This Week in The Journal

Retromer Sends mGluRs to Synapses, Promoting Pain

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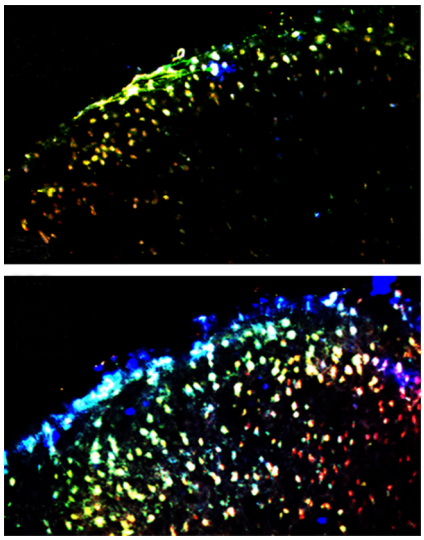
(see pages 14943–14955)

Proper trafficking of membrane proteins in exocytic and endocytic pathways is essential for normal neuronal function. After endocytosis, receptors can be transported to lysosomes, to the trans-Golgi network, or back to the plasma membrane. The route taken is determined by interactions with endosomal protein complexes, such as retromer.

The retromer complex includes a module for recognizing cargoes and a module that targets cargo toward the appropriate destination. The recognition module includes proteins of the vacuolar protein sorting-associated (VPS) protein family, such as VPS26A, whereas the targeting module contains proteins of the sorting nexin (SNX) family. SNX27 is unusual in that it both recognizes endocytosed cargoes that have PDZ domains (including many synaptic proteins), and directs these cargoes to be recycled to the plasma membrane. One such cargo is the AMPA receptor subunit GluA1, which SNX27 delivers to postsynaptic sites to mediate long-term potentiation (LTP).

Neuropathic pain results from plasticity in pain-sensing pathways, and like LTP, it is mediated at least partially by increased delivery of glutamate receptors—in this case, metabotropic glutamate receptors (mGluRs)—to the plasma membrane. Because mGluRs have a PDZ domain, Lin et al. asked whether SNX27, in association with retromer, directs mGluR insertion after spinal nerve ligation, a model of neuropathic pain. Consistent with this hypothesis, ligation-induced mechanical hypersensitivity was accompanied by increased expression of SNX27, VPS26A, and mGluR5 in rat dorsal horn neurons. The interaction between these proteins was also increased by nerve ligation. Moreover, knocking down SNX27 or VPS26A attenuated the increase in synaptic mGluR5 expression induced by nerve ligation and reduced ligation-induced mechanical hypersensitivity.

These results suggest that SNX27, as part of the retromer complex, promotes delivery of mGluR5 to synaptic membranes in dorsal horn neurons after spinal nerve ligation. This delivery appears to enhance synaptic responses to mechanical stimulation, thus resulting in hypersensitivity. Interfering with this targeting might therefore help to alleviate neuropathic pain.



Expression of VPS26A (green), SNX27 (red), and mGluR5 (blue) was higher in the ipsilateral dorsal horn after spinal nerve ligation (bottom) than after sham operation (top). See Lin et al. for details.

Blocking miR-33 Reduces Aβ Levels in Mice

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(see pages 14717–14726)

The strongest genetic risk factor for Alzheimer's disease (AD) is possession of an ε4 allele of apolipoprotein E (ApoE). Like other apolipoproteins, ApoE transports lipids and removes excess cholesterol from cells. It also interacts with β-amyloid (Aβ), the peptide fragment that promotes synaptic loss and neurodegeneration in AD, and it is thought to facilitate Aβ clearance. The ε4 allele appears to perform ApoE functions less efficiently than other alleles, and this likely underlies its association with AD.

Interactions between ApoE and Aβ are enhanced when ApoE is loaded with lipids. Therefore, ATP-binding cassette transporter A1 (ABCA1), a protein that transfers intracellular lipids to ApoE, also influences Aβ clearance. Specifically, loss of ABCA1 increases Aβ accumulation, whereas ABCA1 overexpression decreases Aβ accumulation. Although these effects may stem solely from ABCA1's role in ApoE lipidation, ABCA1 has also been hypothesized to limit Aβ generation by inhibiting amyloidogenic cleavage of amyloid precursor protein (APP).

In peripheral tissues, ABCA1 levels are regulated partly by microRNAs such as miR-33, which binds to ABCA1 mRNA and prevents translation. Kim et al. now report that miR-33 also regulates ABCA1 expression in the brain. miR-33 was found in neurons and glia throughout the brain, and knocking out miR-33 not only increased ABCA1 levels, but also increased the size of ApoE-containing lipoprotein particles, suggesting ApoE lipidation was enhanced. In contrast, treating neuroblastoma cells or astrocytes with synthetic miR-33 decreased ABCA1 levels and reduced cholesterol efflux from cells.

Importantly, miR-33-dependent downregulation of ABCA1 and ApoE lipidation resulted in increased production of Aβ by neuroblastoma cells expressing an AD-linked form of APP, and it also reduced Aβ clearance from cultured cells. Conversely, Aβ degradation was greater in cortical tissue homogenates from mir-33-deficient mice than in control tissue. Moreover, intracerebroventricular delivery of an antisense oligonucleotide of miR-33 increased cortical ABCA1 levels and reduced cortical levels of Aβ in a mouse model of AD.

These results support the hypothesis that ABCA1-dependent lipidation of ApoE promotes Aβ clearance, and they indicate that this pathway can be enhanced by reducing levels of miR-33. It will be important to determine whether miR-33 reduction slows cognitive impairment in AD-model mice. If it does, finding ways to reduce miR-33 in human brain may lead to an effective treatment for AD.

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