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Review

Molecular organization and function of vertebrate septate-like junctions

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ABSTRACT

Septate-like junctions display characteristic ladder-like ultrastructure reminiscent of the invertebrate epithelial septate junctions and are present at the paranodes of myelinated axons. The paranodal junctions where the myelin loops attach to the axon at the borders of the node of Ranvier provide both a paracellular barrier to ion diffusion and a lateral fence along the axonal membrane. The septate-like junctions constrain the proper distribution of nodal Na^+ channels and juxtaparanodal K^+ channels, which are required for the safe propagation of the nerve influx and rapid saltatory conduction. The paranodal cell adhesion molecules have been identified as target antigens in peripheral demyelinating autoimmune diseases and the pathogenic mechanisms described. This review aims at presenting the recent knowledge on the molecular and structural organization of septate-like junctions, their formation and stabilization during development, and how they are involved in demyelinating diseases.

1. Introduction

The septate-like junctions, namely the paranodal junctions, are present in vertebrate myelinated axons forming a physiological barrier at the borders of the node of Ranvier. The paranodal junctions are heterotypic and provide a linkage between the terminal loops of myelin and the axonal membrane on both sides of the nodal gap where Na^+ channels are clustered. The typical ladder-like structure of paranodal junctions depends on the assembly of a ternary complex of cell adhesion molecules (CAMs) with axonal Caspr and Contactin facing Neurofascin-155 on the glial membrane. Nonetheless, the detailed architecture of the septate-like junctions is still incompletely understood. The molecular components of paranodal junctions are highly conserved during evolution and the comparison with invertebrate epithelial septate junctions may give important clues, even if they comprise distinctive features. Recent advances in imaging of the nodes of Ranvier using super-resolution microscopy and structural analyses of the Caspr and Contactin families have brought new insights into the possible arrangement of the paranodal adhesive rows. Finally, the perturbation of septate-like junctions in pathological contexts and the mechanisms of action of autoantibodies directed against the paranodal CAMs have been recently described.

2. The vertebrate paranodal junctions display similarities and differences with the invertebrate septate junctions

Among occluding junctions, tight junctions appeared restricted to chordates whereas septate junctions have been characterized in invertebrates to ensure barrier properties and control paracellular diffusion across epithelial cells and glial cells that are insulating neurons (review in [1,2]). The structural components of septate junctions, such as Neurexin IV, are evolutionarily conserved and already arose in cnidarians [3]. To date, more than 20 membrane or membrane-associated proteins have been implicated in the formation of *Drosophila* septate junctions including the conserved core components Contactin, NeurexinIV, and Neuroglian [4,5]. This complex of three CAMs is also required for the formation of vertebrate paranodal junctions, namely with Contactin, Caspr/Paranodin homologous to Neurexin IV, and Neurofascin-155 homologous to Neuroglian [6] (Table 1). A submembrane scaffold is implicated in the formation of glial and epithelial septate junctions in *Drosophila* including the Four-point-one/Ezrin/Radixin/Moesin (FERM) protein Coracle which binds NeurexinIV [7] and is homologous to the vertebrate band 4.1B interacting with Caspr at paranodes [8]. Besides, a variety of scaffolding and membrane molecules are required for the formation of *Drosophila* septate junctions -that are not described in the vertebrate paranodal junctions- such as the PDZ protein Varicose [9], the claudin-like tetraspan proteins Megatrachea, Sinuous and Kune-kune [10–12], the immunoglobulin (Ig) family member Lachesin [13,14], the Ly-6 family proteins including Boudin and Coiled [15,16], the macroglobulin complement-related protein [17] and the Na^+/K^+ ATPase subunits [18]. All these CAMs and scaffolding molecules are interdependent for their recruitment at the septate junctions of epithelial cells meaning that when a single protein of the complex is missing, all the other ones are mis-expressed or mis-

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Table 1
Molecular components of *Drosophila* septate junctions (SJ) and vertebrate paranodal junctions.

Drosophila molecular components			Vertebrate molecular components		
Gene product	Localization/ Function	References	Gene product	Localization/ Function	References
Neurexin IV	epithelial and glial SJ/ CAM	[4]	Caspr	paranode/axonal CAM	[31, 41]
Contactin	epithelial and glial SJ/ CAM	[5]	Contactin	paranode /axonal CAM	[32, 42]
Neuroglian	epithelial and glial SJ/ CAM	[5, 18]	Neurofascin-155	paranode/glial CAM	[45]
Coracle	epithelial SJ/ scaffold	[7]	4.1B	paranode, juxtaparanode/ axonal scaffold	[47, 48]
Varicose	epithelial and glial SJ/ scaffold	[9]	PALS2/MPP2/MPP6 family		
Claudin-like:			Claudin family	tight junctions/CAM	[23]
Megatrachea	epithelial (and glial for Kune-kune)	[12]			
Kune-Kune	SJ/ CAM	[11]			
Sinuous		[10]			
			Tetraspanin CD9	paranode/myelin CAM	[21]
Na+/K+ ATPase, α and ß (Nervana) subunits	Epithelial SJ/ CAM (pump-independent)	[18]	Na+/K+ ATPase		
Lachesin	epithelial and glial SJ/ CAM	[13, 14]	IgLON family		
			MAG	paranode, internode/ myelin CAM	[76]
Ly6 family:			CD59		
Boudin	epithelial SJ/secreted	[15]			
Coiled	epithelial and glial SJ/CAM	[16]			

distributed along the basolateral membrane. However, the timing of events requiring septate junction genes during *Drosophila* embryogenesis indicates that this multiplicity of genes is likely required for developmental functions that are independent of their role in forming an occluding junction in the lateral membrane of epithelia. Nevertheless, the components of septate junctions in arthropods that include claudin-like proteins also suggest a common molecular basis with vertebrate tight junctions to form a paracellular barrier despite their different morphologies.

