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Review Article

Beyond the Nodes of Ranvier

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Abstract

There are two types of neuroglia in the peripheral nervous system. Satellite cells and Schwann cells. Schwann cells' cytoplasm wraps around axon in certain intervals, insulates them, helps to conduct the action potential and propagates the messages from cell bodies to target cells in a speedy manner. The myelin sheaths are disconnected at nodes of Ranvier. Here, we had an overview beyond the nodes of Ranvier. In fact, a precise view of the molecular structure of a node of Ranvier, paranode, juxtaparanode and internode.

Keywords: *Nodes of Ranvier; Paranode; Juxtaparanode; Internode*

Introduction

Nodes of Ranvier was discovered by the chairman of Anatomy at the Collège de France and physiologist Claude Bernard' student, Louis-Antoine Ranvier (1835-1922) [1]. Mastering several staining techniques including, classic carmine used by Ludwig von Mauthner (1860) who first reported the concentric organization of myelin and periaxonal sheath beneath myelin. Ranvier reported that myelinated axons of mouse thoracic and rabbit sciatic nerves were stained by Carmine and silver nitrate only at regular intervals. Using osmic acid and absence of myelin in certain intervals, Ranvier 1872, announced two important points as follows: One nucleus per internodes and in equal intervals in each node. The size of the axon is proportional to internodes and internode proportional to fiber diameter. Internodes grow longer during development [2].

Schwann cells

There are two types of neuroglia in the peripheral nervous system. Satellite cells and Schwann cells. Schwann cells have an important role in the maintenance and function of the peripheral nerves and accelerate conduction velocity by wrapping their cytoplasm (myelin sheath) around axons called myelination. The myelin sheath is disconnected at intervals leads to limiting the sites of ionic transfer along the axon to the nodes of Ranvier, resulting in a faster, jumping action potential propagation that is termed, saltatory conduction [3].

In myelinated fibers, the axoglial contacts show a very high level of spatial and temporal organization, representing one of the most elegant types of cell-cell interaction.

- The nodes are encapsulated by microvilli emanating from the outer aspect of the Schwann cell membrane in the PNS.
- Each node of Ranvier is flanked by paranodal regions where helicoidally wrapped glial loops are attached to the axonal membrane by a septate-like junction.
- The outermost part, in contact with paranodes, is referred to as the juxtaparanodal region.
- The segment between nodes of Ranvier is termed the internode.

The underlying axon is organized in distinct functional domains, containing different sets of ion channels, cell adhesion molecules and cytoskeletal linker proteins [4-6] (Figure 1).

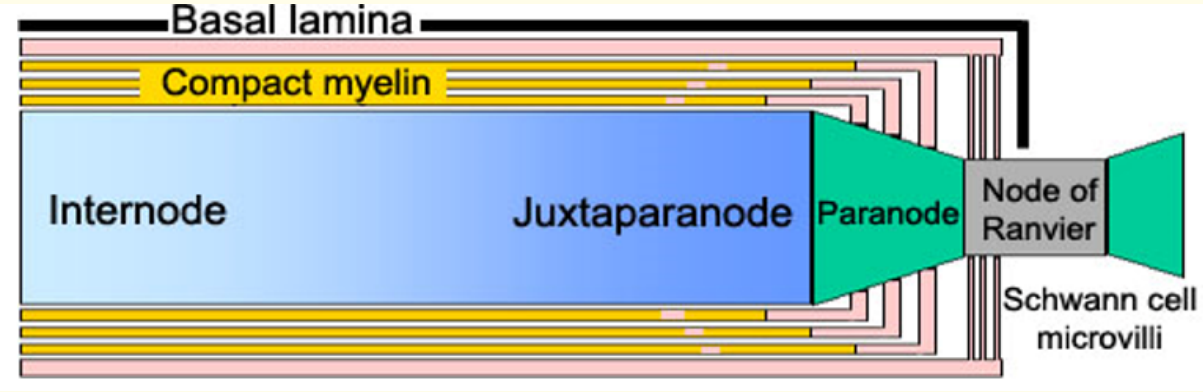

Figure 1: *Specialized region of nodes of Ranvier (Schwann cell microvilli), paranode (Myelin loops), juxtaparanode (Compact myelin) and internode.*

In the PNS, Schwann cell projections, known as microvilli, closely oppose the node of Ranvier. These processes, lead to the impression that in the PNS direct contact is required for the formation of the node. In PNS microvilli a great number of ezrin, radixin, moesin (ERM)-proteins seem to be crucial for the Na1 channel clustering during nodal formation [7].

