal lamina are not shown. The paranodal junctions (green) flank either side of the node. The location of the juxtaparanodes (orange) and internode (red) are also shown. Major constituents of these different domains of the Schwann cell including nodal matrix components synthesized by the Schwann cell (top row) and axonal components including cell adhesion molecules (CAMs), cytoskeletal proteins, and ion channels are listed.

micron, a density 25-fold higher than that along the internode), providing a site for the regeneration of the action potential (Hille, 2001).

Nodes are flanked, in turn, by specialized axo-glial junctions at the paranodes. The junctions are the site of closest apposition (3–5 nm) between the myelinating Schwann cell and the axonal membranes. In longitudinal sections, these junctions have the appearance of a series of loops that closely appose and physically invaginate the axolemma; a series of transverse bands that arise from the outer axolemma leaflet are a characteristic feature of the axo-glial junctions (Peters et al., 1991).

These junctions promote adhesion between the axon and glial cell (see below) and are thought to provide a partial barrier to the diffusion of ions between the node and internode during action potential conduction (Rosenbluth, 1995). The paranodal junctions are the functional and molecular orthologues of invertebrate septate junctions (Banerjee et al., 2006). The axon is further organized into the juxtaparanodes, which lie just under the compact myelin sheath and are enriched in Shaker-type potassium channels, that is, Kv1.1 and 1.2. The precise function of these channels remains unknown although they have been thought to promote repolarization during action potential propagation.

The internode is the remaining and by far largest domain of the myelinated fibers, corresponding to the portion of the axon located under the compact myelin sheath. Along the length of the internode, the inner membrane of the Schwann cell is uniformly separated from the underlying axon by a periaxonal space of 15 nm. The internode can reach 1 mm in length or more in large fibers in the adult PNS (Abe et al., 2004). Thus, both the Schwann cell and axon maintain an enormous amount of closely apposed membranes in this domain. This separation persists following osmotic changes or in various pathologic states (Hirano, 1983). Conversely, the periaxonal space as well as the attachment of the myelin sheath to the axon is disrupted by the action of proteases (Yu and Bunge, 1975). These results indicate that the interactions between the glial and axonal membranes are actively maintained by cell surface proteins. Interestingly, the axon internodal membrane in contact with Schwann cell incisures and the inner mesaxon contains protein complexes characteristic of the paranodes and juxtaparanodes (Peles and Salzer, 2000).

COMPOSITION OF AXONAL DOMAINS

We review here the composition of the nodes, paranodes, juxtaparanodes, and internodes. A recurrent theme is that each domain contains unique sets of interacting adhesion molecules on the Schwann cell and axon membranes. These adhesion molecules are linked, in turn, to a submembranous cytoskeletal complex (Susuki and Rasband, 2008), which contributes to the stability of the complex and, in the case of the node, tethers voltage-gated ion channels.

Nodes of Ranvier

The unique molecular composition of the node was the first domain to be characterized. Nodes are highly enriched in various voltage-gated ion channels, notably sodium channels; the predominant α subunit at the node is $Na_v1.6$ (Caldwell et al., 2000; Tzoumaka et al., 2000). $Na_v1.6$ exhibits user-dependent potentiation, which may be particularly useful during the high-frequency firing characteristic of nodes of Ranvier (Zhou and Goldin, 2004). Sodium channels interact with additional proteins, which modulate their gating properties, notably β subunits (Qu et al., 2001; Yu et al., 2003). Although the exact stoichiometry and composition of the sodium channel/β subunit complex at the node is not yet known, both $\beta1$ and $\beta2$ are localized at this site (Chen et al., 2004). In addition, voltage-gated potassium channels are also expressed at many nodes, in particular, KCNQ2 and KCNQ3 (Devaux et al., 2004; Pan et al., 2006), which may be important in the control of repetitive discharges (Cooper and Jan, 2003). Kv3.1b is also present at a subset of nodes (Devaux et al., 2003).