At the ultrastructural level, fly septate junctions display strong similarities with vertebrate paranodes showing the typical regularly-spaced transverse bands, called septa. However, their intermembrane width differs, which is approximately 15–20 nm for the invertebrate septate junctions instead of 3–5 nm for the paranodal junctions [5,19]. Another different feature consists of homotypic versus heterotypic cell-cell junctions in fly and vertebrates, respectively. In *Drosophila*, homotypic contacts are formed between *Drosophila* epithelial or glial cells whereas heterotypic junctions are established at vertebrate paranodes with distinct CAMs on the glial and axonal membranes. The question of the molecular composition of the transverse bands and whether there are formed by a complex of CAMs, glycolipids or extracellular matrix components is still unresolved for both types of junctions. Whether the conserved core components Contactin/Caspr/Neurofascin-155 in vertebrates and Contactin/NeurexinIV/Neuroglian in *Drosophila* are associated with the presence of transverse bands has been investigated using genetic approaches. As further detailed in the next paragraph, each of the vertebrate CAMs is strictly required for the presence of transverse bands at the axo-glial paranodal junction. In *Drosophila* epithelial cells, the transverse bands are lacking in the NeurexinIV null mutant [4] but are still present in the Contactin or Neuroglian mutant although disorganized [5] and the paracellular barrier is altered in each of these mutants. We may note that in the NeurexinIV mutant, the cell surface targeting of Contactin is prevented so that the two cis-interacting proteins are missing at the cell-cell contact. However, to answer the unresolved question of the molecular composition of septa, experiments are missing such as inducing ectopic assembly of septate junctions or de novo formation of septate-like junctions in a heterologous system. With this respect, it is interesting to mention the tremendous experiments performed to identify the backbone of the vertebrate epithelial occluding junctions. Indeed, the reconstitution of junctional strands of kissing points has been obtained by introducing a single claudin in fibroblasts [20]. Claudins are the major CAMs of tight junctions encompassing four membrane-spanning regions which can polymerize into paired strands at cell-cell contacts. Claudin-like proteins have been identified in septate junctions of invertebrates that are required for the correct function of the paracellular barrier. However, they are interdependent with other CAMs including NeurexinIV, Contactin and Neuroglian, which are conserved in the vertebrate paranodal junctions. Interestingly, the tetraspanin CD9 is a myelin component that is concentrated at paranodes and required for the formation of the transverse bands [21]. Tetraspanins display a similar topology but no sequence identity with claudins and are postulated to organize a network of interaction at the cell surface with integrins, Ig-CAMs and claudins [22]. In conclusion, the relationship between tight junctions and septate junctions in terms of molecular evolution is still unclear [23].

3. Septate-like junctions at synaptic contacts in invertebrates and vertebrates

Intriguingly, some non-conventional synaptic contacts exhibit structural features resembling the invertebrate epithelial septate junctions (review in [24]). In the developing neuromuscular junctions of *Drosophila* embryos and larvae, the presence of regularly structured electron-dense material in the synaptic cleft was observed [25]. However, distinct CAMs mediate adhesive contacts at the neuromuscular junctions including Fasciclin2 and NeurexinI instead of Neuroglian and NeurexinIV which are characteristics of the fly epithelial septate junctions [4,26,27]. In the vertebrates, septate junctions have been found at axo-axonic contacts of cerebellar basket cells that form the pinceau surrounding the Purkinje cell perikaryon and axon initial segment [28]. These junctions display structural features similar to the invertebrate septate junctions with an intercellular distance ranging between 11 and 18 nm and spacing of transverse bands between 16 and 22 nm. Therefore, the basket cell axo-axonic junctions differ from the paranodal junctions which exhibit a narrower cleft between axo-glial cell membranes. Their functional role could be to compartmentalize the extracellular space and regulate the extracellular current flow at the pinceau to provide ultra-rapid electrical inhibition of Purkinje cells [29]. The molecular composition of these axo-axonic septate junctions is still elusive. Noteworthy, Neurofascin is expressed in basket cell axons and is required for the proper organization of the pinceau [30].

