This Week in The Journal

Alzheimer's-Linked SORLA Protein and Neurite Growth

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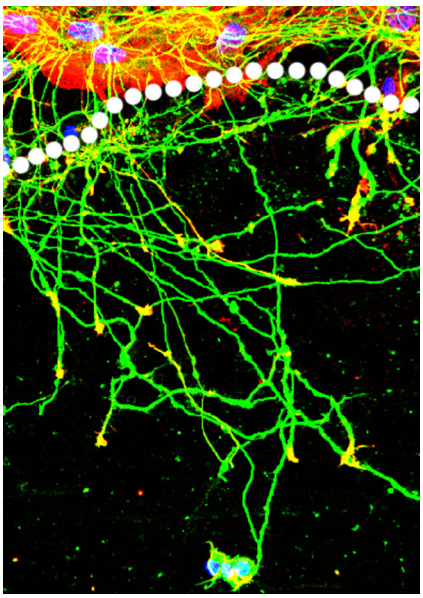
(see pages 5908–5921)

Membrane-associated proteins are constantly moving in cells: from the Golgi to the plasma membrane, from the plasma membrane to endosomes, and from endosomes back to the Golgi, lysosomes, or nucleus. Trafficking of proteins to their proper destination is achieved by various sorting proteins, including sortilin-related receptor with A-type repeats (SORLA). Cargoes guided by SORLA include amyloid precursor protein (APP), which is processed in different cellular compartments to produce β-amyloid and/or other cleavage products. SORLA directs APP away from endosomes, preventing excess production of β-amyloid. Disruption of this role likely explains why reduced SORLA function is associated with Alzheimer's disease. But disruption of other SORLA functions may also contribute to the disease. For example, SORLA is involved in trafficking TrkB, which mediates the beneficial effects of brain-derived neurotrophic factor. And Stupack et al. now reveal a role for SORLA in promoting neurite growth.

SORLA-overexpressing hippocampal neurons grew longer neurites than wild-type neurons in culture, and after a pipette tip was used to mechanically wound cultured cortical neurons, neurites from SORLA-overexpressing neurons grew more quickly into the wound area. Because previous work had shown that SORLA can be cleaved at the plasma membrane to release a soluble fragment extracellularly, the authors asked whether this soluble fragment was responsible for the effects on neurite growth. Indeed, purified soluble SORLA produced by transfected HEK cells enhanced neurite growth in wild-type hippocampal and cortical neurons. Increases in neurite extension were accompanied by increased phosphorylation of the epidermal growth factor receptor (EGFR) and several kinases downstream of this receptor, including ERK and MAP kinases. Furthermore, EGFR coimmunoprecipitated with soluble SORLA. In addition, soluble SORLA increased nuclear levels of the immediate early gene Fos, which promotes neurite outgrowth. Notably, inhibiting EGFR and/or a MAP kinase kinase inhibited the effects of soluble SORLA on neurite outgrowth and Fos translocation.

These results indicate soluble SORLA, which lacks cytoplasmic sequences involved in sorting, stimulates neurite growth and regeneration by increasing activation of EGFR. Loss of this regenerative function might exacerbate the detrimental effects of increased β-amyloid production when SORLA function is reduced.



Soluble SORLA promotes neurite regeneration in cultured cortical neurons after wound injury. Neurons were stained for tubulin (green), F-actin (red), and DAPI (blue). See Stupack et al. for details.

Striatal Cholinergic Interneurons in Parkinson's Disease

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(see pages 6049–6067)

Parkinson's disease (PD) is characterized by slowed movements, resting tremor, and muscle stiffness, sometimes accompanied in the later stages by gait and balance disturbances and an increased risk of falling. Although loss of dopaminergic input from the substantia nigra to the striatum is the root cause of PD, disruption of cholinergic signaling also contributes to the symptoms. Striatal cholinergic interneurons become hyperactive as PD progresses, and because acetylcholine and dopamine exert opposite effects on striatal output, cholinergic hyperactivity is thought to exacerbate the effects of dopamine loss (Liu, 2020, Acta Pharmacol Sin 41:453). In contrast, gait and balance disturbances might result from loss of cholinergic input from the basal forebrain to the cortex, which provides excitatory drive to the striatum. Consistent with this, double-lesion rats, in which both dopaminergic projections and basal forebrain cholinergic neurons are killed, fall more often when walking on a rotating beam than rats with single lesions. The increase in falling has been attributed to loss of attention to sensory cues required to perform the task.

Avila et al. now report that inhibition of striatal cholinergic interneurons also impairs performance on the beam-walking task, as well as on a newly developed cued turning task. In the latter task, rats were trained to walk on a treadmill and to turn and walk in the opposite direction when an auditory or visual cue was presented. Double-lesion rats were less likely to turn in response to the cue than controls. Notably, however, activation of a generally excitatory designer receptor expressed selectively in striatal cholinergic interneurons of double-lesion rats reduced falls on the rotating beam and increased cued turn rates on the treadmill. In contrast, activating a generally inhibitory designer receptor in striatal cholinergic interneurons increased falls and reduced cued turning in rats with intact dopaminergic projections and forebrain cholinergic neurons.

These data suggest that loss of striatal cholinergic interneurons increases falls and disrupts turning in response to cues. Both effects might be explained by a reduced ability to use sensory input to shape motor control. Notably, striatal cholinergic interneurons are lost in the late stages of PD, which might explain why falls increase as the disease progresses.

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