Two neural cell adhesion molecules, NrCAM and the 186 kDa isoform of neurofascin (NF186), which are members of the L1 CAM family, are also concentrated at the node (Davis et al., 1996). These CAMs provide bridging interactions by binding to Schwann cell components and the axon cytoskeleton. In particular, both NrCAM and NF186 bind to gliomedin, a glial matrix protein synthesized by Schwann cells that promotes PNS node formation (Eshed et al., 2005). Gliomedin can be cleaved from a transmembrane precursor and interacts with heparin sulfate proteoglycans (HSPGs) (Eshed et al., 2007). Several HSPGs are present at PNS nodes including syndecans and versican (Melendez-Vasquez et al., 2005; Oohashi et al., 2002). Also enriched in the nodal matrix are specific laminin isoforms (Occhi et al., 2005) and collagen V (Melendez-Vasquez et al., 2005).

NrCAM and NF186 bind, in turn, to the axonal cytoskeletal protein ankyrin G, one of the three vertebrate ankyrins. These multivalent cytoskeletal proteins provide a scaffold that targets and stabilizes a diverse set of proteins at specialized membrane domains in many cell types (Bennett and Baines, 2001). The major ankyrin G isoforms at the node of Ranvier and initial segments are 270 and 480 kDa (Kordeli et al., 1995). The 480 kDa isoform contains a long coiled region and may extend as much as 0.6 μm across (Mohler and Bennett, 2005), nearly the length of the node.

Ankyrin G has an essential role in organizing and stabilizing the nodal, axonal complex (Dzhashiashvili et al., 2007) akin to its role at the AIS (Zhou et al., 1998). The voltage-gated sodium channels (Garrido et al., 2003; Lemaillet et al., 2003) and potassium channels at the node, that is, KCNQs (Pan et al., 2006) have a conserved sequence that mediates their binding to ankyrin G. Some investigators (Malhotra et al., 2002), but not others (Bouzidi et al., 2002; Lemaillet et al., 2003), have also reported that sodium channel β subunits bind to ankyrin G. NF186 and NrCAM have a distinct ankyrin-binding sequence, which is conserved among the L1 CAMs (Zhang et al., 1998). The sites on ankyrin G where these CAMs and ion channels bind, and the stoichiometry of the complex, are not yet known. Ankyrin G also binds to βIV spectrin, a cytoskeletal protein highly enriched at nodes and initial segments (Berghs et al., 2000). βIV spectrin contributes to the overall organization of the nodal complex and physically stabilizes the nodal axolemma. Mice deficient in βIV spectrin exhibit enlarged axon diameters and aberrant protrusions of the axon membrane at the node (Yang et al., 2004).

Other proteins have recently been identified as enriched at nodes including IKK (I κ kinase) (Politi et al., 2008), the sodium calcium sensor (Averill et al., 2004), an isoform of schwannomin-interacting protein-1 (IQCJ-SCHIP-1) (Martin et al., 2008), and the FGF homologous factors FHF2 (Wittmack et al., 2004). The FHF family has recently been implicated in modulating the activity of sodium channels (Goldfarb et al., 2007). The roles of IKK, SCHIP-1, and the calcium sensor at this site are not yet known.

The Paranodal Junctions

The paranodal, axo-glial junctions are composed of a complex of contactin and the contactin-associated protein (Caspr, also known as paranodin and NCP1) on the axon and the 155 kDa isoform of neurofascin (NF155) on the glial, paranodal loops (Charles et al., 2002; Collinson et al., 1998; Einheber et al., 1997; Menegoz et al., 1997; Peles et al., 1997; Rios et al., 2000; Tait et al., 2000). Caspr and contactin form a tight cis complex required for the expression of Caspr at the cell surface and for the localization of contactin at the paranode (Bhat et al., 2001; Bonnon et al., 2007; Boyle et al., 2001; Faivre-Sarrailh et al., 2000; Gollan et al., 2003; Peles et al., 1997; Rios et al., 2000). This complex has been proposed to bind to NF155 directly (Charles et al., 2002) although the precise nature of this interaction remains unclear and may involve additional proteins (Gollan et al., 2003).