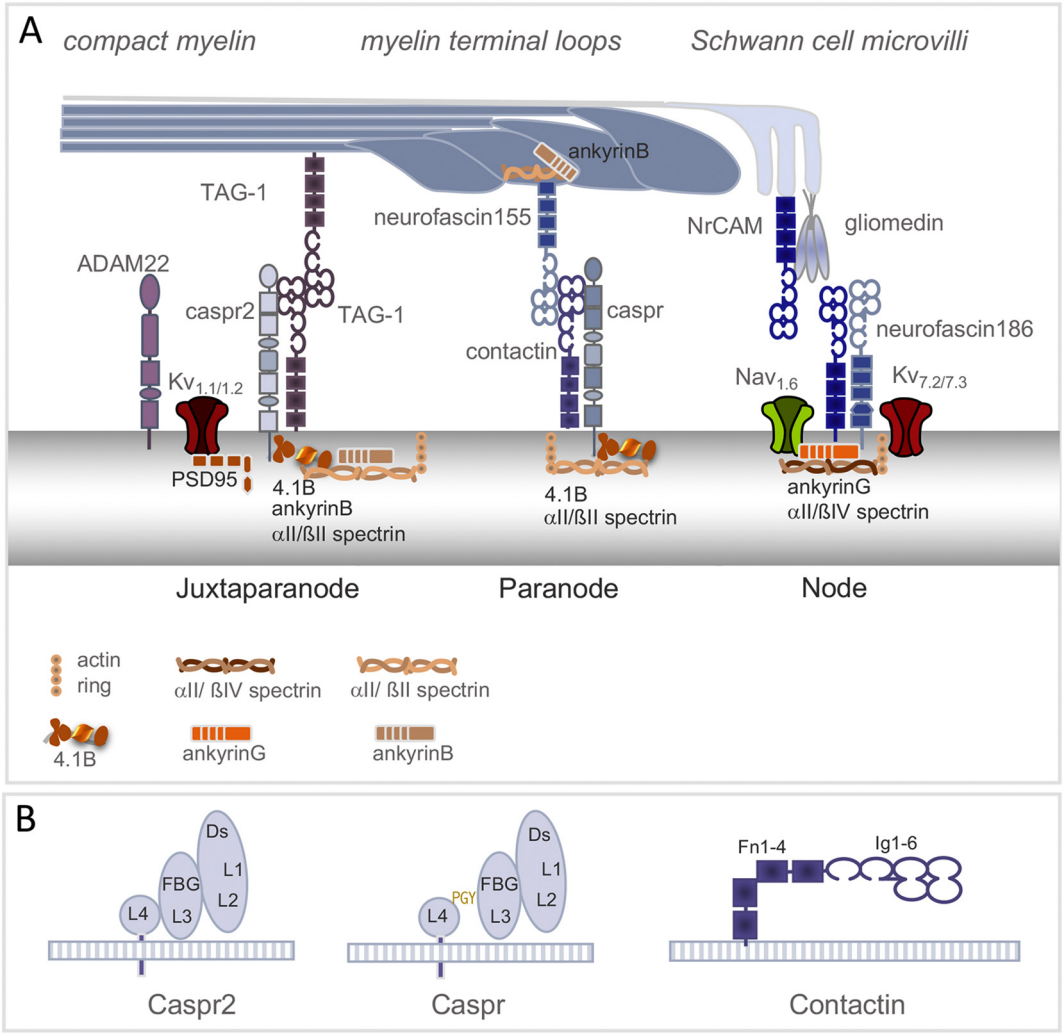

Fig. 1. Molecular organization of the node of Ranvier in the peripheral nervous system.
A: Distinct complexes of cell adhesion molecules are segregated at the different subregions of the node of Ranvier, the nodal gap, the paranode and the juxtaparanode. At the paranodal junction, the cis-complex of Caspr and Contactin interacts in trans with Neurofascin-155 on the myelin loops. The axonal CAMs associated with their subcortical scaffold show a regular periodic organization of 190 nm, which corresponds approximately to the size of a myelin loop. The submembrane cytoskeleton is aligned with axonal βII spectrin facing glial ankyrinB in alternance with actin rings. The paranodal CAMs could be positioned at the side of myelin loops given the very short intermembrane distance of 3–5 nm at paranodes.
B: Structural organization and possible horizontal orientation of Caspr and Contactin ectodomains. Caspr and Caspr2 contain an N-terminal discoidin (Ds) and a central fibrinogen (FBG) domain, four lamininG (L1–4) domains. A module of PGY repeats is only present in Caspr. Contactin is a GPI CAM with six Ig domains that adopt a horse-shoe conformation and four Fibronectin type III repeats.

4. Assembly of cell adhesion and scaffolding molecules at the paranodal junctions

The paranodal junctions are established on both sides of the node of Ranvier between the axon and the terminal myelin loops emanating from Schwann cells in the Peripheral Nervous System (PNS) and from oligodendrocytes in the Central Nervous System (CNS). A similar interacting set of CAMs is vital for the assembly of the paranodes in the PNS and CNS (Fig. 1). On the axonal side, Contactin, which is a GPI-anchored CAM of the Ig superfamily associates in cis with Caspr, a transmembrane glycoprotein related to Neurexins [31–33]. Contactin and Caspr are interacting in trans with Neurofascin-155, the glial isoform of the Ig-CAM Neurofascin, which is expressed on the terminal myelin loops [34]. The cis-interaction of Contactin with Caspr in the endoplasmic reticulum is required for its proper folding and export at the cell membrane [35]. Contactin and Caspr are assembled early during the secretory pathway and exported having been modified with immature mannose-rich N-glycans at the axonal surface [36,37]. These selective glycoforms of Contactin and Caspr bind glial Neurofascin-155, forming a ternary axo-glial complex [38]. The Ig5–6 domains of Neurofascin-155 are required for Contactin binding [39] and conversely, a cluster of three N-glycosylation sites on the Ig5 domain of Contactin is involved in its interaction with Neurofascin-155 [40]. Genetic ablation of genes encoding the axonal proteins Contactin and Caspr, results in the disruption of paranodal junctions [41–44] as also observed when the glial component Neurofascin-155 is missing. In Neurofascin-null mice, lacking both the glial Neurofascin-155 and the neuronal Neurofascin-186 isoforms, the assembly of the nodal and paranodal complexes is prevented. Indeed Neurofascin-186 plays a critical role in the clustering of the Na^+ channels at the node. Transgenic rescue of Neurofascin-155 in myelinating glia indicates its specific role in the formation of paranodes in the PNS and CNS [44,45]. Similarly, it was shown that the specific ablation of Neurofascin-155 in myelinating glial cells alters the formation of axo-glial paranodal junctions [43]. Deficiency in any of the paranodal CAMs results in the disappearance of the transverse bands, enlargement of the junctional gap width and presence

of everted myelin loops. In any of these mutant mice, the proper segregation of ion channels is impaired: the nodal area enriched in Na^+ channels is broadened and strikingly the juxtaparanodal K^+ channels are mis-distributed and found at paranodes close to nodal Na^+ channels. Such paranodal alterations are leading to impaired action potential conduction.

A submembrane scaffold is implicated in organizing the paranodal junctions. On the axonal side, the paranodal scaffold consists of protein 4.1B and αII/βII spectrin. Caspr interacts via its FERM binding domain with protein 4.1B. The phenotype associated with 4.1B deficiency has been reported for different knockout mouse lines. Protein 4.1B is not required for the formation of the transverse bands although moderate disorganization of paranodes is observed [46–49]. In the same manner, βII spectrin-deficiency does not prevent the formation of transverse bands at paranodal junctions [50,51], consistent with the idea of robust and redundant mechanisms. On the glial side, ankyrinG and ankyrinB are found at paranodes in the CNS and PNS, respectively and are interacting with Neurofascin-155. Conditional knockout of ankyrinG in oligodendrocytes disrupts paranodal junction assembly and delays nerve conduction during early CNS development, albeit, the paranodal junctions eventually assemble in the adult [52]. In the PNS, ankyrinB expressed by Schwann cells is not required for paranodal assembly and maintenance in the sciatic nerve. The multivalent binding property of ankyrins may allow them to stabilize many glial Neurofascin molecules in close proximity to each other and to increase binding avidity for axonal Caspr/Contactin and facilitate the assembly of septate-like junctions at paranodes.

What is the developmental schedule for the assembly of paranodal junctions during myelination? In the rat sciatic nerve, the nodal region is flanked by Caspr-positive paranodes by post-natal day 2 and the transverse bands are present at post-natal day 4 [106]. In the CNS, the paranodal transverse bands are not apparent at post-natal day 15 but are seen at post-natal day 23 in the mouse spinal cord although Caspr is already enriched at paranodes before P15 [53]. The dynamics of the paranodal junction assembly can be observed using in vitro paradigms. In mixed cultures of dorsal root ganglia myelinated by oligodendrocytes, the recruitment of axonal Caspr was shown to mirror the increase in Neurofascin-155 at the contact with oligodendrocytes from the time of the initial contact until they reach their final distribution at paranodes [54]. During the wrapping of axons by oligodendrocytes, Caspr and Neurofascin-155 form a loose coil that finally clusters at the paranodes. The paranodal CAMs are restricted from freely diffusing in the lateral plane of the axonal membrane as shown for Caspr using fluorescent recovery after photobleaching (FRAP) in myelinating culture of dorsal root ganglia [55]. Therefore, the clustering of the paranodal CAMs Caspr and Neurofascin-155 occurs before the formation of transverse bands and is crucial for the assembly of these structures.