Two cell adhesion molecules of the L1 family of the immunoglobulin superfamily (IgSF) are essential for sodium channel accumulation at the node and the establishment of axo-glial contact, NrCAM and the 186 kDa isoform of Neurofascin, NF186. NrCAM is expressed both by glial cells and neurons, while NF186 is found exclusively on the axon. gliomedin was identified in Schwann cell microvilli early during nodal formation. Gliomedin belongs to the family of olfactomedin- related molecules and contains collagen repeats and a single olfactomedin domain that enables it to interact with both NrCAM and NF186 [5,8,9].

Nodal formation and stabilization relies to a great extent on the connection of membrane proteins with the cytoskeleton. Submembranous cytoskeletal proteins in the stabilization of molecular complexes at and near nodes. Axonal ankyrin-spectrin complexes stabilize Nav channels at nodes [10-12].

Paranode

Paranodes or the edge of the node of a myelinated axon are characterized by septate-like junctions formed at the axo-glial contact sites. It serves as a membrane barrier for the segregation of sodium (at nodes of Ranvier) and potassium channels (at juxtaparanodes). Paranode is essential for proper function of myelinated fibers and action potential propagation along the axon [5,13,14].

Three molecules are implicated in maintenance of paranodes, ion channel establishment and proper nerve conduction including Contactin (Contactin- 1 or Cntn-1 or F3) and neurofascin (NF155) which are detected on the axonal and glial cell membrane, respectively. The third molecule is contactin-associated protein (Caspr). This molecular interaction indicates axon-glia adhesion [7] (Figure 2).

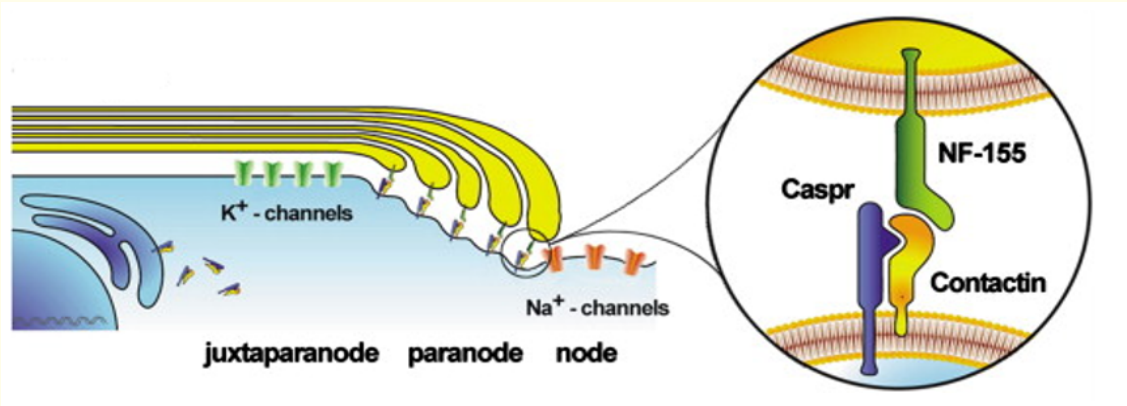

Figure 2: *Molecular organization of paranode.*

The paranodal complex is linked to the actin cytoskeleton through the interaction of the intracellular domain of Caspr with the cytoskeletal adapter protein 4.1B, αII-spectrin, βII-spectrin, ankyrin B and actin organization [12].

Juxtaparanode

The juxtaparanodal complex consists of TAG-1 (Axonin-1/Contactin-2), a GPI anchored adhesion molecule of the IgSF, present on the glial and axonal membranes as well as the Neurexin protein Caspr2 and the Shaker-type voltage-gated potassium channels (VGKCs) on the axon [15]. In addition to the cytoskeletal adapter protein 4.1B, postsynaptic density protein 93/chapsyn-110 and postsynaptic density protein 95 (PSD-93 and PSD-95) [16]. ADAM-22, a transmembrane protein with an extracellular disintegrin and a catalytically inactive metalloproteinase domain. ADAM-22 is responsible for the assembly of PSD-93 and PSD-95 scaffolding proteins at the juxtaparanodes but not for potassium channel clustering [17].

Internode

Internode is the largest domain of the myelinated fiber and is the area of compact myelin between adjacent nodes of Ranvier. Internode is characterized by small parts of looser myelin compaction, the Schmidt-Lanterman incisures. Myelin-associated glycoprotein (MAG), is expressed in the periaxonal glial membrane by oligodendrocytes and Schwann cells during myelination while is also localized in the Schmidt-Lanterman incisures at later stages. Multiple MAG interactors have been identified so far but none of them seems to be crucial for the internodal axon-glial interactions. The nectin-like family of adhesion molecules key regulators of the intermodal domain organization which are linked to the 4.1 protein via a FERM-binding domain. Necl is present at the Schmidt-Lanterman incisures.

