This Week in The Journal

CDK-14 Acts in Wnt Pathway to Promote Axon Regeneration

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(see pages 8309–8320)

A major impediment to axon regeneration in the adult CNS is the loss of axons' intrinsic ability to grow. Deciphering the signaling cascades required for axon regeneration in the PNS and in invertebrates may illuminate ways to overcome this obstacle. To identify such molecules in *Caenorhabditis elegans*, Hisamoto et al. previously performed a genome-wide screen for genes linked to JNK, a kinase that regulates cytoskeletal rearrangements involved in axon growth. They now report that mutating either of two proteins identified in that screen—the Frizzled-family receptor MIG-1a or the cyclin-dependent kinase CDK-14—reduced the proportion of motor axons that regenerated after axotomy. Intriguingly, a yeast two-hybrid screen revealed that CDK-14 interacts with MIG-5, a paralog of Disheveled (Dsh), which mediates the effects of Frizzled. This suggests that MIG-1 and CDK-14 act in the same pathway.

When activated by Wnt ligands, Frizzled receptors regulate axon growth by activating Dbl-family guanine nucleotide-exchange factors (GEFs), which in turn activate Rho GTPases. In *C. elegans*, Rho GTPases promote phosphorylation of the myosin light chain protein MLC-4, partly by inhibiting the myosin phosphatase MEL-11. Phosphorylated MLC-4 promotes actin–myosin interactions that contribute to growth cone function. By examining the effects of various mutations, Hisamoto et al. determined which members of these protein families collaborate with MIG-1 to promote axon regeneration. Specifically, they identified the Wnt ligand EGL-20, the GEF EPHX-1, and the Rho GTPase CDC-42. Notably, CDK-14 interacted with EPHX-1, and overexpressing EPHX-1 rescued regeneration in CDK-14 mutants. In contrast, disrupting CDK-14 kinase activity did not affect regeneration. Finally, expressing constitutively active CDC-42, an inactive form of MEL-11, or a phosphomimetic version

of MLC-4 rescued axon regeneration in worms expressing mutant forms of CDK-14 or MIG-1.

These results suggest EGL-20 binding to MIG-1 promotes activation of CDC-42 by EPHX-1, and this increases MLC-4 phosphorylation by inhibiting MEL-11. Ultimately, this leads to the initiation of axon regeneration. Cdk-14 may regulate this pathway by binding to EPHX-1. Because the kinase activity of CDK-14 is not required for this role, the authors propose that by binding to EPHX-1, CDK-14 prevents an intramolecular interaction that otherwise causes autoinhibition. Thus, CDK-14 frees EPHX-1 to activate CDC-42.

In wild-type flies (top), s-LNv neurite arbors are more elaborate in the morning (left) than in the evening (right). Overexpressing *dpp* in l-LNvs (bottom) prevents the morning elaboration. See Polcowñuk et al. for details.

BMP Signaling Regulates Circadian Structural Remodeling

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(see pages 8338–8350)

Fruit flies are crepuscular animals. Increases in their locomotor activity around dawn and dusk depend on the activity of ~150 clock neurons located in three dorsal and four lateral clusters in the brain. The roles of each cluster and how the clusters interact is poorly understood, but neurons in the small and large ventral lateral clusters (s- and l-LNvs, respectively) are thought to

have particularly important roles in coordinating clock activity and driving circadian changes in behavior. The LNvs release pigment dispersing factor (PDF), a neuropeptide that maintains behavioral rhythms in part by activating receptors on other clock neurons. Remarkably, PDF also drives circadian remodeling of s-LNv neurites that project to dorsal clusters. These arbors are most elaborate at dawn and least elaborate at dusk, and preventing their circadian remodeling disrupts behavioral rhythms. Polcowñuk et al. show that this structural remodeling is also regulated by Decapentaplegic (DPP), a ligand of the bone morphogenetic protein (BMP) family.

The BMP signaling pathway was identified as a regulator of circadian locomotor activity in a previous genetic screen. In that work, disruption of BMP-related signaling pathways in LNvs significantly lengthened the circadian period. Polcowñuk et al. found that this pathway is activated early in the morning in LNvs, but not in other clock neurons. They also found that the BMP ligand DPP is expressed selectively in LNvs. Although knocking down *dpp* in s-LNvs had no apparent effect on daily activity patterns, knockdown in l-LNvs dampened increases in locomotion at dawn and dusk. Furthermore, overexpression of *dpp* in l-LNvs increased activation of a BMP effector in s-LNvs and attenuated the morning elaboration of s-LNv neurite arbors. A similar effect on circadian structural remodeling occurred when Trio—a guanine nucleotide exchange factor that mediates BMP effects on neurite growth during development—was overexpressed in s-LNvs.

These results suggest that DPP released from l-LNvs contributes to the circadian regulation of locomotion at least partly by promoting the elaboration of s-LNv axonal arbors each morning. Future work should determine whether DPP has additional effects on circadian networks and identify the downstream mechanism through which structural remodeling of s-LNvs contributes to circadian rhythmicity.

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