Molecular domains of myelinated axons
Elior Peles* and James L Salzer†

Myelinated axons are organized into specific domains as the result of interactions with glial cells. Recently, distinct protein complexes of cell adhesion molecules, Na⁺ channels and ankyrin G at the nodes, Caspr and contactin in the paranodes, and K⁺ channels and Caspr2 in the juxtaparanodal region have been identified, and new insights into the role of the paranodal junctions in the organization of these domains have emerged.

Addresses
*Department of Molecular Cell Biology, The Weizmann Institute of Science, Rehovot 76100, Israel; e-mail: peles@weizmann.ac.il
†Departments of Cell Biology and Neurology, New York University Medical Center, New York, NY 10016, USA; e-mail: jim.salzer@med.nyu.edu

Current Opinion in Neurobiology 2000, 10:558–565

0959-4388/00/$ - see front matter © 2000 Elsevier Science Ltd. All rights reserved.

Abbreviations
CAM cell adhesion molecule
Caspr contactin-associated protein
CGT UDP-galactose–ceramide galactosyltransferase
DLG discs large
DLT discs lost
ECM extracellular matrix
EGF epidermal growth factor
GPI glycosylphosphatidylinositol
LNS laminin A G, neurexin, sex-hormone binding globulin
MAG myelin-associated glycoprotein
NgCAM neuron–glia CAM
NrCAM NgCAM-related CAM
PDZ domain PSD95, DLG, ZO 1 domain
PSD95 postsynaptic density protein 95
ZO 1 zona occludens 1

Introduction
Myelinated fibers are organized into distinct domains: the node of Ranvier, the paranodal and juxtaparanodal regions, and the internode [1,2•]. This domain organization (shown schematically in Figures 1 and 2) is critical for the efficient conduction of nerve impulses via saltatory conduction and results from complex and poorly understood interactions between axons and myelinating glial cells. Recent studies have clarified the unique molecular composition of these axonal domains, demonstrating the presence of several protein complexes which include Na⁺ channels, ankyrin G and cell adhesion molecules (CAMs) at the nodes, contactin-associated protein (Caspr) and contactin at the paranodes, and K⁺ channels and Caspr2 at the juxtaparanodal region. As discussed below, these studies provide new insights into the generation and maintenance of functional domains along myelinated axons.

Molecular composition of axonal domains
The initial segments and nodes of Ranvier
These domains share many features in common, notably an enormous enrichment of voltage-gated Na⁺ channels that are responsible for inward current flow. A major channel subtype at the nodes was recently demonstrated to be Na⁺,1,6 in both sensory and motor axons of the adult peripheral nervous system (PNS) and central nervous system (CNS) [3,4]. As nodes of mice deficient in Na⁺,1,6 conduct action potentials and can be stained with a pan-specific Na⁺ channel antibody [3], other channel isoforms must be present in the node, possibly compensating for this mutation. Specific isoforms of ankyrin G [5•] which bind to Na⁺ channels, potentially via the cytoplasmic

Figure 1

Action potentials propagate via saltatory conduction in myelinated nerves. Action potentials are generated at the initial segment and propagate to and are refreshed at the nodes of Ranvier, the periodic interruptions between myelin segments. Current flows inward at the node of Ranvier reflecting the high local concentration of voltage-gated Na⁺ channels and propagates to the next node of Ranvier because of the high resistance and low capacitance of the surrounding myelin sheath.
domains of the β subunits [6•], are concentrated at the nodes and initial segments. Ankyrin G also interacts and colocalizes with the CAMs NrCAM and a 186 kDa isoform of neurofascin, as well as with the Na+/K+ ATPase. Other nodal components include specific gangliosides and other glycoconjugates [7]. Schwann cell microvilli in the PNS and glial processes of cells expressing the NG2 proteoglycan in the CNS [8] contact the nodal axolemma. Extracellular matrix (ECM) components at the node include tenascin C in the PNS, and tenascin R and phosphacan in the CNS [9].

**Paranodes**

On either sides of the node of Ranvier, the compact myelin lamellae open up into a series of cytoplasmic loops that spiral around, closely appose and form a series of septate-like junctions with the axon (see Figure 2). The paranodal junctions, which are interposed between the node and juxtaparanode, have been proposed to serve the following functions: first, to anchor myelin loops to the axon; second, to form a partial diffusion barrier into the periaxonal space; and third, to demarcate axonal domains by limiting lateral diffusion of membrane components [10]. They also represent a potential site for bidirectional signaling between axons and myelinating glial cells. Recently, the axonal protein Caspr/Paranodin [11,12] was found to be a component of these septate-like junctions [12,13], together with the glycosylphosphatidyl inositol (GPI)-anchored CAM contactin (Rios et al., Soc Neurosci Abstr 1999, 401.5). An alternatively spliced isoform of neurofascin lacking the mucin-like domain and containing the third fibronectin type III (FNIII) domain is also present in the paranodes [14], where it may be present on the axolemma, on the glial loops, or both [15].