Knockout mice of each of these proteins have been generated and exhibit major defects of the paranodes confirming that they are integral junctional components (Bhat et al., 2001; Boyle et al., 2001; Sherman et al., 2005). A characteristic feature of these mutants is the absence of the transverse bands suggesting that Caspr and contactin are components of the transverse bands. In addition, the Schwann cell paranodal loops are less tightly apposed to the axon in these mutants, although many loops remained attached suggesting other adhesion complexes may substitute. Of note, abnormalities of the paranodes were more severe in the CNS with frequent paranodal loop eversion. The relative preservation of the overall paranode organization in the PNS suggests that interactions mediated by the nodal microvilli and with the basal lamina may contribute to paranodal stability.

The Caspr-contactin complex binds, in turn, to the axonal cytoskeletal protein 4.1B via a FERM (4.1, ezrin, radixin, and moesin)-binding motif in the cytoplasmic segment of Caspr (Denisenko-Nehrbass et al., 2003); this interaction is required for stable membrane expression of Caspr at the paranodes (Gollan et al., 2002). The axonal cytoskeleton at the paranodes also contains ankyrin B and αII and βII spectrins (Ogawa et al., 2006; Voas et al., 2007), further distinguishing it from the nodes. In Zebrafish, αII spectrin is also transiently expressed at and promotes proper node formation (Voas et al., 2007).

The Juxtaparanodes

The juxtaparanodes are enriched in the adhesion molecules Caspr2 and the GPI-anchored adhesion molecule TAG-1 on the axon and TAG-1 on the glial paranodal loops (Poliak et al., 2003; Traka et al., 2003). Adhesion is thought to be mediated by homophilic trans interactions of TAG-1. Unlike Caspr and contactin, TAG-1 and Caspr2 do not comprise an obligate cis complex. Caspr 2 binds to 4.1B on the axon via its FERM domain (like Caspr); it also has a PDZ-binding sequence at its C-terminal domain (Poliak et al., 1999). This PDZ-binding sequence links Caspr2 to a multi-PDZ domain scaffolding protein, which, in turn, anchors Kv1.1 and 1.2 channels at the juxtaparanode. Two candidate scaffolding proteins have been localized to the juxtaparanodes, PSD-95 (Rasband et al., 2002) and PSD-93/chapsyn 110 (Horresh and Peles, unpublished). However, neither PSD-93 nor PSD-95 is required for proper Kv1 channel localization at the juxtaparanodes (Rasband et al., 2002; Horresh and Peles, unpublished).

The Internode

A distinct set of adhesion molecules mediate axon-Schwann cell interactions along the internode. These include the nectin-like (Necl) cell adhesion molecules, a family of immunoglobulin (Ig)-like CAMs also called the cell adhesion molecules (Cadm), the TSLC1-like proteins (Fukuhara et al., 2001) and the synaptic cell adhesion molecules (SynCAMs) (Biederer et al., 2002). Necl-1 and Necl-2 are expressed along the axon internode and are directly apposed by Necl-4, and potentially Necl-2, on the inner turn, that is, the periaxonal Schwann cell membrane (Maurel et al., 2007; Spiegel et al., 2007). As axonal Necl-1 and Schwann cell Necl-4 mediate robust heterophilic binding, they are likely candidates to promote adhesion and to maintain the periaxonal space along the internode. All three Necl proteins are also expressed in the Schmidt-Lanterman incisures where they may promote interactions between the noncompacted Schwann cell membranes and other components enriched in the incisures. The Necl proteins contain a FERM-binding domain and a C-terminal-binding sequence for Class II PDZ domain; their cognate-binding partners have not yet been reported. Candidates include Par-3, a multi-PDZ domain protein expressed along the Schwann cell internode (Chan et al., 2006) and clefts (Poliak et al., 2002), and MUPP1, Pals1, MAGI-2, ZO-1, and ZO-2, all of which have been localized to the incisures (Poliak et al., 2002).

