

Critical Review

Axons and Myelinating Glia: An Intimate Contact

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Summary

The coordination of the vertebrate nervous system requires high velocity signal transmission between different brain areas. High speed nerve conduction is achieved in the myelinated fibers of both the central and the peripheral nervous system where the myelin sheath acts as an insulator of the axon. The interactions between the glial cell and the adjacent axon, namely axo-glial interactions, segregate the fiber in distinct molecular and functional domains that ensure the rapid propagation of action potentials. These domains are the node of Ranvier, the paranode, the juxtaparanode and the internode and are characterized by multiprotein complexes between voltage-gated ion channels, cell adhesion molecules, members of the Neurexin family and cytoskeletal proteins. In the present review, we outline recent evidence on the key players of axo-glial interactions, depicting their importance in myelinated fiber physiology and disease. © 2011 IUBMB

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INTRODUCTION

Vertebrate evolution endowed the nervous system with the myelin sheath, an extended membrane of specialized glial cells. This evolutionary event enabled myelinated axons to transmit faster and with higher efficiency. A number of severe neurological pathologies involve de- or dysmyelination phenomena thus underscoring the importance of myelin and myelinating glia in clinical disorders.

The main function of the myelin sheath is nerve insulation and subsequent increase of the speed at which electrical signals travel. Myelination raises the electrical resistance of the mem-

brane and decreases its capacitance. This is achieved by the tight wrapping of myelin membrane around the axon as well as by periodic clustering of the voltage-gated Na⁺ channels in the myelin-free regions of the fibers, called nodes of Ranvier. Na⁺ channels are the main underlying molecular substrates of the saltatory conduction that assure the rapid propagation of action potentials along nerve fibers.

Around the nodes, glial and axonal membranes come into intimate contact, resulting in the morphological and functional subdivision of axonal domains. Each distinct domain hosts a number of cell adhesion molecules that mediate axo-glial interactions. Moreover, secreted molecules act as myelination and domain organization signals. A successive series of territories is formed, namely the node, paranode, juxtaparanode and internode (Scheme 1A). Axon integrity and function depend on this organization; demyelination destroys axo-glial interactions and consequently axons degenerate. Here we present a current view of the different domains from a cellular and molecular point of view.