**Juxtaparanodes**

This region of the axon is just under the compact myelin sheath beyond the innermost paranodal junction and may therefore be considered a specialized portion of the internode. The delayed-rectifier K+ channels Kv1.1, Kv1.2 and their Kvβ2 subunit are enriched in the juxtaparanodes and may promote repolarization and maintain the internodal resting potential [16–18]. Caspr2, a second member of the Caspr family, colocalizes and interacts with these channels in this region [20••].

**Internodal specialization**

No proteins are known to be specifically enriched in the internode, consistent with the lack of intramembranous particles observed by freeze-fracture studies. An exception is that components of the paranode and juxtaparanode, for

---

**Figure 2**

Longitudinal domains of myelinated axons. A longitudinal section through the nodal region illustrating the organization and composition of axonal domains in relation to their glial ensheathment in the PNS (top half) and CNS (bottom half). In the PNS, the axon is myelinated by a Schwann cell that is surrounded by a basal lamina (BL); in the CNS, myelin is formed by oligodendrocytes. Only a portion of the internode, which is located beneath the compact myelin (CM) sheath, is shown. A spiral of paranodal (green) and juxtaparanodal (blue) proteins extends into the internode in the PNS; this spiral is apposed to the inner mesaxon of the myelin sheath (not shown). K+ channels and Caspr2 are concentrated in the juxtaparanodal region. In the paranodal region, the compact myelin sheath opens up into a series of paranodal cytoplasmic loops (PNL) that invaginate and closely appose the axon, forming a series of septate-like junctions that spiral around the axon. Caspr, contactin and an isoform of neurofascin (NF155) are concentrated in this region. At the node, numerous microvilli (MV) project from the outer collar of the Schwann cell to contact the axolemma; in the CNS, perinodal astroglial processes (PNP) frequently contact the axolemma. The axon is enormously enriched in intramembranous particles at the node that correspond to Na+ channels (Na+ ch). Ankyrin G (ank G) isoforms and the CAMs NrCAM and NF186 are also concentrated in this region.
Potential mechanisms involved in the generation of axonal domains. The initial localization of axonal proteins to distinct domains may be regulated by three mechanisms: (a) intrinsic properties of the axon; (b) soluble factors (S) secreted by oligodendrocytes; and (c) direct contact between myelinating glia and the axon.

**Generation and maintenance of specialized domains**

Dynamic changes in the expression and distribution of Na+ and K+ channels on axons occur during development. In particular, these channels cluster at the node and juxtaparanode respectively during myelination and disperse following demyelination, indicating that myelinating glia play a key role in the generation and maintenance of axonal domains [22]. Recent studies have focused on characterizing the glial signals and the role of intrinsic axonal determinants involved in this remarkable differentiation of myelinated axons; important insights into the molecular interactions responsible for this organization have also begun to emerge.

**Domain formation: glial signals versus intrinsic determinants**

Two related questions have arisen: first, are the requisite glial signals soluble or contact-dependent; and second, are the locations of the nodes of Ranvier determined by the glial cell or intrinsically specified by the axon? These distinct mechanisms are shown schematically in Figure 3. Important insights into both questions have been provided by analyses of the initial events of node formation. In the example Caspr, contactin, Kv1.1, and Kv1.2, extend into the internode as a thin spiral apposed to the inner mesaxon; they are also found apposed to the Schmidt–Lanterman clefts of the myelinating glial cells [12,21*].

Recent tissue-culture studies have directly addressed this question and suggest that, surprisingly, oligodendrocytes and Schwann cells may induce Na+ channel clustering by distinct mechanisms. Oligodendrocytes, but not astrocytes, induce channel clustering on retinal ganglion neurons and this activity is trypsin-sensitive and present in the culture supernatant [29]. These results suggest that the oligodendrocyte factor is a soluble signal, although they do not preclude the possibility that it may be shed from the cell surface and normally act in a juxtacrine fashion. In contrast, clustering of ankyrin and Na+ channels is not induced by conditioned media from myelinating Schwann cells; rather, clustering requires contact, and clusters form in close association with myelinating Schwann cells; rather, clustering requires contact, and clusters form in close association with myelinating Schwann cells [25]. The identity of these two glial-clustering activities and whether they are related is not yet known. These studies do suggest that the mechanisms of clustering may differ between the CNS and PNS, possibly reflecting the fact that central nodes may be free of direct contact by glial processes [30] whereas peripheral nodes are in contact with Schwann cell microvilli.