5. Structural organization of the junctional complex at paranodes

The ultrastructural organization of paranodal junctions as observed with electron microscopy revealed the regularly spaced intermembrane particles - the septate-like junctions - between the axonal membrane and the myelin loops. However, the arrangement of the paranodal cell adhesion molecules and submembrane cytoskeleton concerning the alignment of the transverse bands is not known. Recent advances in the nanoscale organization of the nodes of Ranvier in teased sciatic fibers have been obtained using stimulated emission depletion (STED) microscopy and auto-correlation analysis [56] (Fig. 2). At paranodes, both axonal Caspr and glial Neurofascin-155 form 190-nm periodic arrangements with a high degree of interdependence between their positions along the myelin loops. The defined periodicity of 190 nm is consistent with the typical lattice of actin/spectrin rings along the axon [57] and at the axon initial segment [58] and a continuity is observed between subcortical βII spectrin at paranode and βIV spectrin at the nodal gap [56]. The co-alignment between Caspr and βII spectrin

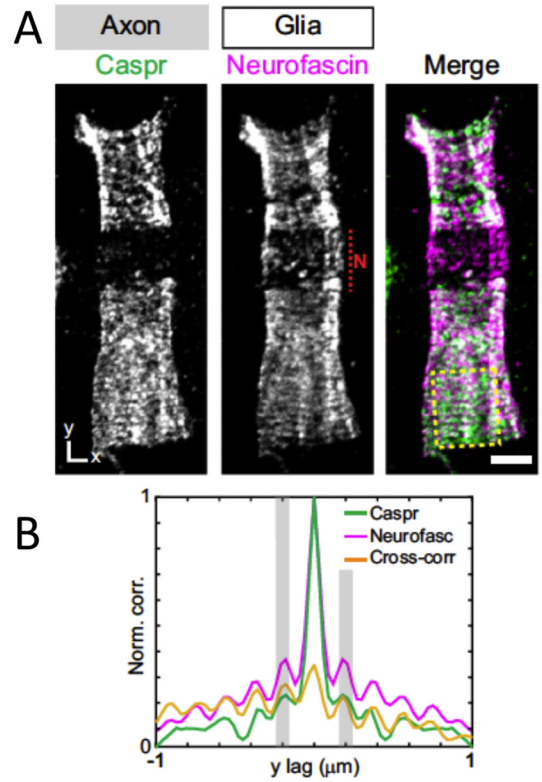

Fig. 2. Nanoscale alignment of the axonal and glial CAMs at paranodes.
(A) Two-color images of sciatic nerve paranodes stained for axonal Caspr and glial Neurofascin. The red dash line indicates the position of the node (N). Scale bar: 1 µm.
(B) Profile of intensities for Caspr and Neurofascin-155 in the region indicated by the yellow dashed box after autocorrelation and cross-correlation for the merge image. The y axis is aligned with the axon. A longitudinal periodicity can be observed in-phase for the axonal and the glial CAMs. The grey bars highlight the ± 0.2 µm lag.
Adapted from D'Este et al., PNAS 2017.

suggests the role of the subcortical cytoskeleton in the arrangement of the paranodal CAMs. As mentioned by the authors, the labeling strategy with antibodies and the imaging technique do not provide sufficient resolution to identify sub-patterns along the Caspr and Neurofascin-155 paranodal bands. Therefore, it is not possible to establish a relationship between the 190-nm periodic pattern formed by CAMs and the patterning of transverse bands spaced by 30 nm as visualized by electron microscopy. Intriguingly, the periodicity of 190 nm corresponds to the width of a single myelin loop estimated to 150–200 nm in the CNS suggesting that one helical coil of Caspr winds around the axon per myelin loop. These data are in favor of the model proposed by [54] in which the Caspr/Contactin/Neurofascin-155 complex is located at the inter-junctional zones of the paranodal loops but is not a constituent of axoglial septa. Indeed, this distribution correlates with the helical pattern observed during the expansion of lamellar glial membranes and the compaction of the paranodal loops during myelinogenesis.

At paranodes where the myelin loops are anchored to the axolemma, the distance between the axonal and glial membranes is reduced to approximately 3–5 nm, while at the internodal region under the compact myelin this distance is 10–20 nm as evaluated using conventional and three-dimensional high-voltage electron microscopy [19]. However, using electron tomography of the mouse corpus callosum in the CNS, the intercellular space between axon and glia at paranodes was measured to 6–8 nm [59]. An intriguing question is how the ternary complex of Contactin, Caspr and Neurofascin-155 might fit within this limited extracellular spacing. Contactin is a GPI-anchored CAM with six Ig-like domains and four Fibronectin type III (Fn)

domains. The crystal structure first reported for Contactin2 indicates that Contactins adopt a horse-shoe conformation of the Ig1–4 domains [60]. The dimensions of the Ig1–4 domains are 9.5 nm for the ellipsoid length, 4.5 nm corresponding to the side-by-side packing of two domains (Ig1,4 or Ig2,3) and 2.5 nm for the thickness of an Ig domain. The structural feature of Contactin in the extended conformation would be consistent with 32 nm if we consider a long axis of a single Ig or Fn domain to be 4 nm. Interestingly, crystallographic analyses indicate that the Fn regions in Contactins adopt a bent conformation that might place the ectodomain parallel to the cell surface [61].