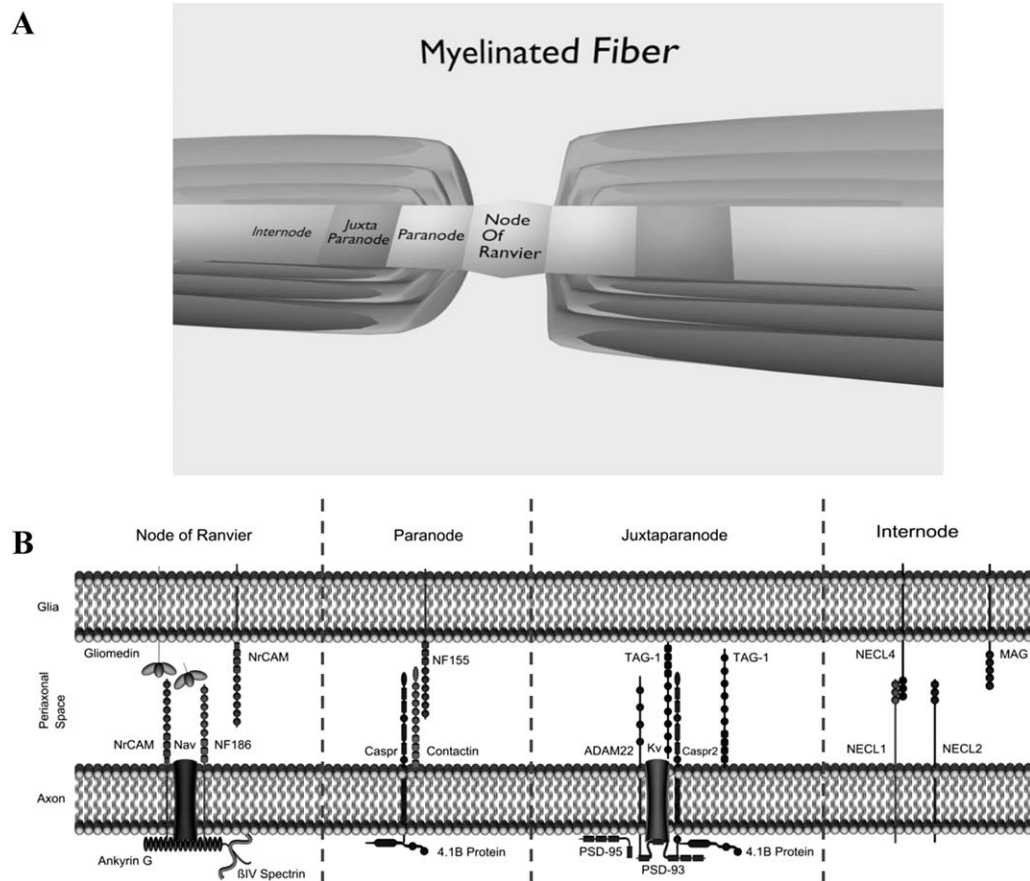
THE NODES OF RANVIER

In myelinated fibers the myelin sheath is interrupted by a ~1 μm, unmyelinated axonal segment, the node of Ranvier. The node is the area where ion flow across the membrane occurs, resulting in the propagation of action potentials along the axon, via saltatory conduction. The generation of action potentials is possible due to the accumulation of voltage gated sodium channels (Na_v), Na⁺/K⁺ ATPases, Na⁺/Ca²⁺ antiporters, as well as specific subtypes of potassium channels (K_v-KCNQ2 and KCNQ3) important for the regulation of repetitive discharges (1, 2). Sodium channels consist of an α subunit that forms the pore and two β subunits responsible for the majority of known interactions with cell adhesion molecules, cytoskeletal and extracellular matrix proteins at the node. Sodium channel subtype Na_v1.2 is expressed at the node during development, whereas it is replaced by the sodium channel isoform Nav1.6 and β1 subunits in the mature node (3, 4).

Peripheral Nervous System and Central Nervous System share some molecular similarities but recently a number of differences were revealed that underlined distinct features in the two

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Scheme 1. (A) Schematic representation of a myelinated fiber cross-section (B). The molecular organization of a PNS myelinated fiber. In each domain the key molecules of the axo-glial interactions are depicted.

systems. In the PNS, Schwann cell projections, known as microvilli, closely appose the node of Ranvier. These processes, lead to the impression that in the PNS direct contact is required for the formation of the node. In contrast, microvilli are absent from CNS myelinated fibers; in these fibers, some nodes are contacted by NG2 positive glial processes. Nodal formation in the CNS is believed to occur mainly via protein secretion by oligodendrocytes and not due to cell-to-cell contact. The nodal area in both systems is surrounded by a specific microenvironment of proteoglycans. In PNS microvilli a great number of ezrin, radixin, moesin (ERM)-proteins seem to be crucial for the Na^+ channel clustering during nodal formation (5). Proteoglycan expression may also differ between CNS and PNS.

In both CNS and PNS, two cell adhesion molecules of the L1 family of immunoglobulin superfamily (IgSF) are essential for sodium channel accumulation at the node and the establishment of axo-glial contact, NrCAM and the 186 kDa isoform of Neurofascin, NF186. NrCAM is expressed both by glial cells and neurons, while NF186 is found exclusively on the axon. A recent study in PNS from Feinberg et al. showed that glial NrCAM is of great importance in sodium channel clustering before the mature node is formed (6). Another protein named

gliomedin was identified in Schwann cell microvilli early during nodal formation. Gliomedin belongs to the family of olfactomedin-related molecules and contains collagen repeats and a single olfactomedin domain that enables it to interact with both NrCAM and NF186. The tripartite interaction specifies the nodal localization in PNS myelinated fibers (Scheme 1B) (7, 8).

