Received: 19 May 2023 | Accepted: 1 June 2023

DOI: 10.1111/jns.12568

REVIEW

WILEY

Nodes of Ranvier in health and disease

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Funding information
Israel Science Foundation; Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

Abstract

Action potential propagation along myelinated axons depends on the geometry of the myelin unit and the division of the underlying axon to specialized domains. The latter include the nodes of Ranvier (NOR), the paranodal junction (PNJ) flanking the nodes, and the adjacent juxtaparanodal region that is located below the compact myelin of the internode. Each of these domains contains a unique composition of axoglial adhesion molecules (CAMs) and cytoskeletal scaffolding proteins, which together direct the placement of specific ion channels at the nodal and juxtaparanodal axolemma. In the last decade it has become increasingly clear that antibodies to some of these axoglial CAMs cause immune-mediated neuropathies. In the current review we detail the molecular composition of the NOR and adjacent membrane domains, describe the function of different CAM complexes that mediate axon-glia interactions along the myelin unit, and discuss their involvement and the underlying mechanisms taking place in peripheral nerve pathologies. This growing group of pathologies represent a new type of neuropathies termed "nodopathies" or "paranodopathies" that are characterized by unique clinical and molecular features which together reflect the mechanisms underlying the molecular assembly and maintenance of this specialized membrane domain.

KEYWORDS
axoglial adhesion molecules, cytoskeleton, node of Ranvier, paranodal junction, peripheral neuropathies, sodium channels

1 | THE ANATOMY OF THE AXOGLIAL INTERFACE

Myelinated axons are divided into distinct domains including the nodes of Ranvier, the paranodal axoglial junctions (PNJ), the juxtaparanodal region (JXP), and the internodes (IND) (Figure 1A). The nodes of Ranvier are short, periodical interruptions in the myelin sheath. In peripheral nerves, the nodal axolemma is contacted by microvilli emanating from the outer aspect of myelinating Schwann cells (Figure 1A). In the nodal gap, these microvillar Schwann cell processes are embedded in extracellular matrix (ECM)-rich material originally termed by Ranvier as the "cement disk." The nodal gap is also covered by a basal lamina that extends throughout the myelin unit. The nodal axolemma contains a high concentration of voltage gated Na^+ channels, as well as several types of K^+ channels that are essential for rapid de- and repolarization of the axolemma and hence for the propagation of action potentials down the axon. The nodes of Ranvier are bordered by the PNJ, a specialized axoglial contact formed between the paranodal loops of the myelinating cells and the axolemma. Here, myelin lamellae open up into a series of cytoplasmic loops that closely spiral around the axon, forming septate-like junctions with the axolemma. In electron micrographs of longitudinal sections