How is the position of nodes determined? The clusters of Na+ channels induced by soluble oligodendrocyte factors are spaced at a distance approximately 100 times the axon caliber, as is expected for nodes of Ranvier, suggesting that the localization of nodes is determined by intrinsic properties of the axon [29]. Conversely, Schwann cell contact appears to have an instructive role in the positioning of the nodes of Ranvier on the basis of analysis of the hypomyelinated mouse mutant *Claw Paw* [31]. These mice exhibit delayed peripheral myelination and have substantially shorter internodes; significantly, Na+ channel clusters are invariably associated with the ends of the shorter myelin segments. Variation in the length of internodes is also observed in the shorter segments characteristic of...
Specialized domains along myelinated axons contain multi-protein complexes. (a) At the nodes of Ranvier, Na+ channels (Na+ ch) are anchored by ankyrin G, which also binds the cytoplasmic tail of the two CAMs NrCAM and NF166. The extracellular regions of Na+ channels also interact with tenasin C, tenasin R, and phosphacan. The localization of the Na+ channels–ankyrin G complex at the nodes may be regulated by interactions of N-CAM, neurofascin and Na+ channels themselves with ligands (labeled by question marks) present on the surface of the contacting Schwann cell microvilli in the PNS or perinodal astrocyte in the CNS. (b) At the paranodes, Caspr is found in association with the GPI-anchored CAM contactin. This creates a receptor complex that is thought to bind an, as yet unknown, ligand found on the opposing paranodal loop. The NF155 isoform of neurofascin, a protein that interacts with contactin, is also present in this region, where it is found on the glial loop. The cytoplasmic domain of Caspr contains a motif that binds members of the protein 4.1 family, which connect membrane proteins to the spectrin cytoskeleton. (c) At the juxtaparanodes, the delayed-rectifier K+ channels (K+ ch) Kv1.1, Kv1.2 and their Kv2 subunit are associated with Caspr2. This association requires the carboxy-terminal tail of both, Caspr2 and the α subunits of the channel, and is probably mediated by interaction with a PDZ-domain-containing protein. C, carboxy-terminal tail; MBD, membrane-binding domain; S, spectrin-binding region.

Remyelination and in the progressive longitudinal growth of developing myelin segments relative to that of the axon [32]. Together, these results indicate that final internodal length, and therefore node location, is determined by the Schwann cell. It is possible that both mechanisms take place, with an initial phase of random clustering of Na+ channels along the length of the axon followed by a contact-dependent positioning of mature nodes.

**Domain formation: temporal and functional relationships**

Is the formation of the node of Ranvier and that of neighboring axonal domains interrelated, or do these domains form independently? Freeze-fracture studies of developing peripheral nerves have demonstrated that paranodal junctions form in a specific sequence, beginning closest to the node and then extending inward [26]. These studies were interpreted as suggesting that clustering of Na+ channels at the node depends on paranodal junction formation; an alternate interpretation is that as the node itself forms, it initiates formation of the adjacent paranodal junctions. Using newly defined markers, the temporal sequence of the formation of these domains has been reexamined. In the developing optic nerve, Caspr clustering slightly precedes, and is immediately adjacent to, Na+ channel clusters, suggesting that channels cluster by exclusion from these zones of close contact [27]. In contrast, in the PNS, Na+ channel clusters are present in the developing sciatic nerve, as well as in myelinating co-cultures, just prior to clustering of Caspr and therefore of paranodal junction formation (C Melendez-Vasquez, G Zanazzi, J Salzer, unpublished data). K+ channel clustering occurs after a significant delay relative to that of Na+ channels and may depend on the paranodal junctions for their proper segregation into the juxtaparanodes [18,33].

