Colloquium 9: Structural and Molecular Dissection of the Node of Ranvier

C09-01

Sodium channel β subunits: multifunctional molecules at the node of Ranvier

L. L. Isom
The University of Michigan, Ann Arbor, MI, USA

Voltage-gated sodium channels are unique in that they combine action potential conduction with cell adhesion. Mammalian sodium channels are heterotrimers, composed of a central, pore-forming α subunit and two auxiliary β subunits. The α subunits are members of a large gene family containing the voltage-gated sodium, potassium, and calcium channels. Sodium channel α subunits form a gene subfamily with at least 11 members. Mutations in sodium channel α subunit genes have been linked to paroxysmal disorders such as epilepsy, long QT syndrome (LQT), and hyperkalemic periodic paralysis in humans, and motor endplate disease and cerebellar ataxia in mice. Three genes encode the sodium channel β subunits with at least one alternative splice product. Unlike the pore-forming α subunits, the sodium channel β subunits are not structurally related to β subunits of calcium and potassium channels. Sodium channel β subunits are multifunctional. They modulate channel gating and regulate the level of channel expression at the plasma membrane. We have shown that β subunits also function as cell adhesion molecules (CAMs) in terms of interaction with extracellular matrix molecules, regulation of cell migration, cellular aggregation, and interaction with the cytoskeleton. A mutation in SCN1B has been shown to cause GEFS + 1 epilepsy in human families. We propose that the sodium channel signalling complex at nodes of Ranvier involves β subunits as channel modulators as well as CAMs, other CAMs such as neurofascin and contactin, RPTPβ, and extracellular matrix molecules such as tenascin.

C09-02

The myelin membrane influences the organization of molecules on the axonal surface

L. Pedraza, J. K. Huang, A. F. Svenningsen and D. R. Colman
Mount Sinai School of Medicine, New York, USA

The paranodal axoglial junction, a highly unique and specialized vertebrate structure, is the most likely domain at which axon-glial communication takes place. The molecular components of this structure are largely unknown. The first identified protein that was localized specifically to the axoglial junction was caspr/paranodin, on the axonal side. The second was neurofascin 155 (NF155), a member of the immunoglobulin superfamily of cell adhesion molecules, on the glial cell side. In the mature myelinating glial cell, NF155 clusters in apposition to axonal caspr at the paranodal junction. These proteins are believed to be important in the establishment and stabilization of the axo-glial contact and in the restriction of sodium channels to the nodal region. We have studied the spatial and temporal organization of the myelin membrane and the way myelin influences the organization of the axon, in particular of membrane proteins at the nodal and paranodal level. We observed that there is a focal increase of caspr along axonal segments that are in contact with oligodendrocyte membrane expansions. This up-regulation or redistribution of caspr on the axonal side is mirrored by an increased of NF155 on the oligodendrocyte side. Therefore, caspr and NF155 codistribute from the time of initial contact, until they reach their final distribution at the paranodal junction. This implicates NF155 and caspr in axoglial recognition and early communication, as well as in the establishment of membrane compartments or domains, where molecules are restricted from freely diffusing in the lateral plane of the axonal membrane.

C09-03

Abstract withdrawn

C09-04

How to dissect the Node of Ranvier

M. N. Rasband, E. W. Park, D. K. Zhen and J. S. Trimmer
University of Connecticut Health Center, Farmington, USA; SUNY Stony Brook, Stony Brook, USA

The node of Ranvier is composed of a complex community of axonal and glial proteins responsible for the propagation of electrical signals in myelinated nerve fibers. Both voltage-dependent sodium and potassium channels are found in high densities in discrete axonal membrane domains, but the underlying molecular mechanisms of targeting, clustering and anchoring these proteins are unknown. We have developed monoclonal and polyclonal antibodies against known components of the node of Ranvier and have used these in immunoaffinity chromatographic procedures to co purify proteins associated with these target antigens. The isolated protein fractions were then (1) separated by SDS-PAGE and analyzed by mass-spectrometry and (2) used to immunize mice to develop monoclonal antibodies against novel components of the node of Ranvier. Taking this approach, we have identified a set of candidate interacting proteins that may be important for clustering, targeting, and/or anchoring proteins known to be present at the node of Ranvier. Further, we have developed a library of monoclonal antibodies against novel components of the node of Ranvier, paranode, and juxtaparanode, to be used in expression cloning and mass spectrometry to identify the corresponding antigens.