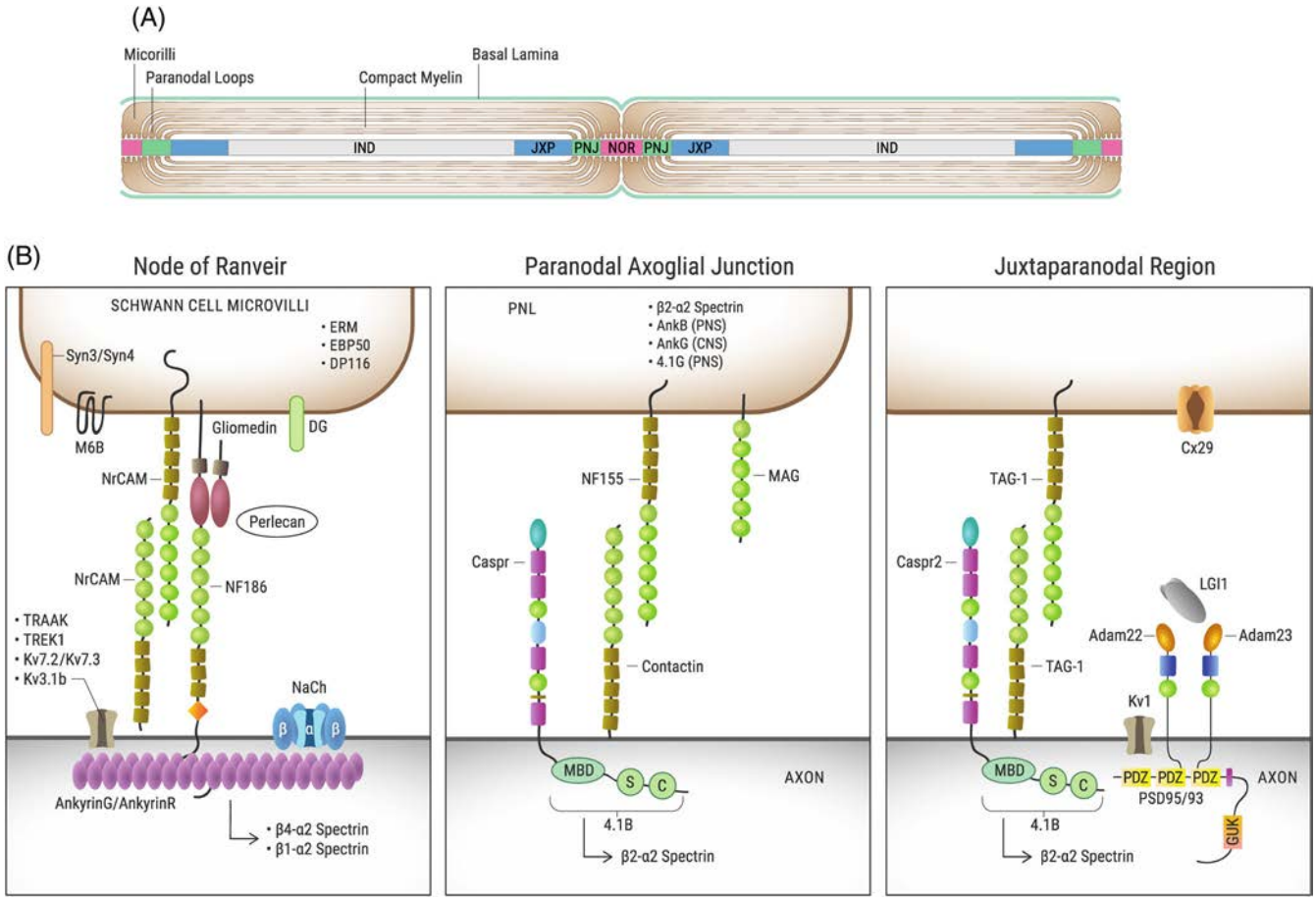

FIGURE 1 Organization of the nodal environ. (A) Schematic organization of myelinated axon in the peripheral nervous system (PNS). The presence of the Schwann cell microvilli, paranodal loops, and compact myelin, as well as the location of the node of Ranvier (NOR), the paranodal junction (PNJ), juxtaparanodal region (JXP), and the internode (IND) are indicated. (B) Molecular composition of the different domains. The nodal axolemma (left panel) is enriched in both Na^+ and K^+ channels, which are associated with NF186, AnkyrinG, and b4 spectrin. The Schwann cell microvilli in the nodal gap are enriched in several transmembrane proteins, including a complex of NrCAM and gliomedin, dystroglycan, syndecan 3 and 4, and M6B glycoprotein. The microvilli are embedded in extracellular matrix containing also perlecan. The formation of the paranodal junction (middle panel) depends on the expression of a ternary CAM complex containing glial NF155, and axonal contactin and Caspr. The latter binds protein 4.1B thereby linking the complex to b2 spectrin that is enriched at this site. On the glial paranodal loops, NF155 is linked to b2 spectrin through AnkyrinB. At the juxtaparanodal region (right panel), Kv1 channels are associated with Caspr2 and TAG-1 CAMs which are further linked to the spectrin cytoskeleton through protein 4.1B. The scaffolding proteins PSD95/93 bind to both Caspr2 and ADAM 22 and ADAM23 proteins present at the axolemma.

