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CELL BIOLOGY OF THE NEURON

Scaffolding at the nodes

Spectrins were first identified in the plasma membrane of erythrocytes and are important in regulating morphological properties such as cell shape and deformability. Although they are now recognized as crucial scaffolding components of membrane micro-domains in almost all cells, their expression and functions in neurons are still not clear. Reporting in the *Journal of Cell Biology*, Lacas-Gervais and colleagues studied the expression of spectrins in the axonal initial segments and nodes of Ranvier, and their functions in nerve conduction.

Of the many spectrin isoforms, only the β IV spectrin is specifically expressed at both of these sites. Alternative splicing of the β IV spectrin gene generates six isoforms, β IV Σ 1– β IV Σ 6, but it is not known which are present at the axonal initial segments and nodes of Ranvier. In this study, the authors found that β IV Σ 1 and β IV Σ 6 are expressed at both sites, and β IV Σ 1 is the essential component of the thick membrane coats beneath these sites, which are areas with assemblies of cytoskeletal proteins that are involved in the focal accumulation of ion channels. This is consistent with the fact that β IV Σ 1 is the only spectrin with an actin-binding domain.

The authors generated β IV Σ 1-knockout mice and studied the morphology of the nodes by staining specific markers. They found that removal of β IV Σ 1 alters the width and length of the nodes in both the CNS and PNS, and expression of

potassium channels is less restricted to the juxtaparanodes and could invade the paranodes — a phenotype that is also observed in a 'quivering' mouse strain that has spontaneous mutations in the β IV gene. Electron microscopy of the nodes of Ranvier showed that removal of β IV Σ 1 leads to reduced amounts of the thick membrane coats, increased node diameters and the appearance of aberrant membrane protrusions that are filled with organelles.

Do these abnormalities in the nodes affect nerve conduction in these mutant mice? To address this issue, the authors measured auditory brainstem responses in β IV Σ 1-knockout mice, as auditory neuropathies are observed in the 'quivering' mice. They found that the latency of auditory evoked potentials in β IV Σ 1-knockout mice was significantly increased. Increased

stimulation rates further increased the latency, which indicates auditory neural fatigue. The authors suggest that these deficits are due to delayed generation of action potentials by cochlear spiral ganglion neurons and impairment in nerve conduction along the auditory pathways.

Overall, these studies support a scaffolding role for spectrins in neurons. The findings have important implications for axonal physiology in normal and pathological conditions.

Jane Qiu

References and links

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FURTHER READING Poliak, S. & Peles, E. The local differentiation of myelinated axons at nodes of Ranvier. *Nature Rev. Neurosci.* **4**, 968–980 (2003)

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