Nodal formation and stabilization relies to a great extent in the connection of membrane proteins with the cytoskeleton. This linkage is mediated by their interaction with two cytoskeletal scaffolding proteins, Ankyrin G and β IV spectrin. Ankyrin G is a large protein, that is, recruited at the node by NF186 and is implicated in nodal complex formation since in vitro ablation caused severe loss of nodal protein localization in DRG neurons (9, 10). β IV spectrin is recruited at the node by AnkyrinG and further connects the nodal complex to axonal cytoskeleton (Scheme 1B) (9, 11).

PARANODES

Paranodes serve as a membrane barrier for the segregation of sodium and potassium channels, found at nodes of Ranvier and juxtaparanodes, respectively. This segregation is crucial for

the proper function of myelinated fibers and action potential propagation along the axon. Morphologically, paranodes are characterized by septate-like junctions formed at the axo-glial contact sites. The molecular composition of paranodes has extensively been studied the last few years due to their fundamental role in the organization and maintenance of myelinated fibers in both CNS and PNS. Three molecules are implicated in paranodal junction formation. Two of them, Contactin (Contactin-1 or Cntn-1 or F3) and the 155 kDa isoform of neurofascin (NF155) belong to the IgSF and are detected on the axonal and glial cell membrane, respectively. The third molecule is contactin associated protein (Caspr), a member of the Neurexin family, containing a 4.1 binding motif on its intracellular domain. In the absence of any of these molecules, paranodes are disrupted with progressive loss of axo-glial interactions, defective ion channel segregation and impaired nerve conduction (12–15). A recent study showed that transgenic expression of glial NF155 in “neurofascin” null mice, where nodes and paranodes are disrupted, is sufficient to rescue the paranodal junction in both PNS and CNS. Surprisingly, paranodal NF155 in those mice was also able to reconstitute the nodal complex in the central but not the peripheral nervous system (16).

The study of the molecular interactions underlying paranodes is of great interest to neuroscientists and will shed light on the mechanism and importance of axon-glia adhesion. Caspr and Contactin are proposed to interact intracellularly, and this interaction is necessary for the membrane targeting of Caspr. When on cell surface, this complex interacts in trans with glial NF155 (17). A recent study proposed a differential mechanism between CNS and PNS fibers for the clustering of Caspr. Caspr accumulation in PNS paranodes occurs only after myelination has proceeded, while in the CNS Caspr is clustered at paranodes upon initial axo-glial contact, before the initiation of myelination (18).

The paranodal complex is linked to the actin cytoskeleton through the interaction of the intracellular domain of Caspr with the cytoskeletal adapter protein 4.1B, which is present both at paranodes and juxtaparanodes (Scheme 1B) (19). In a recent study, the analysis of 4.1B null mice revealed that paranodes are unimpaired and proposed that the loss of 4.1B molecule may be compensated by protein 4.1R of the same family (20). The last 5 years, numerous studies have focused on the identification of new paranodal components that could be important for the physiology of this area. Many components associated with the axonal cytoskeleton have been discovered, including spectrins α II and β II, Ankyrin B, β -adducin, and septin 2 in optic nerve paranodes (21, 22). The specific role of those molecules in paranodal organization remains elusive.

Apart from the molecules comprising the paranodal complex, other membrane proteins have also been detected at paranodes, while their potential role in axo-glial interactions has partially been evaluated. These molecules are protein Nogo-A, netrin-1 and its receptor deleted in colorectal cancer (DCC). Nogo-A is expressed by oligodendrocytes, detected at paranodes, interacting with Caspr and the potassium channels in brain lysates. It is

proposed that Nogo-A may play a role in potassium channel stabilization at paranodes before their final localization to the juxtaparanodes (23). Recently, a study revealed the expression of netrin-1 and its receptor DCC by oligodendrocytes and their localization at paranodes of central myelinated fibers. Ex vivo analysis from *netrin-1* or DCC knockout mice and in vivo transplantation experiments showed that the two proteins are not essential for the myelination or the development and maturation of paranodal junctions but for the maintenance of the proper organization of paranodes (24).