More direct evidence for a role of the paranodal junctions in the organization of axonal domains has been provided by analysis of mice in which the enzyme UDP-galactose–ceramide galactosyltransferase (CGT) was disrupted [34••]. These mice are unable to synthesize two major myelin galactolipids, galactocerebroside (GalC) and its sulfated derivative, sulfatide, and abnormally express glucocerebroside. Unexpectedly, compact myelin was able to form in these mice but the nodal and paranodal regions were significantly perturbed in the CNS, with a high frequency of the terminal loops facing away from the axon [35•]. In the PNS, the anatomy of the paranodes was fairly normal except that the transverse bands, which are the hallmark of the paranodal junctions, were missing. Strikingly, although the clustering of Na+ channels, ankyrin G, and neurofascin at the node was minimally affected, the distributions of Caspr/paranodin and K+ channels were dramatically perturbed. K+ channels were frequently mislocalized to the paranodes or diffusely localized along the internode, whereas Caspr was no longer tightly confined to the paranodes. Of particular interest is that the strict separation between Na+ and K+ channels that is a prominent
feature of normal axons was frequently absent [34**].
These results clearly indicate that nodes are able to form independently of the paranodal junctions, whereas the junctions appear to be a prerequisite for the delineation of axonal domains, including the appropriate localization of K+ channels to the juxtaparanodes.

Mechanisms of domain formation
Recent studies have revealed that each of these domains contains a unique set of CAMs that exist as multi-protein complexes; in the node and juxtaparanodes, these complexes are linked to ion channels via scaffolding molecules in the cytoplasm. These complexes, in turn, are likely to be recruited to these sites as a consequence of extracellular interactions with components of the ECM and receptors on glial processes and, potentially, through interactions with the axon cytoskeleton. The composition and potential interactions of these multi-protein complexes are illustrated in Figure 4 and are considered further below.

Na+ channels at the nodes and initial segments
At the nodes and initial segments, Na+ channels are believed to be in a macromolecular complex with ankyrin G and the CAMs NrCAM and neurofascin (see Figure 4a). The sequence of complex assembly has been analyzed during the development of peripheral nodes [23]. Neurofascin and NrCAM were found to cluster first, suggesting that these CAMs initiate node formation, and ankyrin and Na+ channels are subsequently recruited to these sites. Binding of ankyrin to these CAMs, and therefore its recruitment to nodes, may be regulated, as phosphorylation of the carboxy terminus of these CAMs inhibits ankyrin binding and is under developmental control [36]. NrCAM and neurofascin could potentially be recruited to the node by binding to, as yet unknown, counter receptors on glial processes associated with nascent nodes of Ranvier [26] or components of the ECM such as tenascin or phosphacan. In addition to these CAMs, the β subunits of the Na+ channel are members of the immunoglobulin (Ig) gene superfamily and can mediate homophilic interactions [6*]. The β2 subunit contains an Ig-like domain homologous to the CAM contactin and interacts with tenascin [37,38*]. An interaction of Na+ channels with tenascin may stabilize nodal complexes but is dispensable for the initial clustering and appropriate distribution of these channels [9].

In the initial segments, the sequence of assembly appears to differ from that in the nodes. In particular, ankyrin G is concentrated in the proximal segments of the axons of cultured neurons even in the absence of glial cells [39] where it may present a lateral diffusion barrier for integral membrane proteins [40*]. Evidence that ankyrin G indeed plays a key role in organizing these domains, in particular in the formation of initial segments, has emerged in a tissue-specific knockout of this protein in the cerebellum [41]. These knockout mice exhibit impaired action-potential initiation, and Na+ channels and neurofascin fail to concentrate appropriately in the initial segment. Taken together, these results suggest that intrinsic determinants of the axon initial segment, potentially other cytoskeletal elements, are responsible both for the local concentration of ankyrin, and secondarily for ankyrin-binding CAMs, in this region. By contrast, CAMs may be redistributed to presumptive nodes as a consequence of glial ensheathment and may subsequently recruit ankyrin and Na+ channels to these loci.

Caspr at the paranodes
The localization of Caspr and the development of the septate junctions is strictly dependent on the maturation of the myelinated fiber, suggesting a role for the glial cells in this process [13,27]. Further support is provided by the localization of Caspr to the discrete regions of the axolemma that appose the mesaxon and Schmidt–Lanterman incisures of myelinating Schwann cells [21*]. The extracellular region of Caspr is a mosaic of domains implicated in mediating protein–protein and protein–carbohydrate interactions, including discoidin- and fibrinogen-like domains, EGF motifs and LNS domains [11,42]. LNS domains bind several ligands, including membrane and ECM proteins, heparin and sulfatides [43*,44]. The latter is of particular interest given that Caspr is not confined to the paranodes in CGT knockout mice [34**]. These results raise the possibility that direct binding of Caspr to galactolipids may regulate its localization. However, there is no evidence for the accumulation of galactolipids at the paranodes. Alternatively, given the role of galactolipids in protein trafficking, it is possible that the lack of galactolipids may result in the absence of Caspr ligand from the glial loops.

