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Review

GPI-anchored proteins at the node of Ranvier

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ABSTRACT

Contactin and TAG-1 are glycan phosphatidyl inositol (GPI)-anchored cell adhesion molecules that play a crucial role in the organization of axonal subdomains at the node of Ranvier of myelinating fibers. Contactin and TAG-1 mediate axo-glial selective interactions in association with Caspr-family molecules at paranodes and juxtaparanodes, respectively. How membrane proteins can be confined in these neighbouring domains along the axon has been the subject of intense investigations. This review will specifically examine the properties conferred by the lipid microenvironment to regulate trafficking and selective association of these axo-glial complexes. Increasing evidences from genetic and neuropathological models point to a role of lipid rafts in the formation or stabilization of the paranodal junctions.

1. Introduction

Contactin and TAG-1 are glycan phosphatidyl inositol (GPI)-anchored cell adhesion molecules belonging to the immunoglobulin superfamily (Ig-CAMs) and have been studied extensively for their function during neuronal development. Contactin and TAG-1 interact with multiple ligands including Ig-CAMs and extracellular matrix components and participate to neuroblast migration, axonal growth, fasciculation and guidance, and synaptic function [1–4]. Another important role of Contactin and TAG-1 was discovered in the organization of axonal subdomains at the node of Ranvier of myelinating fibers where they mediate axo-glial selective interactions in association with Caspr-family molecules. This review will examine this last role with a special focus on the properties conferred by their lipid anchor and raft-partitioning.

2. Molecular organization of the axonal subdomains at the node of Ranvier

The node of Ranvier is an attracting model for studying the mechanisms of membrane segregation along the axolemma (Fig. 1A). The formation of nodes is induced by contacts with myelinating glial cells that are ensheathing the axon, the oligodendrocytes in central nervous system (CNS) and Schwann cells in peripheral nervous system (PNS). The nodal gap is highly enriched in voltage-gated sodium and KCNQ channels and the Ig-CAM Neurofascin-186. On both sides of the node, the paranodal junctions anchor the terminal cytoplasmic loops of the myelin onto the axolemma. The paranodes are characterized by septate-like junctions that consist in regularly-spaced intermembrane transverse bands. Paranodal junctions depend on interactions among three CAMs, Contactin and Caspr/paranodin on the axon and Neurofascin-155 on the glial cell. Next, the juxtaparanodal regions are enriched in Shaker-type Kv1 channels co-clustered with TAG-1 and Caspr2. How membrane proteins can be confined in these neighbouring domains along the axon has been the subject of intense investigations over the last years [5–7]. Multiple complementary mechanisms may be implicated such as clustering of adhesive complex mediated by glial ligands, anchoring of CAMs and ion channels by axonal cytoskeletal scaffolds and/or selective trafficking and targeting of transport vesicles towards the axonal subdomains [8].

2.1. Role of Contactin at the paranodal region

Deficiency in either Contactin or Caspr/paranodin, induces severe neurological defects, aberrant organization of the paranodal region and reduction of nerve conduction velocity [9,10]. In both these knock-out mice, the septate-like junctions are disrupted and some terminal loops of the myelin are everted not facing the axolemma (Fig. 1B). The distribution of Contactin and Caspr are

Abbreviations: GPI, glycan phosphatidyl inositol; Ig-CAM, cell adhesion molecules of the immunoglobulin superfamily; CNS, central nervous system; PNS, peripheral nervous system; FNIII, fibronectin type III; ER, endoplasmic reticulum; MAL, myelin and lymphocyte protein; CGT, ceramide galactosyl transferase; MS, multiple sclerosis; EAE, experimental allergic encephalomyelitis

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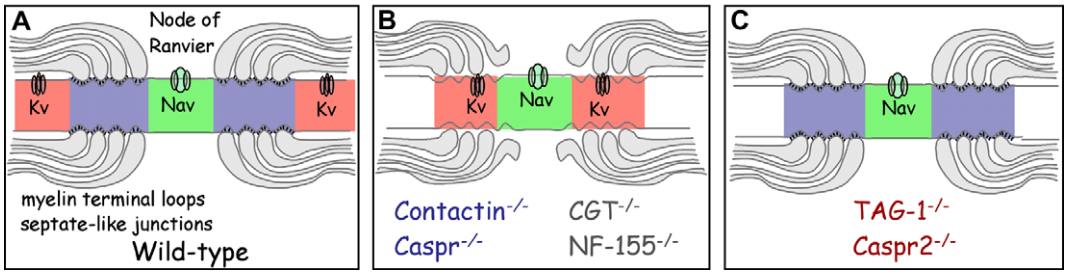

Fig. 1. The axonal subdomains of the node of Ranvier. (A) In wild-type animals, the node of Ranvier (green), which contains high density of voltage-gated sodium channels (Nav) is flanked by the paranodal junctions (blue). Next, the juxtaparanodes (red) are enriched in Kv1 channels. Phenotype of mutants for paranodal junctions (B) and juxtaparanodes (C).