Caspr and Caspr2 both contain an N-terminal discoidin and a central fibrinogen-like domain, four lamininG (Ln) and two EGF-like domains and 34 or 36 Cys residues making disulfide bonds, respectively. Caspr and Caspr2 are highly glycosylated with 15 or 12 putative N-glycosylation sites, respectively. A combination of biophysical techniques including small angle X-ray scattering and single particle negative stain electron microscopy has been employed to relate an overall compact architecture of Caspr2. Caspr2 displays a three-domain clover leaf feature with a large lobe comprising the Discoidin, Ln1 and Ln2 domains, a middle lobe with the fibrinogen-like and Ln3 domains and a small lobe with the Ln4 domain and with the EGF-like domains providing flexibility between lobes. The dimensions of Caspr2 ectodomain are estimated to be 14 nm long, 9 nm wide and 5 nm thick [62]. The molecule should fit horizontally in the juxtaparanodal axo-glial cleft of putatively 7–15 nm. The ectodomain of Caspr is highly homologous to Caspr2 except for a short motif adjacent to Ln4 termed PGY, since it includes 10-fold imperfect repetitions of Pro-Gly-Tyr. The PGY may act as a conformational ER retention signal in Caspr that compels its association with Contactin to be exported at the cell surface [37]. The PGY may also provide an additional conformational variability to modify the orientation of Caspr relative to the cell membrane plane. Whether the orientation of the long axis of paranodal CAMs forming a ternary complex should be parallel to the axonal membrane or not, remains to be determined using super-resolution microscopy and site-directed antibodies. As a matter of comparison, it has been shown that the related molecules α-Neurexins which are synaptic organizers may lie parallel to the pre-synaptic and post-synaptic membranes. The ectodomain of α-Neurexins consists of six lamininS and three EGF-like domains with a maximum overall length of 16–22 nm. The crystal structure of Neurexin1-α revealed that it adopts an unexpected L-shaped so that it may fit horizontally into the synaptic clefts (12–24 nm) to form trans-synaptic bridges with different partners [63].

Therefore, the question of how the paranodal CAMs may participate in the structure of transverse bands is still unresolved. As discussed below, glycolipids could play a role as implicated in the targeting and stabilization of paranodal CAMs, but do not appear to be concentrated at paranodes. To my knowledge, extracellular matrix components and proteoglycans have not been described at paranodes whereas enriched at the nodal region. Nevertheless, even if located on the side of the myelin loops at the inter-junctional zone, Contactin, Caspr and Neurofascin-155 are strictly required for the formation of transverse bands and for establishing a fixed distance between the apposed axo-glial membranes. Indeed, the junctional gap width was estimated to 6–7 nm in the Caspr KO mice instead of 3.5 nm in the wild-type [19]. Similarly, the axo-glial gap at paranode was estimated to be enlarged in the Contactin KO mice (10.2 versus 5.5 nm in the wild-type) [42]. It is important to note that the presence of transverse bands and the reduced paranodal width are critical parameters that determine the extent to which nodal action currents can be short-circuited underneath the myelin sheath ensuring saltatory conduction.

6. The paracellular barrier function of the paranodes

The paranodal junctions are separating the nodal region enriched in Na^+ channels from the juxtaparanodal region beneath myelin where the K^+ channels are concentrated. An intriguing question is whether the paranodal region constitutes a pathway for current flow to and from the juxtaparanodal K^+ channels. Electrophysiological studies showed that the K^+ channel blockers had no significant effect on conduction except during development [64] or in small caliber myelinated fibers in the CNS [65]. It was therefore important to examine whether the paranodal junctions could be penetrable to ion diffusion. In invertebrates, the septate junctions of the subperineural glia are forming the occluding barrier protecting the nervous system from the high concentration of K^+ in the hemolymph [2]. The classical way to analyze the role of invertebrate epithelial septate junctions in forming a paracellular barrier is to inject fluorescent 10 kDa dextran in the body cavity of *Drosophila* embryos and to assess the dye exclusion from salivary glands or tracheal tube. The role of paranodal junctions as permeability barrier was investigated by injecting a fluorescent 70 kDa (diameter 12–16 nm) dextran tracer in peripheral nerves. The dextran tracer has been shown to penetrate from the nodal gap into the paranodes and to reach the internodal space with a rate (approximately 5 μm in 100–150 min) consistent with diffusion through the helicoidal pathway between paranodal loops rather than across the transverse bands [66]. As an illustration, a 1 μm-diameter axon in the CNS displays a paranode of 5 μm length with 15 myelin lamellae, which corresponds to a helicoidal trajectory of 47 μm. Hence, this pathway may serve as a route for current flow activating the juxtaparanodal channels, and also for antibodies or toxic molecules in pathological conditions. The presence or absence of transverse bands is not correlated with the diffusion parameters of dextran across the paranodes - meaning it is compatible with diffusion through the helicoidal pathway between loops [67].

7. Role of paranodal junctions in the segregation of membrane domains: the paranodal fence function

The paranodal junctions play also a critical role in the segregation of membrane subdomains at the node of Ranvier and participate in the lateral restriction of the nodal gap enriched in Na^+ channels both in the CNS and PNS [68]. Mice that are deficient for one of the paranodal CAMs, Contactin, Caspr or Neurofascin-155, show disrupted paranodal junctions, with the absence of transverse bands and increased axo-glial distance. Also, these mice have broadened Na^+ channel clusters at the node and strikingly, Kv1 channels that are misdistributed at the paranodes instead of being restricted at juxtaparanodes [41–44]. However, the presence of transverse bands is not strictly correlated with the lateral segregation of nodal and juxtaparanodal ion channels. Instead, the submembranous cytoskeleton at paranodes comprising protein 4.1B, αII spectrin and βII spectrin has been shown to function as a boundary restricting the lateral diffusion of Kv1 channels. Indeed, in the βII spectrin KO mice, the transverse bands are intact while the Kv1 channels invade the paranodes [50]. This observation indicates that the paranodal submembranous cytoskeleton rather than the extracellular junctional complex is implicated in limiting the lateral diffusion of membrane channels. Such a paranodal fence function may be based on similar mechanisms than those underlying the lateral diffusion barrier at the axon initial segment (AIS). The restricted lateral diffusion at the AIS has been observed for phospholipids [69] and membrane proteins such as the Na^+ channels [70] and could be related to the high density of membrane molecules tethered at this axonal subdomain according to the picket fence model [71]. More recently, the confinement at the AIS of membrane proteins such as GPI-anchored molecules has been also shown to reflect the periodic arrangement of the submembrane actin rings [72]. Interestingly, the septin cytoskeleton may also be implicated in the segregation of membrane subdomains at the node of Ranvier. Septins are a large family of cytoskeletal GTP-binding proteins conserved from yeast to mammals forming heteromeric complexes and acting as scaffolds to promote compartmentalization of membrane proteins [73]. Multiple septins (including septin 2, 6, 7, 8, 11) are associated with myelin and enriched at the node and paranode [74]. Besides, septin 6 is interacting with the raft-associated proteolipid MAL

Table 2
Neurological disorders associated with the molecular components of paranodal junctions.