The only protein known to bind the extracellular domain of Caspr is contactin/F3 (Figure 4b) [11], a GPI-anchored protein that is found along with Caspr at the paranodes in the PNS and the CNS (Rios et al., Soc Neurosci Abstr 1999, 401.5). Binding of contactin to Caspr occurs when both proteins are on the surface of the same cell (cis-interactions) [11], and involves the fibronectin type III domains and the GPI-anchor of contactin [45*]. Furthermore, this association is required for the cell-surface expression of Caspr [45*]. Treatment of myelinated co-cultures with a soluble RPTPβ (receptor protein tyrosine phosphatase β)-Fc protein, which binds tightly to contactin, perturbs the localization of the Caspr–contactin complex at the paranodes, suggesting that its localization is determined by extracellular interactions (Rios et al., Soc Neurosci Abstr 1999, 401.5). These results raise the possibility that a single glial ligand that binds to either member of the complex may be sufficient to direct both Caspr and contactin to the paranodes. Although such a protein remains to be discovered, one candidate is the glial form of neurofascin [15], a protein that binds the chick homologue of contactin F11 [46]. Members of the Caspr family also interact with protein 4.1 [12,47,48], which connects membrane proteins to...
spectrin and the cytoskeletal network [49]. Thus, localization of Caspr at the paranodes may include an initial targeting of the Caspr–contactin complex by virtue of the interaction of this complex with a glial ligand, followed by stabilization of the complex through additional interactions with cytoskeletal adapter molecules.

**K⁺ channels at the juxtaparanodes**

Subcellular targeting and localized clustering of ion channels was proposed to be regulated by scaffolding molecules such as members of the PSD95 family [50]. Although the presence of a PSD95-like protein in the juxtaparanodes along with K⁺ channels was recently demonstrated [51], the exact molecular identity of this protein is still unknown. Insight into the mechanism by which ensheathing glial cells regulate the localization of K⁺ channels was recently provided with the identification of Caspr2, the second member of the Caspr family [20••]. At the amino acid level, Caspr2 is more related to Drosophila neurexin IV (Nrx-IV) than Caspr is, and also contains a short amino acid sequence at its carboxyl terminus that serves as a binding site for type II PDZ domains. Caspr and Caspr2 are both expressed on axons; in contrast to Caspr, however, Caspr2 was shown to localize with K⁺ channels in the juxtaparanodal region in both PNS and CNS fibers. It was demonstrated that Caspr2 associates with Kv1.1, Kv1.2 and Kvβ2 subunits, probably through a PDZ-domain-containing protein, thus linking a cell recognition molecule to ion channel clustering (Figure 4c) [20••]. One potential candidate for this PDZ-domain-containing protein is discs lost (DLT), a Drosophila protein that is required for proper localization of Nrx-IV [52•]. This protein contains four PDZ domains, two of which interact with the carboxy-terminal tails of Nrx-IV and Crumbs, another cell surface molecule containing EGF and LNS domains that is required for establishment of epithelial polarity [52•,53]. Whether the vertebrate homologue of DLT will be found at the juxtaparanodes and shown to be involved in K⁺ channel and Caspr2 clustering is not yet known. Connecting cell recognition with the localization of ion channels may be an important general mechanism employed at other specializations of the neuron, notably at the synapse. Thus, Shaker K⁺ channels associate with the cell recognition molecule fasciclin II through the PDZ-containing protein DLG (discs large) at the neuromuscular junction of Drosophila [54], and neurexin associates with PSD95, a scaffolding protein that binds NMDA receptors and K⁺ channels at the postsynaptic cleft [55].

**Conclusions**

Recent studies implicate intrinsic and extrinsic signals in the generation, localization and maintenance of specialized microdomains of myelinated axons. It is likely that, within the axon, multi-protein complexes organized by scaffolding molecules are appropriately targeted via interactions with glial ligands. Given the rapid pace of progress, the molecular identity of the glial signals, as well as an understanding of the mechanisms of channel clustering and node formation, is likely to emerge soon.

**Update**

The work described as Rios et al., Soc Neurosci Abstr 1999, 401.5 is now in press [56•,57•].