In addition to the Necls, myelin-associated glycoprotein (MAG), an Ig-like adhesion molecule is also highly expressed by myelinating glia along the internode (Trapp, 1990). MAG interacts with a number of axonal components (Hannila et al., 2007). Like the Necls, and other adhesion molecules (Fannon et al., 1995; Poliak et al., 2002), MAG accumulates in the Schmidt-Lanterman incisures with myelin sheath maturation (Trapp, 1990).

As mice deficient in MAG myelinate appropriately and exhibit only modest alterations in the periaxonal space (Li et al., 1994; Montag et al., 1994), the precise role of MAG in mediating these interactions remains uncertain. MAG has been suggested to mediate interactions that regulate axon diameter (Yin et al., 1998).

MECHANISM OF DOMAIN ASSEMBLY

The mechanisms that drive domain assembly, in particular of nodes and paranodes, have begun to emerge recently. Important insights into how domains assemble have been provided by the analysis of mice deficient in key domain components. In general, loss of one key domain component results in the loss of the entire domain complex indicating a mutual interdependence on domain assembly and maintenance. In addition, although domains assemble in progression, beginning with the node and progressing to the paranodes and the juxtaparanodes (Salzer, 2003), individual domains can be independently ablated based on analysis of the knockouts. Finally, as will be discussed below, complementary mechanisms cooperate to promote domain assembly.

Nodes of Ranvier

The node itself assembles in sequence. The earliest event of PNS node formation is the accumulation of the cell adhesion molecules NrCAM and NF186, followed by ankyrin G and sodium channels (Lambert et al., 1997). The accumulation of these CAMS is driven by contact-dependent signals provided by Schwann cell processes that overlay these early nodal intermediates (Ching et al., 1999; Melendez-Vasquez et al., 2001; Tao-Cheng and Rosenbluth, 1982). A key insight was the identification of gliomedin as the Schwann cell signal that promotes clustering of ankyrin-binding CAMs (Eshed et al., 2005). Gliomedin is present at the earliest nodal intermediates and binds to and clusters the axonal CAMs, that is, NF186 and NrCAM, and with them ankyrin G and sodium channels (Eshed et al., 2005). Recent studies indicate that gliomedin is released as a soluble protein by proteolytic cleavage and that it forms multimers by binding to HSPGs at the nodal gap, thereby clustering axonodal CAMs and sodium channels (Eshed et al., 2007).

The critical role of both nodal CAMs, and of NF186, in particular, in promoting node assembly has been confirmed by the analysis of the corresponding knockout mice. Thus, pan-NF knockout mice exhibit severe defects in node formation, with deficiency of all known components (Sherman et al., 2005); reintroduction of NF186 by transgenesis restores the nodal complex (Zonta et al., 2008). In contrast, nodes form in the NrCAM knockout mice, but do so with a significant delay (Custer et al., 2003). The key role of NF186 in driving node assembly was shown to reflect its critical role in recruiting ankyrin G to the node (Dzhashiashvili et al., 2007); ankyrin G coordinates and is required for the assembly of the entire nodal complex (Dzhashiashvili et al., 2007). Thus, PNS nodes assemble from the outside in, specified by Gliomedin on Schwann cell processes, which direct the NF186-dependent recruitment of ankyrin G; this contrasts with AISs that are specified by the intrinsic accumulation of ankyrin G via an inside-out mechanism (Dzhashiashvili et al., 2007). NF186 has also been reported to interact in cis with sodium channel β subunits (Ratcliffe et al., 2001); the physiological relevance of this interaction is not yet established but it may serve to stabilize the nodal complex.