JUXTAPARANODES

The juxtaparanodal region is adjacent to the paranode comprising part of the internodal compact myelin. Its organization and maintenance depends on the combination of two distinct processes. First the lateral diffusion barrier created by the paranodal domain and second, the formation of the juxtaparanodal membrane complex and its linkage to the cytoskeleton (9).

The juxtaparanodal complex consists of TAG-1 (Axonin-1/Contactin-2), a GPI anchored adhesion molecule of the IgSF, present on the glial and axonal membranes as well as the Neu-rexin protein Caspr2 and the Shaker-type voltage-gated potassium channels (VGKCs) on the axon (25, 26). The absence of either TAG-1 or Caspr2 results in the disruption of this complex and the subsequent diffusion of VGKCs towards the internode (25–27). TAG-1 is vital in organizing the juxtaparanodes of myelinated fibers, and it also plays an important role in optic nerve structural organization (26, 28, 29). It is able to form homodimers whereas a series of in vitro studies and immunoprecipitation experiments in tissue lysates have proved the direct interaction of TAG-1 with Caspr2 and VGKCs via its Ig-like domains (26, 30). Moreover, a thorough in vivo study showed that the glial expression of TAG-1 alone at the juxtaparanodes was able to rescue the phenotype of *Tag-1* knockout mice and restore the complex via an in trans interaction with axonal counterparts (31).

The juxtaparanodal complex is connected to the actin cytoskeleton. The cytoplasmic region of Caspr2 contains a short sequence that enables the binding with the cytoskeletal adapter protein 4.1B that subsequently links the complex to the cytoskeleton (19, 32). 4.1B protein absence in the PNS leads to the disruption of the juxtaparanodal complex, similarly to *Caspr2* and *Tag-1* knockout animals (32). The above studies led to the hypothesis that 4.1B protein is responsible for Caspr2 clustering probably via membrane insertion and stabilization of the latter in the axolemma (32). Apart from 4.1B, two other adapter proteins were found to be localized in the majority of juxtaparanodes: postsynaptic density protein 93/chapsyn-110 and postsynaptic density protein 95 (PSD-93 and PSD-95) (33, 34). They both belong to the MAGUK family of proteins and are able to interact via their PDZ-binding domain with the carboxy-terminal part of Caspr2 and the α subunit of potassium channels (25, 32). Depletion of both MAGUKs from the juxtaparanodal area

didn't affect Caspr2 nor VGKC clustering suggesting that they are not essential for the juxtaparanodal complex formation (32). Another molecule that was recently identified in juxtaparanodes is ADAM-22, a transmembrane protein with an extracellular disintegrin and a catalytically inactive metalloproteinase domain. ADAM-22 is a VGKC complex component responsible for the assembly of PSD-93 and PSD-95 scaffolding proteins at the juxtaparanodes but not for potassium channel clustering (Scheme 1B) (20).

INTERNODES

The internode comprises the largest domain of the myelinated fiber and is the area of compact myelin between adjacent nodes of Ranvier. PNS internodal myelin sheath is characterized by small parts of looser myelin compaction, the Schmint-Lanterman incisures, which are rare in the CNS fibers.

One member of the IgSF, myelin associated glycoprotein (MAG), is expressed in the periaxonal glial membrane by oligodendrocytes and Schwann cells during myelination while is also localized in the Schmint-Lanterman incisures at later stages. Multiple MAG interactors have been identified so far but none of them seems to be crucial for the internodal axon-glial interactions (35). More recently another small group of Ig cell adhesion molecules was identified as key regulators of the internodal domain organization. Those are the members of the Nectin like family of adhesion molecules (Nec1 proteins, also known as SynCAM or Cadm), which consist of 3 Ig-like repeats, a single transmembrane domain and a short cytoplasmic tail. These proteins are linked to the cytoskeleton via a FERM-binding domain and a class II PDZ sequence found on their C-terminus, that is, capable of 4.1 protein binding (3, 36, 37). Nec11 (SynCAM3) localization was identified at different neuronal contact sites (astrocytes surrounding synapses in the cerebellum) but it is predominantly expressed by the axon along the internodes (36–38). Nec12 (SynCAM1) is also localized at the internodal axolemma, whereas Nec14 (SynCAM4) is the only nectin-like protein expressed by Schwann cells. All three Necls are also present at the Schmint-Lanterman incisures. Nec11 and Nec14 are expressed early on apposed membranes along the internode and mediate axon-Schwann cell adhesion via strong heterophilic interaction. Blockage of this interaction results in failure on the onset of myelination. Nec14 knockdown experiments lead to abolishment of Nec11 but not Nec12 from the internodal area (37). Nec14–Nec12 interaction is feasible but with lower affinity than Nec11–Nec14 binding. It seems that Nec12 binds to Schwann cells independently of Nec14, but its ligand remains to be determined (36, 37) (Scheme 1B).