**Acknowledgements**

Due to space limitations, we regret any omissions in citing other relevant publications. We thank George Zanazzi, Jack Rosenbluth and Steve Lambert for helpful comments on the manuscript and Jill Gregory for assistance in preparing the figures. Work from the authors’ laboratories cited in this review has been supported by grants from the National Institutes of Health and from the National Multiple Sclerosis Society. E Peles is Incumbent of the Madeleine Haas Russell Career Development Chair.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest


22. Vabnick I, Trimmer JS, Shragar P, Peles E: Ankyrin G is required for clustering of voltage-gated Na channels in the proximal segment even in the absence of glial cells, indicating that this region is intrinsically specified; multiple regions of ankyrin G are involved in its targeting and function of ankyrin G in this domain. Ankyrin G is concentrated in the proximal axon segment requires both its GPI-anchor and its fibronectin type III repeats. J Cell Biol 1998, 149:1295-1304.


24. Benzer S, Davis JQ, Bennett V: The glycosylphosphatidyl inositol-anchored Na+ channel beta subunits of Na+ channel may function as a homophilic CAM and recruit ankyrin to cell–cell junctions in transfected Drosophila S2 cells. Together with [6,37], these studies show that the auxiliary β subunits mediate interactions of the Na+ channel with extracellular proteins and may play a role in their localization at the node.


This study analyzed the formation of the node and juxtaparanodes in the CGT knockout mouse, which is unable to synthesize galactocerebroside and fails to form septate-like junctions. Sodium channels still cluster at the nodes, indicating that initial node formation does not require paranodal junctions, whereas generation of the juxtaparanodal domain is perturbed.


An up to date discussion of the function of myelin galactolipids in axon–glial interactions.


The authors demonstrate that the β subunits of Na+ channel may function as a homophilic CAM and recruit ankyrin to cell–cell junctions in transfected Drosophila S2 cells. Together with [6,37], these studies show that the auxiliary β subunits mediate interactions of the Na+ channel with extracellular proteins and may play a role in their localization at the node.


This paper and [39,41] characterize the proximal segment of the axon and the targeting and function of ankyrin G in this domain. Ankyrin G is concentrated in the proximal segment even in the absence of glial cells, indicating that this region is intrinsically specified; multiple regions of ankyrin G are involved in its targeting [39]. Similarly, certain membrane proteins exhibit a polarized accumulation at the initial segment as the result of a diffusion barrier; this barrier is maintained in the absence of cell–cell contact and depends on the cytoskeleton [40]. A cerebellar-specific knockout of ankyrin G confirms its crucial role in organizing the initial segment, as Purkinje cells from these mice do not initiate action potentials or accumulate neurofascin appropriately [41].


This paper describes the structure of the LNS domain of neurexin Iβ. It is composed of two antiparallel seven-stranded β sheets arranged in a globular fold, similar to lectins and lectin-like domains.


This study demonstrates that contactin promotes the expression of Caspr at the cell surface by recruiting it into lipid rafts. This function of contactin requires both its GPI-anchor and its fibronectin type III repeats.


52. Bhat MA, Iazaddoost S, Lu Y, Cho KO, Chei KW, Bellen HJ: Discs • Lost, a novel multi-PDZ domain protein, establishes and maintains epithelial polarity. Cell 1999, 96:833-845. This paper describes the identification of DLT, a multi-PDZ Drosophila protein that interacts with the carboxyl terminus of neurexin IV and is required to maintain its localization at the septate junctions. DLT precedes the expression of neurexin IV and extends into the apical portion of the septate junction; it plays a key role in establishing and maintaining the molecular complexes of the apical domain.


This paper describes evidence that Caspr and a lower molecular weight isoform of contactin form a cis complex at the neuron surface that is targeted to the paranodal junctions and juxtaaxon during myelination; targeting is disrupted by treating myelinating cocultures with receptor protein tyrosine phosphatase β (RPTPβ-Fc), suggesting that extracellular interactions with a glial ligand are involved. Contactin not associated with Caspr is also present at central nodes of Ranvier, suggesting that its distribution is regulated via its association with Caspr.

57. Tait S, Gunn-Moore F, Collinson JM, Huang J, Lubetzki C, Pedraza L, Sherman DL, Colman DR, Bredy PJ: An oligodendrocyte cell adhesion molecule at the site of assembly of the paranodal axo–glial junction. J Cell Biol 2000, 150:657-666. This paper reports that in the CNS, an isoform of neurofascin (NF155) is expressed by oligodendrocytes in the paranodal region; it is similarly found in the paranodes of peripheral myelin. NF155 is thus the first glial CAM of the paranodal junction to be identified; it is therefore a candidate to interact with axonal proteins in these junctions.