through the paranodal region, the junctions appear as a series of ladder-like densities (i.e., transverse bands or septa) that arise from the axon and contact the glial membranes.[1] The PNJ serves several functions that include separating the electrical activity of nodal axolemma from internodal axolemma, establishing a boundary that limits the lateral diffusion of axonal membrane proteins that is essential for the formation and maintenance of nodal and JXP membrane domains, and the attachment of the myelin sheath to the axon which regulates myelination.[1–3] Adjacent to the PNJ lays the JXP, which is located beneath the compact myelin at the interface between the PNJ and internode, and thus could be considered as part of the latter (Figure 1A). This region is characterized by clusters of intramembranous particles in freeze-fracture replicas that correspond to delayed rectifier K^+ channels.[4] While the function of these channels under the myelin sheath is not entirely clear, they may stabilize conduction and help to maintain the internodal resting potential, especially during myelination and remyelination during the formation of the paranodal junction.[4–7]

2 | THE MOLECULAR COMPOSITION OF THE NODAL ENVIRON

The nodes of Ranvier, PNJ, and the JXP contain a unique repertoire of cell adhesion molecules (CAMs), ECM proteins, and cytoskeletal scaffold components (Figure 1B), that enable the clustering of ion channels which is required for rapid propagation of action potentials.

The axolemma at the nodes of Ranvier contains a high density of voltage-gated Na^+ channels. The nodes of Ranvier are also enriched in several types of K^+ channels, including Kv3.1b, Kv7.2, and Kv7.3

(KCNQ2 and KCNQ3), as well as the leak K^+ channels TRAAK and TREK-1.[8–11] These channels are associated with two CAMs, the 186-kDa isoform of neurofascin (NF186) and NrCAM[12] through their mutual interaction with the scaffolding proteins ankyrin G and ankyrin R.[13,14] Na^+ and K^+ channels and the CAM complex (often referred to as the nodal complex) are further linked to the underlying cytoskeleton by b4-aII and bI-aII spectrin.[14,15] NrCAM is also present at the glial microvilli together with gliomedin, which binds NF186 and clusters the nodal complex on the axon.[16] In addition, a soluble form of gliomedin is present with several ECM proteins including Laminin,[17] Versican V1[18] and Perlecan[19] at the nodal gap. The microvilli also contain several other transmembrane proteins including Syndecan 3 and 4,[20] the tetraspanin protein M6B,[21] and dystroglycan.[22] These proteins, together with ECM components present in the nodal gap assist in the assembly and maintenance of the nodal complex. Finally, several intracellular scaffold proteins including ezrin, radixin, and moesin, EBP50, and DP116 are localized at the microvilli and regulate the cytoskeleton rearrangement required for their formation.[17,23–25]

In addition to the clustering of ion channels at the nodes of Ranvier, low voltage-activated Shaker-type potassium channels (Kv1 family) are sequestered under the myelin sheath in the JXP. Here, these channels are associated with an axoglial CAM complex containing Caspr2 and TAG-1 (cotactin2), the scaffolding proteins PSD95 and PSD93[26,27] and protein 4.1B.[28,29] Genetic deletion of Caspr2, TAG-1 or protein 4.1B results in marked reduction in the presence of Kv1 K^+ channels at the JXP.[29–33] The JXP also contain ADAM22 and ADAM23, two members of the ADAM proteinases that lack metalloproteinase activity.[5,34] ADAM22 is required for the recruitment of PSD95 and PSD93 to the JXP but not for the clustering of Kv1 channels at this site.[34] ADAM23 in a process that depends on its extracellular ligands LGI2 and LGI3, is necessary for both the accumulation and stability of the juxtaparanodal Kv1 complexes.[5]

