This Week in The Journal

NT-3 Promotes Synapse Assembly by Enhancing TrkC–PTPσ Interactions

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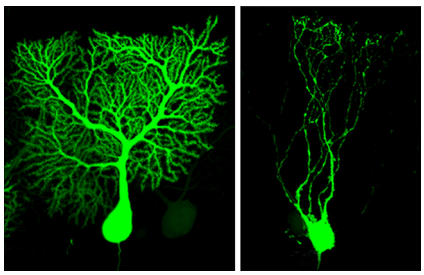
(see pages 12425–12431)

Efficient synaptic communication requires precise alignment of the presynaptic vesicle-release apparatus with neurotransmitter receptor clusters in the postsynaptic membrane. This is accomplished through coordinated assembly of multi-protein presynaptic and postsynaptic structures, and it is initiated by synaptic organizing proteins. Many such synaptogenic proteins are transmembrane proteins that are localized to either presynaptic or postsynaptic membranes, have extracellular adhesion domains, and bind with specific partner proteins in the partner cell membrane. Transsynaptic interactions between such proteins are thought not only to tether the presynaptic and postsynaptic membranes together, but also to trigger assembly of protein complexes through interactions involving the adhesion proteins' intracellular domains.

Previous work (Takahashi et al., 2011, Neuron 69:287) revealed that assembly of presynaptic and postsynaptic components of excitatory synapses can be induced by trans-interactions between axonal receptor protein tyrosine phosphatase σ (PTPσ) and dendritic TrkC receptors. Surprisingly, although TrkC is a receptor tyrosine kinase that initiates signaling when activated by neurotrophin-3 (NT-3), neither NT-3 nor the TrkC tyrosine kinase domain are required for TrkC–PTPσ interactions to induce synapse formation. Because NT-3 and PTPσ bind to different TrkC domains, however, it was speculated that NT-3 may regulate synaptic induction by modulating TrkC–PTPσ interaction.

Ammendrup-Johnsen et al. now provide support for this hypothesis. NT-3 increased binding between PTPσ ectodomain fragments and COS cells expressing the non-catalytic isoform of TrkC. Furthermore, NT-3 increased the size and number of presynaptic specializations induced in hippocampal neuronal axons growing in contact with TrkC-expressing COS cells. Finally, NT-3 increased the number of recycling synaptic vesicles at functional synapses in hippocampal cultures. Interestingly, none of these effects required the TrkC tyrosine kinase domain.

Given that NT-3 secretion is enhanced by neuronal activity, these results suggest that NT-3 may contribute to activity-dependent synaptic plasticity by enhancing TrkC–PTPσ interactions. This may lead to a rapid increase in the number of synapses, which may subsequently be stabilized by tyrosine-kinase-dependent NT-3–TrkC signaling.



Knocking down RORα beginning at E11.5 led to abnormal PC morphology at P14. Whereas control cells (left) had a single highly branched dendrite extending from the soma, RORα-deficient PCs retained multiple primitive dendrites, which were thin and sparsely branched. See Takeo et al. for details.

RORα Has Many Roles in Purkinje Cell Dendritic Growth

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(see pages 12518–12534)

Cerebellar Purkinje cells (PCs), like many neuronal types, are easily identifiable by the distinctive morphology of their dendritic arbors. These arbors are shaped during development by the combined effects of genetic programs, environmental cues, and synaptic inputs, and they continue to be modified during adulthood. At embryonic day 17 (E17), mouse PCs have a fusiform shape with primitive apical dendrites, but these dendrites retract. By postnatal day 4 (P4), the cells take on a stellate shape with numerous dendrites extending from the soma. All but one of these dendrites retract by P8, however. Only then do PCs begin to take on their characteristic morphology with a highly branched and spiny dendritic arbor anchored to the soma by a single thick stem.

PC dendritic development is abnormal in *staggerer* mice, which harbor a null mutation in the transcription factor retinoic acid-related orphan receptor α (RORα). RORα is expressed in PCs beginning at ~E12.5, when the cells are migrating from the ventricular zone, and its expression continues into adulthood. Which stages of PC dendritic development are affected by RORα loss has remained unknown. To address this question, Takeo et al. conditionally knocked down RORα expression beginning before PC migration (E11.5), at the stellate stage (P4), during the maturing PC stage (P10), or after dendritic development was complete (P21). RORα knockdown affected dendritic growth no matter when it was initiated. In all cases, dendritic arbors were shorter with fewer branches in RORα-deficient PCs than in controls. Moreover, RORα-deficient PCs had fewer dendritic spines, often lacking them altogether. Importantly, knocking down RORα at E11.5 or P4 inhibited retraction of primitive dendrites, whereas knockdown at P10 or P21 caused retraction of maturing dendrites. The loss of dendritic branches and spines was accompanied by reduced amplitude of EPSCs evoked by stimulation of parallel or climbing fibers.

All together, the results suggest that RORα is required at all stages of PC dendritic growth, from the early pruning of primitive dendrites, to the growth and maintenance of mature dendrites. Previous studies have shown that RORα regulates transcription of a metabotropic glutamate receptor along with several of its associated molecules and downstream effectors related to intracellular Ca^{2+} release (Gold et al., 2007, Brain Res 1140: 19). Future studies should investigate which, if any, of these is involved in PC dendritic growth and maintenance.

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