In addition to recruiting proteins to the node, other mechanisms may further contribute to the distinctive localization of proteins at this site including (i) clearance of mistargeted proteins from extranodal sites, (ii) selective protein targeting, and (iii) formation of a lateral diffusion barrier by the paranodal junctions. Studies of $Na_V1.2$ targeting to the AIS are consistent with a similar combination of mechanisms. Thus, expression of $Na_V1.2$ in axons results, at least in part, from its specific endocytotic removal from the somatodendritic compartment; its subsequent recruitment to the AIS is due to interactions with ankyrin G at this site (Fache et al., 2004). These findings suggest that endocytosis might similarly reinforce the restricted expression of channels, and other components, at the node. Myelination does promote NF186 removal from the internodal region but, unexpectedly, by a mechanism(s) requiring its extracellular, not its intracellular sequences (Dzhashiashvili et al., 2007). Whether this results from endocytosis, proteolytic cleavage, or both is not yet known. In addition, selective transport and fusion of nodal proteins might also contribute to nodal localization. In potential support, zebrafish with mutations in the protein NSF, which enhances vesicle fusion, exhibit impaired node formation (Woods et al., 2006). These results suggest that node formation relies on vesicle fusion, although it is not known whether this occurs locally or remotely. Finally, there is good evidence that after the nodal complex forms, the paranodal junctions maintain the density of channels at the node by limiting lateral diffusion of nodal components (Rios et al., 2003; Rosenbluth et al., 2003). However, in neurofascin knockout mice, reconstitution of the paranodal adhesion complex using transgenic NF155 cannot promote the assembly of the PNS nodal complex in the absence of NF186 (Sherman et al., 2005). This is in marked contrast to the CNS where paranodal junctions, reformed by transgenesis with NF155 in neurofascin-null mice, seem to be just as effective as NF186 in rescuing the nodal complex (Zonta et al., 2008).

Assembly and Function of the Paranodes

Accumulation of the Caspr/contactin complex at the paranodes depends on the extracellular interactions of this complex with myelinating Schwann cells (Rios et al., 2000), likely involving NF155 on the glial loops (Charles et al., 2002; Gollan et al., 2003). Stable reten-

tion of the axonal complex is then promoted by interaction with the cytoskeleton (Gollan et al., 2002). Interestingly, defects associated with lipid rafts, and raft-associated proteins, all lead to significant paranodal defects. Thus, loss of glycosphingolipids in both the CGT (ceramide galactosyl transferase) and CST (cerebroside sulfotransferase) mutants is associated with severe and relatively specific defects in the paranode organization (Dupree et al., 1999; Honke et al., 2002). Similar but less severe defects are observed in mice with ganglioside deficiency (Susuki et al., 2007a). These findings, and the presence of paranodal components in lipid rafts (Schafer et al., 2004), have suggested that transport of glial paranodal components, including NF155, and thus assembly of the paranodes may depend on trafficking of components in lipid rafts. Interestingly, paranodal defects are also observed in mice deficient in two tetraspanin proteins: CD9 with defects in PNS paranodes (Ishibashi et al., 2004) and MAL (myelin and lymphocyte protein) a tetraspan lipid raft-associated proteolipid, although defects are only present in CNS paranodes (Schaeren-Wiemers et al., 2004).

Mice deficient in key components of the paranodes (i.e., contactin, Caspr, and NF) have very similar junctional defects with loss of transverse bands and paranodal loops that do not tightly attach to the axon (Bhat et al., 2001; Boyle et al., 2001; Sherman et al., 2005); defective attachment may become more pronounced over time. Defects of the paranodal junctions, in turn, result in striking effects due to the loss of the diffusion barrier provided by the paranodes. This is manifested by the displacement of juxtaparanodal components into the paranodal region, intrusion of microvillar processes between the loops and the axon, and gradual widening of the nodal complex. Additional findings include slowing of nerve conduction, and accumulation of intracellular organelles in the paranodal/nodal compartment, notably of mitochondria (Einheber et al., 2006); the latter findings suggest that normal axonal transport in myelinated axons depends on the integrity of the paranodal junctions (Sousa and Bhat, 2007). In the CNS, these transport changes may be responsible for neuronal degeneration observed in junctional mutants (Garcia-Fresco et al., 2006). In all cases, nodes form fairly normally in the PNS suggesting that the paranodes are not required for node assembly. A potential difficulty in interpreting the latter finding, however, is that even in the absence of the transverse bands, attached paranodal loops appear to retain some function as a diffusion barrier (Rios et al., 2003; Rosenbluth et al., 2003).