interdependent at paranodes. Indeed, in Caspr-deficient mice, Contactin is not detected at paranodes and becomes enriched at the nodal gap in the CNS. Reciprocally, in Contactin$^{-/-}$ mutant mice, Caspr is not addressed to the axolemma. In the two types of mutants, the clustering of sodium channels at the nodal region is still observed, which is displaying an enlarged distribution. In addition, the distribution of Caspr2 and Kv1.1/1.2 channels is strongly modified since these components are found at paranodes instead of juxtaparanodes. Therefore, paranodal junctions act as a fence separating the lateral domains enriched in sodium and potassium channels. As a consequence, the velocity of nerve conduction is decreased. Genetic disruption of Neurofascin-155 expression in myelinating glial cells prevents clustering of the axonal Caspr/Contactin complex and results in alteration of paranodal junctions [11–13]. In the different genetic animal models generating disruption of septate-like junctions (mutant mice for Caspr, Contactin or Neurofascin-155), axonal swelling and degeneration is observed in Purkinje cells. Axonal transport seems to be disturbed with mis-orientation of microtubules and neurofilaments together with accumulation of mitochondria and smooth endoplasmic reticulum (ER) at the paranodal region [14]. These observations indicate a correlation between the disruption of septate-like junctions and axonal degeneration.

2.2. Role of Contactin at the nodal gap

Expression of axonal CAMs at paranodes and juxtaparanodes is similar in the PNS and CNS, but differs at the node. Neurofascin-186 is found at the node both in the CNS and PNS, Contactin is present at the node only in the CNS and NrCAM only in the PNS [12,15]. In the PNS, the nodal extracellular matrix protein gliomedin is secreted by Schwann cell microvilli and binds Neurofascin-186 and NrCAM on the axon initiating the clustering of the voltage-gated sodium channels through ankyrin$_G$ scaffolding [16]. In the CNS, the nodal extracellular matrix contains Versican V2 secreted by the perinodal astrocyte, which assembles tenascin-R and phosphacan [17,18] (Fig. 2). This complex of matrix components by virtue of its ability to bind Neurofascin-186 and Contactin may be crucial for the clustering of the voltage-gated sodium channels. Indeed, Contactin displays a broad activity of binding and interacts with the β1-subunit of the voltage-gated sodium channels, Neurofascin-186, tenascin-R, and phosphacan/RPTPßz [19–21].

Neuronal sodium channels are heterotrimers composed of the pore-forming α-subunit and two auxiliary β-subunits. The β-subunits contain an extracellular Ig domain with homology with CAMs that allows binding with CAMs and extracellular matrix components. The β2-subunit displays homology with Contactin [22] and interacts with tenascin-C and tenascin-R [23,24]. The β1-subunit shares similarity with the myelin CAM Po and interacts with Neurofascin-186, RPTPß and Contactin [21,25,26]. Contactin co-transfected in mammalian fibroblasts together with the α- and

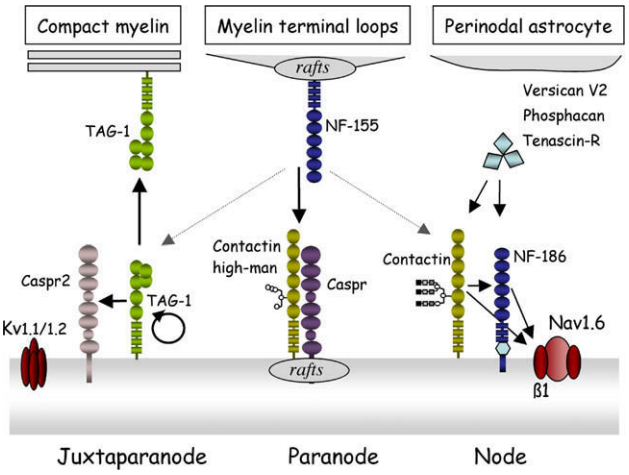

Fig. 2. Segregation of ion channels and CAMs in distinct axonal subdomains of the node of Ranvier in the CNS. Members of the Ig-CAM family show broad binding activity (arrows). Their selective association requires fine-tuning by N-glycosylation (Contactin), alternative splicing (Neurofascin) or raft-partitioning.

β1-subunits of the sodium channel Nav1.2, increases the sodium currents due to a higher density of sodium channels at the surface membrane as assessed by ^{3}H-saxitoxin binding [27]. These results point out the role of Contactin for enhancing sodium channel expression at the cell surface through interactions with the β1-subunit, by increasing channel insertion or stabilization in the membrane.

2.3. Role of TAG-1 at the juxtaparanodes

TAG-1/Axonin-1/Contactin-2, originally described as a protein transiently expressed in axons during development [3], is the juxtaparanodal counterpart of Contactin (48% amino acid identity), which has the particularity to be expressed by both neurons and myelinating glial cells [28]. The phenotype of TAG-1-deficient mice indicates that this protein is crucial for juxtaparanodal organization and required for Caspr2 and Shaker-type Kv1 channels enrichment in this region in the CNS and PNS (Fig. 1C) [29]. Similarly, Caspr2-deficient mice display alteration of TAG-1 and Kv1 clustering at juxtaparanodes [30]. From these studies, a tripartite complex has emerged at juxtaparanodes formed by cis-interaction (heterophilic) between TAG-1 and Caspr2 within the axolemma and by trans-interaction (homophilic) of neuronal TAG-1 with TAG-1 present on the glial membrane. The nodal gap and paranode organization do not appear to be affected in both the sciatic and optic nerves of TAG-1-deficient mice [29], but recently some more quantitative studies indicated shorter internodes in particular in the optic nerve [31,32]. Interestingly, the myelin sheath thickness and