Gene	Autoimmune neuropathy	References	Genetic disease	References
Caspr	CIDP, Guillain-Barré syndrome	[98,100]	Congenital hypomyelinating neuropathy	[113,114]
			Arthrogryposis multiplex congenita	[112]
Contactin	CIDP, Guillain-Barré syndrome	[94,98]	Lethal congenital myopathy	[116]
Neurofascin-155	CIDP	[102–104]	Congenital severe hypotonia, amimia and areflexia	[110]
	MS	[88,89]		
4.1B/DAL-1			Tumor suppressor in cancer including meningiomas	[117]

(myelin and lymphocyte protein) that plays a critical role in the maintenance of CNS paranodes [75].

8. Role of glycolipids and lipid rafts in the formation and stabilization of paranodal junctions

Myelinating glial cells elaborate large quantities of a specialized membrane that is ensheathing axons and contains an unusual lipid composition with a large proportion of the glycolipid galactocerebroside (GalC) and its sulfate form sulfatide. GalC is synthesized from ceramide by the ceramide-galactosyl-transferase (CGT) enzyme and sulfatide by cerebroside sulfotransferase (CST). These glycolipids are components of the outer leaflet of myelin and their carbohydrate moieties may be involved in intercellular recognition and potential intermembrane stabilization of the compacted myelin sheath. However, the CGT null mutant mice lacking both galactocerebroside and sulfatide, apparently develop normally myelinated axons but exhibit with age a behavioral phenotype suggestive of dysmyelination with tremor and paralysis and prematurely death. Among ultrastructural abnormalities of myelinated axons in the ventral spinal cord, the nodes of Ranvier are dramatically altered with paranodal loops facing away from the axon and transverse bands that do not form [76]. Precisely, the paranodal junctions initially form at 2 postnatal weeks without transverse bands and thereafter rapidly deteriorate. The absence of transverse bands is correlated with the diffuse distribution of glial and axonal paranodal CAMs, Neurofascin-155 and Caspr [77]. It has been also reported that the Myelin-associated glycoprotein (MAG), which is an Ig-CAM localized at the periaxonal side of the myelin sheath, is interacting with galactolipids to stabilize the paranodal junctions [53]. As observed in CGT-deficient mice, the CST null mice only lacking sulfatide, display strong alteration of paranodes in the PNS and CNS, without clustering of Caspr and misdistribution of ion channels at the node of Ranvier whereas the compact myelin is preserved [78]. By which mechanisms are glycolipids involved in the stabilization of Neurofascin-155 at paranodes? It is known that glycolipids, which are associated with lipid rafts, are involved in the trafficking and topographical organization of membrane proteins. The galactolipids, which are not enriched at paranodes, might be required for the proper targeting or clustering of Neurofascin-155. Neurofascin-155 which is a palmitoylated protein [79] becomes partitioned to the low-density Triton X-100-insoluble fraction, as an indication it is associated with the lipid rafts, only from the second postnatal week in the sciatic nerve, at a developmental stage corresponding to the formation of paranodal junctions [80]. The axonal ligands of Neurofascin-155, the GPI-anchored Contactin and Caspr are also associated with the lipid rafts [35] indicating that the partitioning of the paranodal CAMs into the raft microdomains may favor their assembly and stabilization at the axo-glial junctions. The raft-association of Neurofascin-155 is reduced in the CGT mutant mice as an indication that the galactolipids may favor the assembly of paranodal CAMs within lipid microdomains [80].

Complex gangliosides are widespread in both neuronal and glial membrane and their biosynthesis requires β-1,4-*N*-acetyl galactosaminyl-transferase 1 (GalNac-T) enzyme activity. In particular, the GM1 ganglioside is present at paranodes. As observed for the CGT and CST null mutants, mice deficient for the GalNac-T enzyme show alterations of paranodes with everted myelin loops, absence of transverse bands and mis-distribution of ion channels at the nodes of Ranvier [81]. Selective reintroduction of complex ganglioside expression in neuronal but not in glial membranes rescue the paranodal phenotype [82]. The neuronal gangliosides GT1b and GD1a are trans-receptor for MAG stably associated with sulfatide expressed at the glial membrane [83,84]. Using a combination of mice mutant for CST and GalNac-T, the study from [85] establishes that glial sulfatide and axonal gangliosides play interdependent roles in the tethering of Neurofascin-155 and MAG to maintain the integrity of axo-glial paranodal junctions [86].

9. The paranodal junctions are targeted in autoimmune demyelinating diseases

The question of whether the paranodal junctions could be a vulnerable site for autoantibody attack in demyelinating inflammatory diseases of the CNS and PNS has been tackled (Table 2). Nodal or paranodal antigens have been identified as autoimmune targets in multiple sclerosis (MS) although in a minor subgroup of patients [87–89]. Autoantibodies that recognize both Neurofascin-186 and -155 have been characterized in MS patients. Passive transfer experiments in a rat model of the disease, the experimental allergic encephalomyelitis (EAE), indicate that these anti-Neurofascin autoantibodies may be pathogenic by selectively targeting the nodes of Ranvier, mediating complement deposition, axonal injury and disease exacerbation [88]. Also, the nodal and paranodal domains are vulnerable in an environment of microglial inflammation as observed in MS normal-appearing white matter and EAE [90,91]. Therefore, the disruption of paranodal junctions in inflamed CNS would impinge on normal saltatory conduction and contribute to the disease.

In peripheral autoimmune diseases such as the Guillain-Barré syndrome, myelin breakdown is seen in motor and sensory nerves, and retraction of myelin is observed at nodes of Ranvier leading to focal demyelination. The acute inflammatory demyelinating polyneuropathy (AIDP) is the most common form of Guillain-Barré syndrome in Europe and North America. The axonal variant of Guillain-Barré syndrome, which is the acute motor axonal neuropathy (AMAN), is more commonly found in Asia and has been shown to result from infection with *Campylobacter jejuni* associated with diarrheal illness. Carbohydrate mimicry between human ganglioside GM1 and *Campylobacter jejuni* lipo-oligosaccharides could contribute to the disease [92]. In animal models, passive transfer of anti-galactocerebroside antibodies causes focal paranodal disruption and subsequent demyelination. The immune attack directed against gangliosides (GM1, GQ1b and GD1a) may lead to axonal degeneration and paralysis. Anti-GM1 and anti-GQ1b antibodies bind to peripheral nerves and neuromuscular junctions and anti-GD1a antibodies bind to the node of Ranvier, paranodal myelin and neuromuscular junctions. Upon binding, the antibodies activate the complement cascade, resulting in the formation of the membrane attack complex, disruption of the nodal architecture and dispersion of sodium channel clusters [93]. The relationship between anti-ganglioside antibodies and AMAN is well established, whether less evidence indicates an association with AIDP.

