In This Issue

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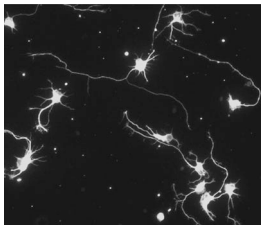
Syndecan-3 gets the message



Immobilized GDNF spurs neurites to elongate in these hippocampal cells.

Bespalov et al. catch several growth factors that are essential for brain development being unfaithful. The researchers show that the molecules consort with a second receptor.

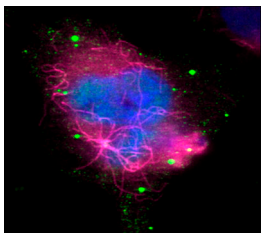
Glial cell line–derived neurotrophic factor (GDNF) and three related growth factors make up the GDNF family ligands, or GFLs. The molecules are movers and shapers in the nervous system. GFLs nurture neurons, trigger their neurites to grow, and prod the cells to migrate as the brain develops. Previous work identified GFR-α as the GFL co-receptor. GFR-α relays the signal to either of two other membrane receptors, RET or NCAM. However, researchers have found that some neurons can respond to GDNF even though they lack RET and NCAM, suggesting the GFLs can switch to a different receptor.

Their other partner, Bespalov et al. discovered, is syndecan-3, a heparan sulfate proteoglycan. Which receptor GFLs use depends on the situation, the team found. Free-floating GFLs hook up with GFR-α. But the growth factors often build up on the extracellular matrix (ECM), boosting their local concentrations. When attached to the ECM, three of the four GFLs send messages through syndecan-3.

In the embryo, GABAergic neurons, which are key inhibitory cells, travel from their birthplace in the medial ganglionic eminence into the brain cortex. To determine whether GFLs spur this behavior through syndecan-3, the researchers set beads that exude GDNF atop slices of rat brain. GABAergic neurons slithered toward the beads in slices from control animals, but not in tissue from animals lacking syndecan-3. The interaction between GFLs and syndecan-3 might therefore be critical for shaping the developing brain.

Bespalov, M.M., et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201009136.

Cancer cells mothball mRNA after microtubule collapse



Depolymerization of microtubules (magenta) spurred this cancer cell to make more P-bodies (green), where it stores HIF-1α mRNAs.

Tumor cells are often short of oxygen. Carbonaro et al. explain how microtubules (MTs) help control production of a protein that lets the cells survive.

By switching on more than 100 genes, the transcription factor HIF-1 helps cancer cells endure low oxygen levels. HIF-1α, a component of HIF-1, is a promising drug target because more than 70% of tumors overproduce it. How cells control HIF-1α expression remains unclear. The researchers previously discovered that taxol and other drugs that disrupt MT dynamics also reduce production of HIF-1α. The unanswered question was how MTs affect HIF-1α synthesis.

Carbonaro et al. discovered that HIF-1α mRNA attaches to microtubules and scoots along them, presumably traveling to locations where it is translated. When this movement stalled after treatment with taxol or related drugs, cells stowed HIF-1α mRNA inside cytoplasmic structures called P-bodies, where abundant microRNAs shut down translation of HIF-1α mRNA. The researchers found that when they dosed cells with the microtubule-disassembling drug nocodazole and then removed it, the HIF-1α mRNA emerged from hiding, and the cells once again began manufacturing the protein. The researchers also showed that they could thwart taxol's inhibitory effect on HIF-1α by blocking microRNAs and knocking down the P-body protein Argonaute2.

The work indicates that HIF-1α expression depends on the state of the microtubule cytoskeleton. Drugs such as taxol that interfere with microtubule dynamics might kill cancer cells by preventing them from making HIF-1α protein. The findings also raise the possibility that translation of HIF-1α mRNA—and possibly other mRNAs—occurs on MTs.

Carbonaro, M., et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201004145.

Receptors flex to remove neurotransmitter brake

Kupchik et al. reveal how shape-shifting synaptic receptors help set neurotransmitters free.

Researchers have known for more than 50 years that calcium controls neurotransmitter release. When an action potential reaches the synapse, calcium rushes into the pre-synaptic neuron, prompting it to rapidly unload neurotransmitters. But several lines of evidence suggest that calcium gets assistance from G protein–coupled receptors (GPCRs) at pre-synaptic nerve endings. The receptors' best known job in synapses is adjusting the amount of acetylcholine and other neurotransmitters that the neuron discharges. Because this task takes seconds or even minutes to perform, how GPCRs regulate a process that occurs in milliseconds is unclear. Four years ago, the researchers furnished a possible answer, discovering that the arrival of the action potential at the synapse spurs "charge movements" in GPCRs. Charged amino acids in the proteins change position, altering the receptors' shape.

To determine whether these molecular twitches help unleash neurotransmitters, the researchers used the compound carbachol to inhibit charge movements in the M_2R receptor, which governs the release of acetylcholine. Kupchik et al. could apply carbachol at precise times with a flash of UV light, which liberates a caged version of the molecule. The team found that blocking charge movements just before or during the action potential cut neurotransmitter release. But adding the inhibitor just afterward had no effect.

The researchers suggest GPCRs serve as a brake that prevents neurotransmitter vesicles from merging with the presynaptic membrane. When an action potential reaches the synapse, the receptors change shape, removing this inhibition. Thus, GPCR charge movements dictate the timing of neurotransmitter release, whereas calcium spurs exocytosis. The researchers now want to determine whether the same mechanism works for other neurotransmitters, such as glutamate.

Kupchik, Y.M., et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201007053.