The PNJ separates between the nodes and the JXP and contains a different ternary CAM complex (Figure 1B) consisting of the 155-kDa isoform of neurofascin (NF155)[35] and an axonal complex containing Caspr and contactin.[36] However, whether NF155 binds directly to the Caspr/contactin complex[37] or through a yet to be identified component[38] is presently unclear. The interaction between Caspr and contactin occurs in the endoplasmic reticulum (ER) and is necessary for transporting Caspr to the plasma membrane.[39,40] This point should be considered when designing cell– based assays that require the expression of Caspr on the surface of transfected cells, such as those used to test the presence of autoantibodies in human sera. Accordingly, Caspr accumulates in the neuronal cell bodies and is not exported to the axon in peripheral nerves in mice lacking contactin.[41] Furthermore, the association between Caspr and contactin regulates the glycosylation of both proteins[38,42] which could change their antigenicity and thereby may affect autoimmune-mediated neuropathies. Genetic ablation of either one of these proteins disrupts the formation of the PNJ and results in translocation of Kv1 channels and other juxtaparanodal proteins (Figure 1B) toward the nodes of Ranvier, demonstrating that the PNJ provides a barrier that limits the diffusion of membrane proteins.[41,43–45] Further studies revealed that this barrier is indeed directed by axoglial contact mediated by the paranodal axoglial CAMs, but it essentially formed by the underlying axonal cytoskeleton and involves the adapter protein 4.1B which is present at the PNJ[46] and binds the cytoplasmic region of Caspr[28,47] as well as spectrins.[48] The presence of an intra-axonal boundary at the PNJ was unequivocally demonstrated by findings showing that while the deletion of bII spectrin did not disrupt the formation of the PNJ, it resulted in an aberrant localization of Kv1 channels together with Caspr at this site.[49]

3 | UNDERLYING MECHANISMS OF NA^+ CHANNELS CLUSTERING AT THE NODES OF RANVIER

During the development of nerves in the peripheral nervous system (PNS), different nodal domains follow a stereotypical sequence of events: Na^+ channels are first clustered at the nodes, followed by the generation of the paranodal junction and only then by the clustering of K^+ channels at the JXP.[50,51] Clustering of ion channels at the nodes is dictated by the overlying myelinating Schwann cells who direct the placement of several cytoskeletal and tethering proteins along the axolemma. The assembly of the nodal complex is controlled by two overlapping mechanisms that involve two distinct axoglial adhesion systems operating at the nodal gap and the PNJ. The first, a so called "heminodal clustering" mechanism involves the initial clustering of Na^+ channels at heminodes that flank each of the forming myelin segments.[51,52] Heminodal clustering depends on the interaction of axonal NF186 with glial gliomedin and NrCAM.[16,53] Gliomedin binds to NrCAM present on the microvillar membrane, and also associates with other nodal ECM components to create high avidity CAM-binding multimolecular complexes that drive the accumulation of NF186 in the underlying axolemma, thereby recruiting AnkG, b4 spectrin and Na^+ channels.[16,53–57] Gliomedin contains an olfactomedin domain that mediates its binding to both NF186 and NrCAM[53,58] and a collagen-like region that enables its oligomerization.[55,59] The presence of these two functional domains within gliomedin enables gliomedin to cluster NF186 on the axolemma.[55,60] The clustering activity of gliomedin is negatively regulated by Bone Morphogenetic Protein-1 (BMP1)/Tolloid-like (Tll) proteinases, ensuring the correct spatial and temporal assembly of PNS nodes of Ranvier.[61] Notably, continuous axon-glia interaction mediated by gliomedin, NrCAM and NF186 is required for long-term maintenance of Na^+ channels at nodes of Ranvier.[62] The second mechanism for the accumulation of Na^+ channels is provided by the establishment of a cytoskeletal barrier at the paranodal junction that can restrict their lateral diffusion and cluster these channels in the nodal gap. This so called "Paranodal barrier" mechanism requires the formation of the paranodal junction and hence depends on Caspr, contactin, NF155, and bII spectrin. It allows the accumulation of ion channels at mature nodes independently of the axonodal CAMs.[16,63] These two cooperating processes provide reciprocal backup systems to ensure that Na^+ channels are clustered at nodes in the PNS.[16,64]