Recently, it has been reported that up to one-third of patients with peripheral diseases, either Guillain-Barré syndrome or chronic

inflammatory demyelinating polyneuropathy (CIDP) show IgG reactivity against the nodes of Ranvier as tested using preparations of teased mouse sciatic nerves [94]. The field of CIDP has undergone a major advance with the identification of autoantibodies against nodal or paranodal proteins in a subset of patients with specific disease phenotypes [95]. CIDP is a very heterogeneous disorder with sensorimotor alterations, predominantly proximal weakness and relapsing or progressive disease. Autoantibodies of the IgG4 subtype directed against Contactin, Caspr or Neurofascin-155 were identified in patients with severe subtypes of CIDP and poor response to intravenous immunoglobulin [96].

9.1. Pathogenic autoantibodies against Contactin

Two independent studies first reported anti-Contactin autoimmunity in Guillain-Barré syndrome and CIDP patients using different strategies, either candidate approach or unbiased mass-spectrometry analysis. In the first study, IgG from a Japanese cohort were analyzed using binding assay on HEK cells transfected with nodal or paranodal CAMs and 12–16% reacted against Contactin [97]. In the second study of Spanish patients, CIDP IgG bound on cultured hippocampal neurons were immunoprecipitated to identify target antigens revealing 4 patients (6%) with antibodies against Contactin mainly of the IgG4 subtype [98]. Passive transfer of anti-Contactin IgG4 purified from these patients is pathogenic in a rat model of autoimmune neuropathy, the experimental allergic neuritis, and induces the selective loss of paranodal markers without demyelination, strong nerve activity loss, progressive clinical deterioration and gait ataxia [99]. After intraneural injection, IgG4 (and not IgG1) access the paranode borders near the nodal gap and fill the paranodal junctions after 3 days (Fig. 3A). The mechanisms by which anti-Contactin IgG4 cause paranode dismantling have been analyzed in vitro in myelinating culture of sensory neurons [40]. Cell aggregation assays indicate that anti-Contactin autoantibodies are function-blocking and prevent the trans-interaction of Neurofascin-155 together with Caspr/Contactin expressed in heterologous cells (Fig. 3C). By preventing assembly of the ternary complex, autoantibodies may, in turn, provoke the lateral dispersion of paranodal CAMs along the axon and disruption of septate-like junctions. Finally, epitope mapping of autoantibodies combined with mutagenesis of the N-glycosylation sites of Contactin pointed to the critical role of N-linked carbohydrates in CAM interaction. The IgG of one CIDP patient were selectively directed against Contactin bearing mannose-rich N-glycans. Strikingly, it was previously shown that oligomannose type sugars of Contactin promote its association with its glial partner Neurofascin-155 [37]. Next, a cluster of 3 N-glycosylation sites (N_{467}, N_{473}, N_{494}) has been mapped on the Ig5 domain of Contactin, which is implicated in Neurofascin-155 binding [40]. Interestingly, the reactivity of IgG from another CIDP patient was precisely dependent on this cluster of N-glycans. Worth noting, the anti-Contactin IgG4 may be pathogenic by interfering with the assemblage of the axo-glial junctional complex. Autoantibodies targeting Caspr at paranodes were also described in CIDP and Guillain-Barré syndrome associated with severe pain [98,100].

9.2. Pathogenic autoantibodies against Neurofascin-155

Antibodies against Neurofascin-155 are also implicated in the pathogenesis of CIDP. Autoantibodies to Neurofascin155, predominantly of the IgG4 subtype, have been identified in CIDP patients (7% of all patients with CIDP) with an aggressive onset. These patients share specific clinical features including predominant distal weaknesses, tremor and ataxia with cerebellar features [101–104]. Sural nerve biopsies show paranodal demyelination in the absence of inflammation and loss of the transverse bands between the paranodal loops and axolemma [105] (Fig. 3B). The pathogenic effects of patient-derived anti-Neurofascin-155 IgG4 have been examined using chronic intrathecal infusion in the rat [106]. Severe clinical deficits are observed with complete tail paralysis and paraparesis associated with slowing nerve conduction in the ventral spinal roots. Paranodal alterations are observed in animals treated with anti-Neurofascin-155 IgG4 without nodal defects or demyelination. However, the pathogenic mechanisms of anti-Neurofascin-155 antibodies are still elusive. They do not