DISRUPTED AXO-GLIAL INTERACTIONS LEAD TO PATHOLOGICAL CONDITIONS

In this review we have outlined the molecular organization of the distinct myelinated fiber domains. The multiprotein com-

plexes formed at contact sites between glial cells and neurons lend specific properties in each domain that result in an upright myelinated fiber function and proper nervous system coordination. Disruption of axo-glial interactions leads to a number of pathologies like multiple sclerosis (MS), a chronic inflammatory demyelinating disease of the CNS.

Nodes of Ranvier are severely affected during MS. Studies in both rodents and MS human patients have shown that in demyelinated axons $\text{Na}_v1.2$ isoform replaces $\text{Na}_v1.6$ expression at the nodes of Ranvier. $\text{Na}_v1.2$ channels can support conduction during demyelination through the propagation of rapidly activating and inactivating currents (4, 39). In addition, the remaining $\text{Na}_v1.6$ positive nodes along with $\text{Na}^+/\text{Ca}^{2+}$ exchanger function are thought to aggravate the state of axonal degeneration (39).

A recent study revealed the existence of autoantibodies against the nodal and paranodal Neurofascin isoforms (155 and 186) in MS patients and their correlation with axonal injury (40). Furthermore, paranodes are disrupted in rodent models of demyelinating diseases such as in experimental autoimmune encephalomyelitis (EAE) rat or in Shiverer mouse, or neurological diseases such as the shambling mutation (shm) mouse (23, 41, 42). Paranodal demyelination results in the diffusion of juxtaparanodal material closer to the node causing the dampening of the propagation of the electric signal along the nerve.

TAG-1, Caspr2 and VGKCs were found to be implicated in different neurodegenerative diseases. More specifically, TAG-1 was identified as an autoantigen in a proportion of MS patients and was related to both white and grey matter pathology (43). VGKCs antibodies were identified in the sera of patients with neuromyotonia, Morvan's syndrome, limbic encephalitis and some cases of adult onset epilepsy. Further analysis of these sera revealed that immunoreactivity against potassium channels in those patients quite exclusively originated from the presence of antibodies against Kv-interacting proteins Lgi1 and Caspr2 (44). Lgi1 is a secreted protein that interacts specifically with Kvs in presynaptic terminals of the CNS, whereas Lgi1 gene mutations are held responsible for temporal lobe epilepsy. Polymorphisms in Caspr2 gene in humans (CNTNAP2/contactin-associated protein-like 2) were also related with neurodevelopmental syndromes like Autism Spectrum Disorders (ASD), proposing CNTNAP2 as an autism-risk gene (45–47).

During the past years there is a growing interest in the identification and the correlation of new protein markers in distinct pathological conditions. The above molecules appear to be promising candidates for a more thorough diagnosis and probably a more effective treatment of neurodegenerative diseases.

The elucidation of the cellular and molecular mechanisms responsible for the functional subdivision of myelinated axons represent one of the most fascinating areas of research in the nervous system. As outlined above, these subdivisions are of primary importance in demyelinating diseases since disrupted axoglial interactions underlie axonal degeneration phenotypes. In addition to the fine detail employed by myelin and axons in

organizing specific macromolecular complexes in each region around the node, one has to also consider the extraordinary evolutionary conservation of these complexes that result in one of the most intriguing biological systems in vertebrates.

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