4 | THE NODE OF RANVIER AS A TARGET FOR ACQUIRED AND INHERITED DISEASES

Peripheral neuropathies have been traditionally divided into axonal and de-myelinating disorders, however diseases affecting the node of Ranvier and neighboring membrane domains have immerged as a new type of neuropathies termed autoimmune nodopathies. These include diseases affecting the node of Ranvier, the paranodes, and the juxtaparanodes.[65] Differential diagnosis is especially important when dealing with autoimmune neuropathies as these diseases often display unique clinical features and respond poorly to first line therapies like IVIG while a part of them better respond to B cell depleting therapies.[66] These therapies, when given early enough, can improve the outcome and prevent disease progression to axon degeneration.[67]

CAMs are natural candidate targets for auto antibodies as they are presented extracellularly and at high expression levels. CAMs are expressed at the node of Ranvier and surrounding domains. Since it is not covered by myelin, this region represents a "hot spot" for autoantibody attack.[68] Electrophysiological analyses of nodopathy patients often display reversible conduction failure (RCF). The fact that the conduction block can be rescued in a short period of time or after plasmapheresis indicates that the underlying pathophysiology is antibody-mediated (by blocking protein–protein interactions or complement activation) and not demyelination. In most cases, the areas primarily prone to immune attack are the axon terminal and the spinal roots, where blood nerve barrier is more permeable.

Non autoimmune nodopathies are recently emerging as genetic diseases specifically targeting the node of Ranvier and vicinal domains and thus often involve abnormal nerve conduction. We herein review the different autoimmune as well as genetic nodopathies affecting the node of Ranvier, paranode, and juxtaparanodal domains.

5 | DISEASES INVOLVING THE NODE OF RANVIER

5.1 | Immune-mediated neuropathies

The node of Ranvier is the primary target in the pathophysiology of GBS (Gullian Barre Syndrome), especially of AMAN type (acute motor axonal neuropathy). GBS, an autoimmune polyneuropathy, is characterized by acute and progressive symmetric limb weakness with or without cranial nerve involvement. The pathogenicity of anti-nodal auto antibodies usually involves complement activation.[68] The fact that the node is prone to complement attack may relate to the absence of complement regulatory proteins, which inhibit MAC formation at this site (Karbian and Mevorach, personal communication). The typical pathologies found in GBS-like nodopathies are lengthening of the node, disruption of Na^+ channels, paranodal detachment, and disorganized axonal domains. The final common outcome is disruption of the nodal excitability resulting in a RCF that may or may not progress to axon degeneration, depending on the underlying immune-mediated mechanism and the timing and efficiency of treatment.

Anti-gangliosides antibodies were the first to be described in GBS patients.[69] 60% of GBS patients are seropositive for these antibodies.[70] Given that GM1 is enriched at the nodal axolemma and at Schwann cell microvilli, it is not surprising that anti-GM1 antibodies are the most common antibodies in both AMAN and MMN (multifocal motor neuropathy).[71,72] Autopsy studies and also rabbits injected with gangliosides showed deposits of anti-GM1 and complement at the node of Ranvier and dispersion of Na^+ channels from the node.[73]

Antibodies to NF186 or gliomedin were found in 62% of patients with MMN and only in 1% of patients with CIDP (chronic inflammatory demyelinating polyneuropathy),[74] supporting the notion that MMN is a primary nodopathy like GBS/AMAN and unlike CIDP which affects the myelin and the paranodes. Why are these antibodies pathogenic? In EAE, injection of anti-neurofascin antibodies with encephalitogenic T cells resulted in complement deposition at the node, axonal degeneration and worsening of the disease. In hippocampal slices anti-neurofascin blocked conduction by complement.[75] In addition, it was shown that anti-gliomedin Abs isolated from GBS patients could activate complement.[76] This indicates that anti-nodal Abs could activate complement and induce conduction block and muscle weakness in MMN patients. In an ultrastructural analysis of an anti-NF140/186 seropositive patient, there was almost a complete loss of Schwann cell microvilli with an overgrowth of flanking Schwann cells that blocked the nodal gap.[77] Displacement of the SC microvilli is likely pathogenic as continued axon-glial contact is required to maintain the nodal complex, including Na^+ channels at the axolemma.[62]

The pathogenic potential of anti-gliomedin antibodies was also demonstrated in a study that showed that passive transfer of anti-gliomedin Abs to rats resulted in nodal disruption and paranodal demyelination with Ab deposition and complement activation.[76]

Moesin antibodies have also been described in 12.5% of GBS patients. These antibodies bind to SC microvilli and probably mediate complement activation as well.[78]

In a study where patients sera were used for labeling rodent sciatic nerves, it was found that 44% of patients with AIDP, 42% of AMAN and 30% of CIDP had antibodies that labeled the nodal region.[79] Only a few of the patients had Abs to NF186, gliomedin, or contactin. The fact that specific antigen targets were not detected in most of these patients suggests there are novel nodal antigens to be discovered.

