This Week in The Journal

Quaking Regulates Alternative Splicing of Neurofascin

Lama Darbelli, Gillian Vogel, Guillermina Almazan, and Stéphane Richard

(see pages 4106 – 4120)

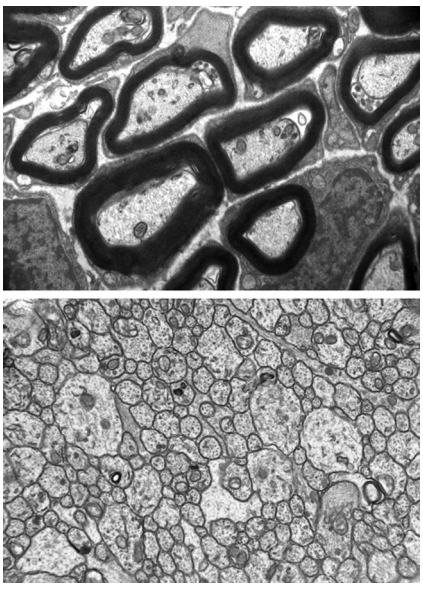
Schizophrenia is a complex disease with diverse psychopathological symptoms. The underlying causes are poorly understood, but interactions between environmental and genetic risk factors likely set the stage for neuropathogenesis. One of many genes linked to schizophrenia risk is quaking (Qk1), an RNA-binding protein involved in myelination.

Quaking was first discovered during investigations of a spontaneous mutation (called *quaking viable*) that caused mice to develop limb tremors shortly after birth. The phenotype results from deletion of a *qk1* regulatory region, and it results in reduced quaking expression and extensive demyelination in the CNS. Quaking regulates the stability, transport, and/or splicing of multiple mRNAs encoding myelin proteins. Thorough elucidation of quaking functions has been hampered, however, because germline deletion of *qk1* causes embryonic death. Therefore, Darbelli et al. generated conditional knockout mice in which quaking was deleted selectively in oligodendrocytes.

Like *quaking viable* mice, mice whose oligodendrocytes lacked *qk1* throughout development began to exhibit tremors, seizures, and ataxia within 2 weeks of birth. No myelin was detected in the brains of these mice. Consistent with the role of *qk1* in mRNA regulation, splicing of 31 targets—including several mRNAs that encode myelin proteins—was altered in oligodendrocytes that lacked *qk1*.

One newly identified quaking target encodes neurofascin, a protein that helps form junctions between axons and myelin sheaths. Axons and oligodendrocytes express different alternatively spliced isoforms of neurofascin, and notably, *qk1* knockout prevented generation only of the myelin-specific isoform (Nfasc155). Importantly, knocking out oligodendrocyte *qk1* in mature mice also caused loss of Nfasc155, and consequently led to disruption of axoglial junctions. Adult knockout of *qk1* also produced tremors and paralysis, but this likely involved mechanisms unrelated to neurofascin splicing.

These results confirm the role of quaking in regulating numerous myelin proteins, and they reveal that quaking is required for generating the myelin-specific isoform of neurofascin. The latter discovery is especially intriguing, not only because the factors regulating neurofascin splicing were previously unknown, but also because genetic variation in neurofascin has been linked to schizophrenia risk. Thus, these results add to accumulating evidence (reviewed in Roussos and Haroutunian 2014 Front Cell Neurosci 8: 5) that defects in myelination contribute to schizophrenia.



Knocking out *qk1* in oligodendrocytes (bottom) greatly reduces myelination in the optic nerve. Dark rings in (top) panel represent myelin in control mice. See Darbelli et al. for details.

Cortical Interneuron Types Receive Similar Inputs

Nicholas R. Wall, Mauricio De La Parra, Jordan M. Sorokin, Hiroki Taniguchi, Z. Josh Huang, et al.

(see pages 4000 – 4009)

The ability to label specific types of neurons and their synaptic partners has allowed rapid growth in our understanding of cortical interneurons and their connectivity. Cortical interneurons can be broadly classified by their expression of three proteins: parvalbumin, somatostatin (SST), and vasoactive intestinal peptide (VIP). These classes have distinguishing physiological properties and local connection patterns. Do they also differ in their sources of long-range input?

To address this question, Wall et al. labeled selected neuron types and their presynaptic partners. To do so, they first expressed a rabies-virus coat protein in a subset of interneurons of a given class. Rabies virus lacking the coat-protein gene but containing the mCherry gene was then injected into the brain. Only cells made to express the coat protein can generate rabies virus, which, when released, binds to receptors located on adjacent presynaptic terminals. Infected presynaptic cells then express mCherry.

This technique revealed that all of the main cortical interneuron classes in mouse primary somatosensory cortex received inputs from the same brain areas. These input areas included several cortical areas, thalamic nuclei, and a cholinergic nucleus of the basal forebrain. Although the proportion of inputs received from each of these areas was similar across interneuron types, VIP-expressing interneurons received more cortical input overall and received a greater proportion of inputs from layer 5/6 of these regions than the other classes did.

While the study suggests that VIP-expressing interneurons receive more corticocortical inputs than other interneurons do, the functional impact remains unknown. Do VIP neurons need to integrate input from more neurons before they are induced to fire? This might be the case if axons innervating VIP neurons form fewer and/or weaker synapses than those innervating SST neurons. Alternatively, the results may indicate that VIP neurons are the interneurons most strongly driven by corticocortical inputs, which may ensure VIP neurons can effectively inhibit SST neurons. More work is needed to fully map cortical circuits and understand their function, but the work by Wall et al. is an important step toward that goal.

This Week in The Journal is written by Teresa Esch, Ph.D.