Pathologic Implications

Myelinated fiber pathology results from insults to either the Schwann cell or the axon. In the former instance, disorders that result in demyelination lead to acute conduction block, loss of temporal coherence (Waxman et al., 1976), and frequently, loss of axon integrity over time (Martini, 2001; Scherer and Wrabetz, 2008, this issue). These pathological changes reflect, in part, the functional and structural dependence that axons acquire with myelination due to their reorganization into discrete domains. Thus, conduction block following acute PNS demyelination reflects disruption of passive cable properties coupled with the persistence of sodium channels at sites of former nodes despite the loss of the myelin sheath (Rasband et al., 1998; Vabnick and Shrager, 1998). During this time, there are inadequate numbers of intervening channels in the formerly myelinated internode. Conduction is restored when remyelinating Schwann cells initiate the clustering of sodium channels. The improvement in cable properties afforded by the Schwann cell layer, combined with the shorter distance between clusters of channels, is sufficient to restore conduction; however, the velocity remains low until remyelination is more complete. In addition, Kv1 channels are transiently expressed at the node prior to full remyelination, potentially impairing nerve conduction (Rasband et al., 1998). Misexpression of ion channels in the paranodes and nodes may also contribute to the morbidity of myelinated nerves in peripheral neuropathies (Devaux and Scherer, 2005).

Much of the morbidity resulting from myelin disorders is secondary to the resultant loss of axons (Martini, 2001; Scherer and Wrabetz, 2008, this issue). Indeed, loss of distal axons due to Schwann cell defects is a common feature of the hereditary neuropathies (Sahenk, 1999). The pathogenesis of axon loss in demyelinating disorders remains to be elucidated although effects on axonal transport in the paranodal region (discussed earlier), alterations of the axonal cytoskeleton, and loss of glial trophic support are likely to contribute (Nave and Trapp, 2008). An important focus for future studies will be to identify the signals that regulate axonal transport and sustain axonal integrity, including whether such signals are localized to specific domains.

Finally, components of domains described in this review have begun to emerge as targets in autoimmune neuropathies. Autoantibodies to GD1a, which bind preferentially to the nodal region, are associated with acute motor axonal neuropathy, a form of Guillain-Barre (Gong et al., 2002). The nerve pathology depends, at least in part, on the activation of the complement cascade (Susuki et al., 2007b). Autoantibodies to another nodal component, βIV spectrin, are associated with paraneoplastic motor neuron disease (Ferracci et al., 1999). Whether the pathology in this latter case reflects the effects of autoantibodies on nodes or initial segments is not yet known. Antibodies to Kv1.1 and 1.2 result in a potassium channelopathy associated with generalized peripheral nerve hyperexcitability (Arimura et al., 2002; Hart et al., 2002).

CONCLUSIONS

Substantial progress has been made in identifying key molecules that mediate the domain-specific interactions between the apposed axon and Schwann cell membranes

in myelinated nerves. Future studies are certain to expand the roster of proteins that are localized to and contribute to the organization of these domains; likely candidates include cytoskeletal scaffolds and potentially, signaling pathway components that regulate domain assembly and axo-glial interactions. Elucidation of the domain organization of myelinated nerves may thus yield significant new insights into the axo-glial signals that regulate myelination, promote axon function, and maintain axon integrity in myelinated fibers.

ACKNOWLEDGMENT

Work in the lab of J.L.S. is supported by the NIH and the National Multiple Sclerosis Society; work in the lab of P.J.B. is supported by the Wellcome Trust, MRC and the MS Society; and work in the lab of E.P. is supported by the NIH, National Multiple Sclerosis Society, Israel Academy of Sciences, and the Dr. Miriam and Sheldon Adelson Medical Research Foundation. The authors thank Peter Shrager for comments on the manuscript.

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