Necl2 (SynCAM1) is also localized at the internodal axolemma, whereas Necl4 (SynCAM4) is the only nectin-like protein expressed by Schwann cells. Necl4 are expressed early on apposed membranes along the internode and mediate axon-Schwann cell adhesion via strong heterophilic interaction (Figure 3).

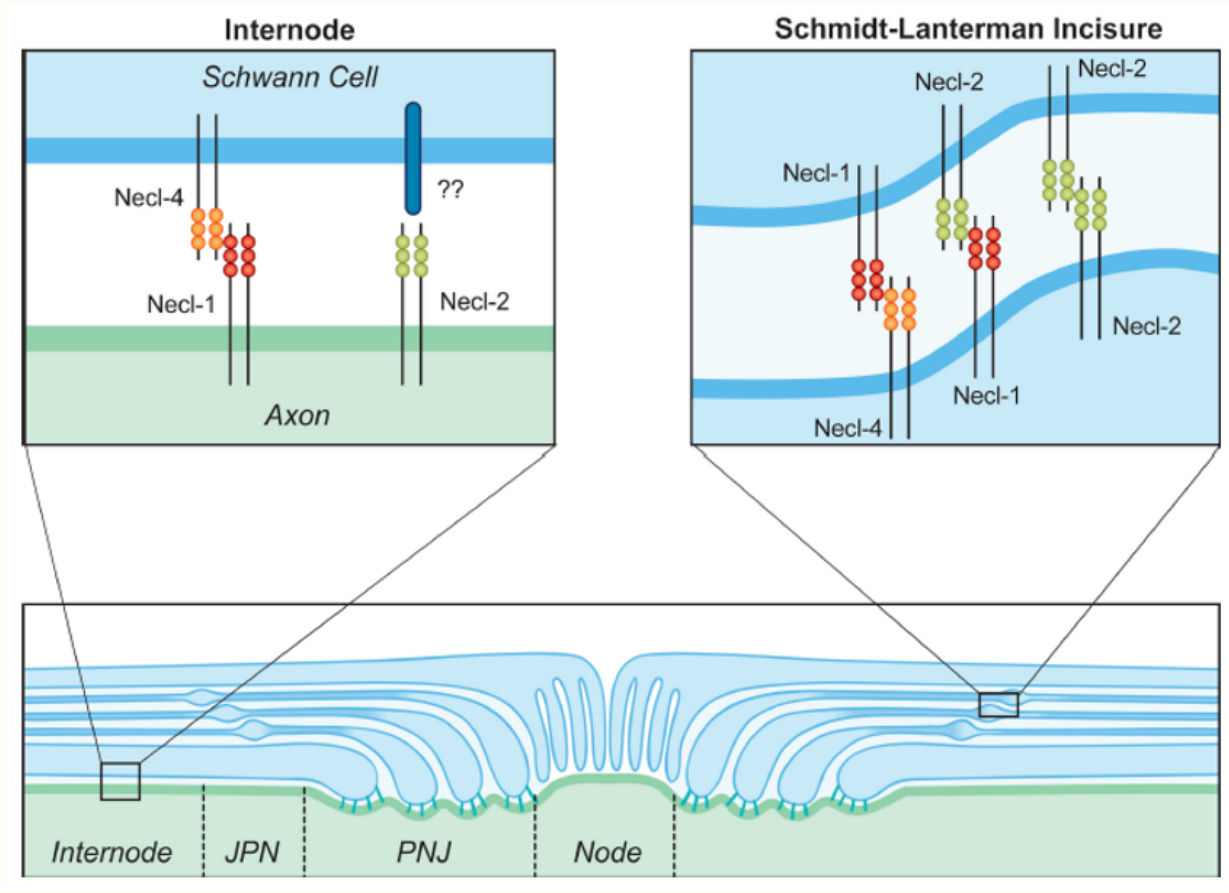

Figure 3: *Cellular junctions in internodal and Schmidt-Lanterman incisures [18].*

Conclusion

Myelination of axons helps to fast conduction of action potential referred to salutatory conduction by means of the node of Ranvier or myelin sheath gaps. The axoglial junctions flanking node of Ranvier are special adhesion sites between myelinating glial cells and axons. The molecular structure of these special composition leads to correct position of ion channels which have an important role in the conduction of action potentials.

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