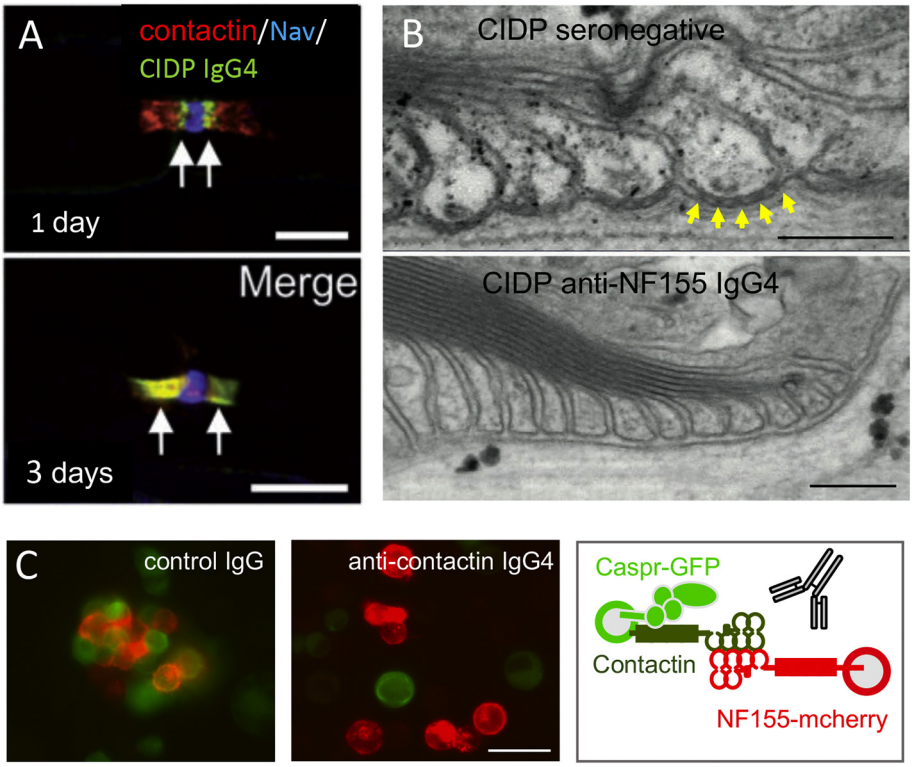

Fig. 3. The paranodal CAMs are targeted by autoantibodies in chronic inflammatory demyelinating polyneuropathy (CIDP).
(A) Anti-contactin IgG4 from CIDP patients (green) progressively invade (arrows) the paranodes of the sciatic nerve after intraneural injection in rats. Teased sciatic nerves 1 or 3 days after injection were immunostained for contactin (red) and panNav (blue) as markers for paranodal and nodal regions, respectively. Bar: 10 µm.
(B) Ultrastructure of sural nerve biopsy from CIDP patients. A selective loss of paranodal transverse bands (yellow arrows) is observed in patients with anti-Neurofascin155 antibodies. Bar: 200 nm.
(C) Anti-contactin IgG4 from CIDP patients display function blocking activity in cell aggregation assays. N2a cells transfected with either Neurofascin-155-mCherry or Contactin/Caspr-GFP were incubated with control or anti-contactin IgGs. Bar: 40 µm.
Adapted from Manso et al. [99] (A), Vallat et al. [105] (B) and Labasque et al. [40] (C).

penetrate the paranodal barrier after intraneural injection of rat sciatic nerves in contrast to anti-Contactin IgG4. Instead, anti-Neurofascin-155 IgG4 are deposited on Schwann cell surfaces and microvilli around the nodes of Ranvier [106]. The autoantibodies to Neurofascin-155 do not perturb the interaction of Neurofascin-155 with its axonal partners Contactin and Caspr, as tested in cell aggregation assays [106]. These autoantibodies are directed against the third fibronectin domain of Neurofascin-155, which is specific for the glial splicing variant. This domain is not implicated in interaction with Contactin since this is the Ig-like domains 5 and 6 which are required for Contactin binding and paranodal assembly [39]. Interestingly, the third fibronectin domain of Neurofascin-155 contains a thrombin cleavage site [107] and is also subject to proteolytic processing by metalloproteases that regulates its adhesive function [108]. Hence, it could be possible that anti-Neurofascin-155 IgG4 may favor Neurofascin-155 shedding by affecting the fibronectin domain structure thus preventing axo-glial interaction with Contactin. Therefore, autoantibodies to Contactin and Neurofascin-155 induce paranodopathies through subtle perturbing molecular mechanisms. These autoantibodies to paranodal proteins, especially IgG4 subclass, are associated with unique features and treatment strategy because often refractory to conventional immunotherapies. IgG4 do not mediate complement attack, or internalization of the target antigens but can interfere with protein-protein interaction [109]. Thus, the primary role of IgG4 anti-paranodal protein antibodies may be the blockade of paranodal assembly -with intact internodes in the absence of inflammation- leading to conduction failure.

10. Genetic disorders associated with paranodal disruption

Recent reports indicate that inherited neuropathies affecting peripheral nerves and neuromuscular junctions are associated with bi-allelic mutations in genes coding for paranodal CAMs (Table 2). Recently a recessive mutation of the Neurofascin gene (*NFASC*) was identified in a proband creating a stop codon in the third fibronectin domain so that it is predicted to selectively affect glial Neurofascin-155 leaving the neuronal isoforms intact. This was confirmed by an immunofluorescence study of skin biopsies showing the absence of glial Neurofascin-155 at paranodes and concomitant loss of axonal Caspr. The child suffered from severe congenital hypotonia, contractures of fingers and toes and no reaction to touch or pain [110]. These pathological features resemble the phenotypic alterations observed in mice with conditional deletion of glial Neurofascin. The lack of paranodal Neurofascin-155 in mice causes a reduction of conduction velocities in peripheral nerves associated with severe defects of motor coordination [43,111].

Loss-of-function mutations in *CNTNAP1* coding for Caspr were identified in patients with a rare neonatal syndrome responsible for hypotonia, weakness and sometimes arthrogryposis. In these patients, abnormal axon myelination is associated with severe abnormalities of the nodes of Ranvier, absence of transverse bands at paranodes and marked reduction of motor nerve conduction velocity [112–114]. Heterozygous mutations in *CNTNAP1* were also identified in a patient with a Charcot Marie Tooth disease, presenting abnormal nerve conduction consistent with focal motor/sensory demyelinating neuropathy [115]. Finally, a mutation in *CNTN1* coding for Contactin was reported in a familial form of lethal congenital myopathy. The underlying cause of muscle weakness could be neuropathic also implicating Contactin at the neuromuscular junctions [116]. Therefore, possible overlapping molecular mechanisms of paranodal damage at peripheral nerves may be involved in both the immune-mediated and the genetic diseases.

11. Concluding remarks

Recent advances in the study of pathogenic mechanisms of inflammatory demyelinating neuropathy with the identification of autoantibodies directed against paranodal CAMs have clinical implications from diagnosis to personalized therapeutic approaches. Besides, these pathogenic autoantibodies appeared to be useful as functional tools to evaluate the molecular basis of CAM interactions at septate-like junctions, i.e. underlining the importance of selective N-glycosylation. In the future, the discovery of novel antigenic reactivity in CIDP may reveal new partners implicated in the assembly of paranodal junctions and highlight their mode of interaction. Molecular structural analyses of Contactin and Caspr family members have unveiled the possibility of a horizontal orientation for the cell-cell adhesive complex allowing it to fit into the reduced intermembrane width at paranodes. Along with nanoscale imaging of the nodes of Ranvier, further studies are needed for the comprehensive understanding of the role of the Caspr/Contactin/Neurofascin-155 complex in the assembly of the ladder-like structure of paranodal junctions.

Transparency document

The Transparency document associated with this article can be found, in online version.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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