In This Issue

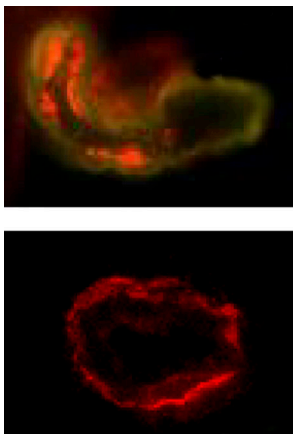
Fighting Alzheimer's by defusing a death receptor

A receptor that incites cell suicide also promotes the accumulation of β-amyloid plaques in Alzheimer's disease (AD), as He et al. show on page 829. In mice prone to the brain buildups, eliminating the receptor cut the number of plaques and spared memory. The results point to new treatments for the incurable disease.

As plaques of β-amyloid collect in the brains of AD patients, large numbers of neurons die. Scientists suspect that this devastation stems from abnormal processing of APP, which leads to too much β-amyloid, or out-of-control inflammation—or a combination of the two.

A potential link between these two mechanisms is the tumor necrosis factor type 1 death receptor (TNFR1), which triggers brain cells to kill themselves. TNF-α, which is activated during brain inflammation, switches on the receptor. Three years ago, the researchers showed that β-amyloid could also stimulate TNFR1. He et al. wanted to determine whether TNFR1 affects plaque accumulation and APP processing.

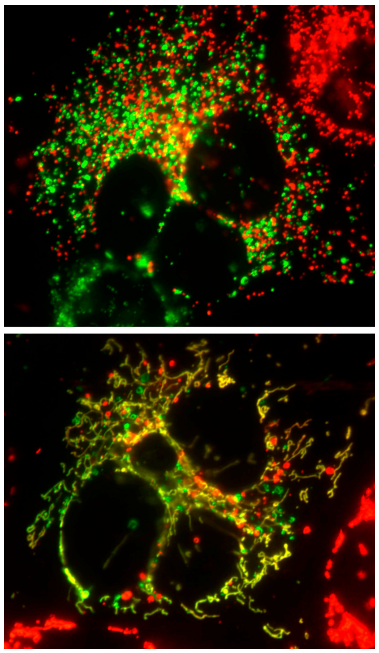
Their subjects were mice that lack TNFR1 and pump out excess APP. Without the receptor, more neurons survived, and the animals carried fewer, smaller plaques. Their brains sported smaller numbers of activated microglia, inflammation-promoting immune cells that are switched on in AD. The rodents also performed better on two memory tests.



β-amyloid (green) clumps in the blood vessels of control mice (above), but the vessels of rodents lacking TNFR1 are clear (below).

Removal of TNFR1 also slashed the amount of β-amyloid the mice fashioned by cutting the amount and activity of β-secretase, one of the enzymes that snips APP to make β-amyloid. TNF-α normally spurs β-secretase production through a pathway that requires NF-κB, the researchers found.

Overall, the study indicates that TNFR1 is pivotal in a destructive positive feedback loop. Inflammation boosts the amount of TNF-α, cranking up the death receptor pathway and producing more β-amyloid, which in turn further stimulates TNFR1. Drugs that block TNFR1 might short-circuit this pathway and save the brain cells of AD patients. JCB



In a cell lacking OPA1 (top), mitochondria (red and green) remain aloof, but the combination of long and short OPA1 isoforms spurs them to fuse (bottom).

The long and short of mitochondrial fusion

Mitochondria malfunction unless they occasionally fuse with each other. Papers by Song et al. (page 749) and Griparic et al. (page 757) now elucidate the protein processing necessary for these mergers and pin down one of the responsible enzymes.

A protein matchmaker that promotes mitochondrial unions is OPA1, which is located in the organelle's inner membrane. The protein is faulty in dominant optic atrophy, an inherited form of blindness. OPA1's many varieties—there are eight mRNA splice variants, each of which encodes polypeptides that undergo further processing—fall into two categories: long and short. Yeast harbor a similar protein and require both lengths for fusion. But a previous study suggested that only the long form is responsible for mitochondrial fusion in mammals.