Interestingly, in EAN (experimental allergic neuritis), a model for de-myelinating GBS (AIDP, acute inflammatory demyelinating polyradiculoneuropathy) that was induced by myelin proteins, the expression of NF186 and gliomedin was affected and antibodies to these proteins were detected already before disease onset.[80] No complement deposition was found at the node. This was accompanied by disruption of Na^+ channels at the nodes and conduction deficits in ventral spinal roots. The authors speculated that immunity toward gangliosides may have triggered secondary immune reaction against neurofascin and its partners, as NF186 is found in lipid rafts at the node, along with GM1. That is, antibodies to nodal antigens can disrupt the node by complement dependent or independent mechanisms. This also suggests that nodal disruption is a feature not only of AMAN and MMN but also of de-myelinating GBS (AIDP) and CIDP.

Indeed, Devaux et al. showed that while anti-NF186 antibodies were more prevalent in AMAN, anti-gliomedin antibodies were more prevalent in AIDP.[79]

5.2 | Genetic nodopathies

Genetic nodopathies affecting proteins expressed at the node of Ranvier have recently been identified. They still represent a small proportion of patients but the numbers are rising as exome and genome sequencing is becoming more common. A mutation in a family that was shown to result in the specific loss of Nfasc186 (neuronal isoform), was reported in 2019.[81] Two siblings displayed progressive ataxia and muscular weakness but they were not as severely affected as the one described by Smigiel et al.[82] in which the glial isoform Nfasc155 was absent. This supports previous observations in mice where the neuronal nodal neurofascin isoform was selectively deleted and the mice, although ataxic, had a somewhat extended lifespan.[62,83]

NF186-gliomedin interaction at the node plays an important role in the assembly of peripheral nodes of Ranvier.[53] Mutations in gliomedin (GLDN) in four different families were predicted to abolish or reduce the effectiveness of gliomedin interaction with Nfasc186 and result in a lethal form of arthrogryposis multiplex congenita (AMC) associated with, among other features, widened nodes, reduced numbers of PNS myelinated fibers, joint contractures and pulmonary hypoplasia.[84] Those fetuses that came to term died shortly after birth.

Subsequently, new biallelic mutations in GLDN were identified in which some individuals with AMC survived into adolescence but these individuals required considerable support.[85] At present it is difficult to correlate the nature of the mutation with the severity of the disease since even within a single family and individuals of the same genotype one individual died at 2 days whereas another was still alive at 22 years. The authors concluded that other genetic or environmental factors might modify the clinical phenotype; however, their nature remains elusive. It has been proposed that sub-lethal variants of GLDN mutations might be grouped under the category of fetal akinesia deformation sequence (FADS), although once again, the correlation between specific mutations, morphological consequences and clinical outcomes remain unclear.[86]

