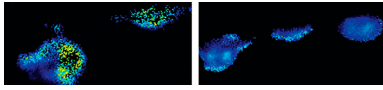


Wait! Don't throw away those proteins!



A heat map shows the ratio of old to young proteins (red = high, blue = low) at control synapses (left) and at synapses from *skywalker* mutants (right).

fill the vesicles with neurotransmitters, promote vesicle fusion, and perform other tasks necessary for synaptic transmission. But these proteins eventually wear out, so neurons continually steer the vesicles to endosomes, where the proteins are sorted. Functional proteins return to the synaptic vesicles to continue working, and the worn-out ones travel to the lysosome for destruction.

Fernandes et al. found that replacement of synaptic proteins was more efficient in flies with mutations in the gene *skywalker*, the insect homologue of *TBC1D24*, a human gene linked to neurodegeneration and epilepsy. The researchers tagged synaptic proteins

Too many fresh proteins at synapses might trigger neurodegeneration, Fernandes et al. reveal.

Synaptic vesicle-associated proteins help

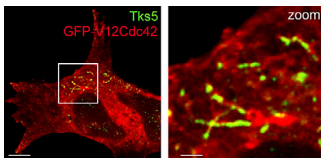
with a fluorescent molecule that changes from blue to red over time, allowing them to determine the ages of the proteins. Young proteins were more abundant at synapses in the mutant flies than in controls. Synapses also were more active in mutant insects: they released larger quantities of neurotransmitters and triggered a larger postsynaptic electrical current after stimulation.

The researchers discovered that mutations in the gene encoding Dor counteract the effects of *skywalker* mutations, curtailing neurodegeneration, damping neurotransmitter release, and slowing synaptic protein turnover. Dor is part of the HOPS complex that helps direct endosomes to the lysosome for digestion. When HOPS is disabled, fewer old vesicle-associated proteins are lost from synapses.

The study suggests that aging is not always bad: without enough of these aged and less efficient vesicle-associated proteins, synapses become overactive and prompt neurodegeneration.

Fernandes, A.C., et al. 2014. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201406026>.

DDR1 key for cancer cell escape



Activated Cdc42 (red) colocalizes with a marker of linear invadosomes (green), as shown in a whole-cell image (left) and a close-up (right).

sions called invadosomes that break down collagen and allow the cells to slip through. Although invadosomes—the term encompasses the invadopodia of cancer cells and the protrusions of healthy cells—form in a variety of situations, type I collagen induces cancer cells to produce linear invadosomes that orient along collagen fibers. To their surprise, the researchers previously found

Juin et al. identify the receptor that allows cancer cells to recognize and break through type I collagen.

Type I collagen is prevalent in many tumors. But in contrast to what researchers long thought, it does not corral cancer cells. Instead, cancer cells grow actin-containing exten-

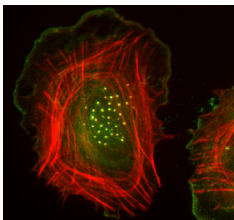
sions called invadosomes that break down collagen and allow the cells to slip through. Although invadosomes—the term encompasses the invadopodia of cancer cells and the protrusions of healthy cells—form in a variety of situations, type I collagen induces cancer cells to produce linear invadosomes that orient along collagen fibers. To their surprise, the researchers previously found

that integrins, the main collagen receptors, aren't involved in formation of this type of invadosome. Juin et al. determined that Discoidin Domain Receptor 1 (DDR1), a protein overexpressed in many cancers, senses type I collagen and induces the formation of linear invadosomes. When the researchers knocked down DDR1, cells were unable to infiltrate a 3D collagen gel, suggesting that the protein is important for metastasis.

Although DDR1 is a tyrosine kinase, blocking its kinase activity didn't inhibit linear invadosomes. The invadosome inducer Src had no role in their growth either. The researchers found that DDR1 indirectly activated the guanine nucleotide exchange factor Tuba, which then switched on Cdc42. In turn, Cdc42 promoted actin polymerization and spurred invadosomes to grow. The results suggest that blocking DDR1's ability to induce linear invadosomes might curtail metastasis.

Juin, A., et al. 2014. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201404079>.

Melanoma cells travel on calcium cycles



Several invadopodia (yellow dots) are visible sprouting from a melanoma cell labeled for actin (red) and cortactin (green).

Oscillating calcium levels enable melanoma cells to become invasive, Sun et al. report.

Two proteins, STIM1 and Orai1, are vital for store-operated calcium entry, a process that enables cells to absorb calcium. When calcium levels in the ER dip, STIM1 oligomerizes and travels to the junction between the ER and the plasma membrane. There, it stimulates Orai1 to form a pore in the plasma membrane that admits calcium.

Breast cancer cells require STIM1 and Orai1 to metastasize, but the underlying mechanism wasn't clear.

Sun et al. found that melanoma cells lacking STIM1 and Orai1 sprouted about half as many invadopodia, the extensions that cancer cells use to bore into and dissolve the ECM, as did controls.

But it takes more than an influx of calcium to induce the protrusions. Compounds that induce a surge of calcium into cells inhibited invadopodium growth. Instead, invadopodium formation requires oscillating intracellular calcium levels. Depleting STIM1 and Orai1 suppresses these cycles.

Calcium oscillations also promote invasion in another way, the researchers discovered. MT1-MMP, one of the proteases that cancer cells use to dissolve ECM, normally cycles in and out of the invadopodium's plasma membrane. But depleting STIM1 and Orai1 trapped MT1-MMP inside endosomes, thus preventing the enzyme from recycling to the plasma membrane, where it can attack the ECM.

Why cells rely on oscillations—rather than just an increase—in calcium levels isn't clear. Large amounts of calcium can be lethal to cells, so one possibility is that the fluctuations prevent it from reaching toxic levels.

Sun, J., et al. 2014. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201407082>.