This Week in The Journal

Sonic Hedgehog and Axon Growth

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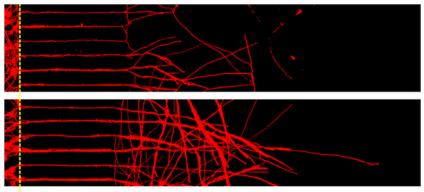
(see pages 16126–16141)

Sonic hedgehog (Shh) is an important morphogen for patterning tissues and specifying cell fates. To perform these functions, soluble Shh binds to Patched1 (Ptch1) receptors at the base of primary cilia—short microtubule-based protrusions found in nearly all cell types. When Shh is absent, Ptch1 prevents Smoothened (Smo), another transmembrane protein, from entering the cilium. When Shh binds to Ptch1, however, the barrier is removed, and subsequent accumulation of Smo in the cilium leads to activation of Gli transcription factors. These transcription factors translocate to the nucleus to activate transcriptional programs (Louvi and Grove, 2011, Neuron 69:1046).

Later in development, Shh takes on a different role in the nervous system: guiding axons. Shh causes axonal growth cones to turn within minutes by activating specific kinases. The rapid effect of Shh on axons suggests that it does not require changes in gene expression. In any case, activation of Gli transcription factors is not required (Yam and Charron, 2013, Curr Op Neurobiol 23:965).

Yao et al. provide evidence that Shh promotes axonal growth in cultured rat hippocampal neurons via a different mechanism. Applying Shh selectively to neuronal somata and dendrites promoted axon growth, whereas selectively treating axons did not. Shh treatment increased Ptch1 expression and Gli1 activity, whereas inhibiting Gli1 or knocking down Smo prevented Shh-induced increases in axon growth. These data suggest that Shh regulates axon growth by altering gene transcription, rather than by activating axonal kinases. But only 20% of cultured hippocampal neurons had an obvious primary cilium, and surprisingly, Shh increased Smo levels and stimulated axonal growth regardless of whether a cilium was present. Thus, the mechanism by which Shh regulates axon growth appears to differ from both previously described mechanisms.

These results challenge the hypothesis that Shh-dependent activation of Gli transcription factors requires a primary cilium. It is possible, however, that cilia were present, but not detected in these neurons. Future experiments should determine whether mutations that disrupt primary-cilia function impair axonal growth in hippocampal neurons. Such experiments may provide insight into the etiology of ciliopathies, many of which are attributed to disrupted Shh signaling.



In compartmented chambers, neuronal somata are restricted to the left compartment by a barrier (indicated by vertical yellow line), and axons grow along narrow channels (indicated by horizontal black line) to the right chamber. Axons grow longer when Shh is added to the somatic compartment (bottom). See Yao et al. for details.

A Role for Amyloid Precursor Protein's C-Terminus

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(see pages 16018–16033)

Accumulation of β-amyloid (Aβ) peptides is a hallmark of Alzheimer's disease (AD). Aβ is generated from amyloid precursor protein (APP) by sequential cleavage first by β-secretase, which creates a soluble protein (APPsβ) and a transmembrane C-terminal fragment (β-CTF), and then by γ-secretase, which cleaves β-CTFs to yield the APP intracellular domain (AICD) and Aβ. Aβ is neurotoxic and has been hypothesized to cause the cognitive deficits and neurodegeneration that occur in AD. But loss of normal functions of APP and its proteolytic fragments—including those generated by a third secretase (α-secretase)—may also contribute to AD neuropathology. The normal functions of these proteins remain unclear, however.

To investigate the physiological roles of the C-terminal region of APP, Klevanski et al. replaced endogenous mouse APP with a mutant form lacking the last 15 amino acids of the C-terminal (APPΔCT15). This was done in mice that also lacked the APP-like protein APLP2, which otherwise compensates for APP loss. Mice lacking both APP and APLP2 die shortly after birth, likely because abnormal development of neuromuscular junctions (NMJs) prevents adequate respiration. Although APPΔCT15 knock-in mice had a higher survival rate than double-knockout mice, they were more likely to die after birth than wild-type mice, and their NMJs remained abnormal. Specifically, acetylcholine-receptor patches were smaller, more fragmented, and more dispersed across the diaphragm muscle than normal, and the presynaptic area and the overlap of presynaptic and postsynaptic sites were reduced. Furthermore, APPΔCT15-expressing mice were unable to sustain neurotransmitter release during prolonged stimulation of motor nerves. In addition, β-secretase-mediated cleavage of APP was disrupted in surviving knock-in mice, and Aβ, β-CTF, and APPsβ levels were reduced. Finally, several hippocampus-dependent behaviors, including spatial memory, nesting, and burrowing, were impaired in APPΔCT15-expressing mice.

These data indicate that the last 15 amino acids of APP are required for normal synaptic development and function. This region contains a protein-interaction domain important for endocytosis, and its loss may prevent trafficking of APP to compartments where β-secretase-mediated cleavage occurs. The results support the hypothesis that loss of normal protein functions contributes to synaptic deficits in AD. If this is true, treatments aimed solely to reduce Aβ levels may be ineffective.

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