6 | DISEASES INVOLVING COMPONENTS OF THE PARANODAL AXOGLIAL JUNCTION

6.1 | Immune-mediated paranodopathies

CIDP is considered a macrophage-mediated de-myelinating disease. However about 10% of the patients show distinct phenotype that is associated with antibodies to contactin and NF155, that are rarely found in GBS.[87,88] Their disease is more aggressive and motor, includes ataxia and tremor and is unresponsive to IVIG treatment. Most paranodal neuropathies are IgG4-positive, hence do not activate complement and do not respond to IVIG treatment.[66] These antibodies probably exert their pathogenic effect by blocking protein–protein interactions. Nevertheless, since an initial IgG3 phase usually precedes IgG4, early diagnosis is critical. In anti-NF155 seropositive patients, absence of macrophage mediated demyelination and the lack of complement activation both point to an alternative pathogenesis, that is, interfering with NF155-Caspr interactions thereby interrupting the axo-glial contact at the paranodes and disrupting paranodal resistance.[89,90] EM studies indeed suggest that these antibodies disrupt the paranodal transverse bands. Disruption of the paranodal junction also results in mislocalization of Kv1 channels further leading to slowed or blocked conduction. Unlike anti-contactin that probably indeed blocks protein–protein interactions at the paranodes, anti-NF155 depletes the protein from the paranodes which also eventually leads to conduction failure.[91] In NF155 IgG4 seropositive patients, a decrease in myelinated axons is observed, although demyelination is secondary to axonal changes and axo-glial detachment, unlike anti-CNTN patients where macrophage mediated demyelination was observed. In EM studies, widening of the node of Ranvier was demonstrated.[89]

Another type of auto antibodies targeting the paranode is anti-pan neurofascin (panNF), which recognize both glial and neuronal isoforms of neurofascin. As these antibodies can target both nodes and paranodes, it is not surprising that the affected patients present with the most severe nodopathy.[92] Starting as GBS with a short recovery, they then develop a severe disease with tetraplegia, autonomic instability, cranial nerve involvement, respiratory failure, and a high mortality. Anti-NFpan antibodies can activate complement in vitro. Patient sera showed strong nodal labeling on rodent sciatic nerve. When added to DRG myelinating cultures, these sera interfered with node and paranode formation and maintenance. Abnormalities in non-compact myelin structures were reported in these cultures as well. In patients' peripheral nerves there were no signs of cellular infiltration, inflammation or segmental demyelination. There was no evidence for paranodal detachment either. Nevertheless there was axonal loss, probably mediated by complement toxicity.

Anti-caspr Abs represent a small proportion of CIDP patients, some of whom have autoantibodies reactive for the caspr-contactin protein complex and not for the single proteins.[93] Anti-caspr disease is characterized by neuropathic pain without involvement of small fibers, suggesting that the pain phenotype arises from paranodal disruption in Adelta or type III myelinated nociceptor fibers. Histological analysis showed node/paranode destruction and diffusion of Caspr and NF155 labeling from the paranodes.[94] It is unclear why anti-caspr Abs manifests different clinical features as all three autoantibodies mentioned above target the same axolemmal domain.

6.2 | Inherited paranodopathies

A homozygous mutation in the cntn1 (contactin) gene causes lethal congenital myopathy syndrome. Similarly, mice lacking contactin, in which the paranodal junction is disrupted, show severe ataxia and muscle weakness, growth retardation and postnatal lethality.[41] The two major protein isoforms encoded by the Nfasc (neurofascin) gene are glial Nf155, expressed at the paranodal junction in both oligodendrocytes in the CNS and Schwann cells in the PNS, and neuronal

Nf186 expressed at the node of Ranvier. Loss of both proteins in mice has catastrophic consequences.[95] In the absence of both proteins, mice are unable to cluster Na^+ channels at the node and die at post-natal days 6–7. Therefore, it was a considerable surprise to discover an infant patient with a homozygous mutation in the NFASC gene.[82] Further analysis revealed that this particular mutation exclusively affected the glial isoform, Nf155, whereas the neuronal isoform was apparently unaffected. Confirmation of the absence of Nf155 was made by immunocytochemical analyses of skin biopsies. This meant that, although the patient was severely affected, and displayed hypotonia, amimia, and areflexia, she was able to survive for a limited period of time. Studies in mice showed that although disruption of the paranodal junction does permit the initial clustering of Na^+ channels at nodes in the CNS and PNS leading to prolonged survival, these channels subsequently diffuse away from nodes with a concomitant reduction in nerve conduction velocity.[45,62,96,97] The clinical phenotype in humans and mice due to Nfasc155 loss is thus comparable.

Since this first report several new cases of individuals with mutations in the human Nfasc gene have been described. Therefore, it seems likely that such mutations are more common than previously suspected and that more will be revealed by more extensive use of whole exome sequencing. Out of six cases reported in 2019, four involved variants in both major neurofascin variants, glial and neuronal, one was predicted to be glial-specific and one neuron-specific.[98] Although the extent of the neurodevelopmental disability was difficult to attribute to the influence of specific mutations, all displayed hypotonia and moderate to severe intellectual disability, together with major reductions in peripheral nerve conduction velocities in most cases. Interestingly, two children with an intact glial variant, and therefore presumed to have intact paranodal axon-glial junctions, had a significantly older age of onset.

More recently a loss of function mutation in Nfasc has been attributed to be the cause of hypotonia, developmental delay and in particular auditory neuropathy.[99] Although not specified by the authors, it appears that the sequence containing this frame shift mutation would not encode the mucin domain found in neuronal neurofascin but would encode the fibronectin type III domain specific to glial Nfasc155. Hence, it appears that this may also be a mutation predominantly affecting the glial isoform.

Loss of function mutations in the gene encoding Caspr (CNTNAP1) might be expected to have a similar consequence to the loss of glial neurofascin since they would both disrupt the PNJ. Caspr null mice have disrupted paranodal junction, show lateral diffusion of ion channels into paranodes, and have a reduced compound AP conduction velocity. Mice exhibit tremor, ataxia, and significant motor paresis.[43] In humans, Caspr mutations caused severe hypotonia, facial diplegia and a lack of swallowing, autonomous respiratory and deep tendon reflexes disfunction.[100] Motor nerve conduction velocity was also reduced. In all patients, death occurred within the first 2 months of life. More recent reports of homozygous mutations in the CNTNAP1 gene have included hypotonia together with epilepsy, cerebral hypoplasia, holoprosencephaly, defects in neuronal migration, pyramidal tract degeneration, and cerebellar degeneration.[101]

Congenital hypomyelinating neuropathy has also been observed in patients with compound heterozygous mutations in CNTNAP1.[102] A related condition was also observed in several cases with, respectively, three missense variants, four nonsense variants, one frameshift variant, and one splice site variant.[103] Variations in the nature of different CNTNAP1 mutations appears to have significant implications for the severity of the congenital hypomyelination commonly observed, although epileptic seizures, dystonia, and impaired communication skills are consistently observed.[104]

7 | DISEASES INVOLVING JUXTAPARANODAL COMPONENTS

Antibodies to juxtaparanodal proteins like LGI1 and Capsr2 result in reduction in Kv1 channel density and neuronal hyperexcitability. Antibodies to Caspr2 have been described in patients with peripheral nerve hyperexcitability or as part of acquired neuromyotonia, which involves neuronal hyperexcitability in both CNS and PNS.[105,106] Similarly, mutations in the Kv1.1 (*KCNA1*) gene result in a syndrome of episodic ataxia and myokymia.[107] Moreover mutations in CNTN2 (TAG-1) and in Caspr2 (CNTNAP2) were identified in patients with complex epilepsy syndromes[108,109] and autism spectrum disorder.[110]

8 | SUMMARY

The molecular integrity of the node of Ranvier is critical for proper nerve conduction. The node and surrounding domains contain a large variety of adhesion molecules, each of which is a potential target for autoimmune attack as well as for loss of function mutations. The pathogenetic processes underlying peripheral nodopathies involve perturbation of protein–protein interactions, complement activation and specific protein deficiency, all resulting in mislocalization or dispersion of ion channels leading to reduced nerve conduction or even conduction block.

ACKNOWLEDGMENTS

This work was supported by research grants from the Israel Science Foundation, Dr. Miriam and Sheldon G. Adelson Medical Research Foundation, and the Sagol Center for Research on the Aging Brain. Elior Peles is the Incumbent of the Hanna Hertz Professorial Chair for Multiple Sclerosis and Neuroscience.

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How to cite this article: Eshed-Eisenbach Y, Brophy PJ, Peles E. Nodes of Ranvier in health and disease. *J Peripher Nerv Syst*. 2023;28(Suppl. 3):S3-S11. doi:10.1111/jns.12568