Song et al. wanted to determine what the short forms were doing. They engineered mouse fibroblasts that lacked the gene for OPA1 to manufacture different combinations of long and short variants. Long versions alone didn't spur mitochondria to get together, the researchers found. Nor did the short forms. But mitochondria coalesced in cells that produced a mixture of long and short OPA1. The researchers suspect that their results differ from the previous finding because that group used RNAi to knock down OPA1, and some residual short proteins might have persisted in the cells.

Several proteins might cut OPA1 down to size. Song et al. found that the enzyme Yme1L triggers cuts at one position in OPA1, suggesting that it directly or indirectly helps produce the short form. Work by Griparic et al. also implicated the enzyme in slicing OPA1 to promote fusion. Their results also suggest that another unidentified protein is involved. The next question for researchers to tackle is why fusion requires both types of OPA1. JCB

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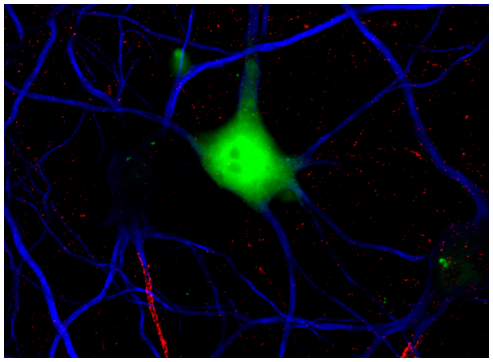
AIS neurofascin'd to matrix

Thoughts and movements depend on the axon initial segment (AIS), which instigates action potentials. On page 875, Hedstrom et al. show how a protein crucial for nerve development helps build the AIS by coating it with a layer of extracellular matrix.

The AIS passes on an action potential to the nodes of Ranvier, which relay it along the rest of the axon. Although the two kinds of structures harbor almost the same molecules, they form differently. In the peripheral nervous system, neighboring Schwann cells draw the axonal protein neurofascin-186 (NF-186) to an incipient node. In turn, NF-186 lures other components, such as the cytoskeleton protein ankyrin G and sodium channels. The AIS, by contrast, assembles from its own internal signals. Studies disagree about which molecule recruits the others.

To clear up the confusion, Hedstrom et al. used RNAi to eliminate AIS molecules one at a time from cultured neurons. When they knocked down ankyrin G, the other components stayed away from the AIS. However, the molecules congregated even when NF-186 or the sodium channels were missing, indicating that ankyrin G gets there first.

The researchers discovered that NF-186 does have an important job during AIS formation: it attracts extracellular matrix rich in the proteoglycan brevican and hooks it to the AIS. Hedstrom et al. now plan to investigate how this layer helps the AIS fire up an action potential. JCB

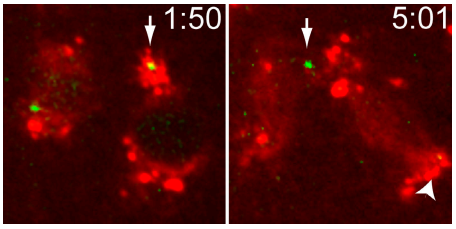


Brevican (red) keeps clear of the AIS in neurons in which NF-186 is blocked (green).

Centering the centriole

Like a sailboat, centrioles drift away if they aren't properly moored, as Lucas and Raff show on page 725. The researchers pin down a protein that helps keep the structures in place.

A pair of centrioles sits inside a cloud of pericentriolar matrix (PCM), creating the centrosome. It serves as a hub for the microtubules that form the spindle apparatus, which divvies up the chromosomes during mitosis. What connects the centrioles to the PCM and keeps them in position isn't clear. Previous work suggested that the protein centrosomin (Cnn) attracts other proteins to the centrosome. Lucas and Raff wanted to determine whether Cnn tethered the centrioles.



A centriole (green) speeds away from the PCM (red) in a Cnn mutant embryo.

They started with syncytial fly embryos, in which hundreds of dividing nuclei share a common cytoplasm. In embryos lacking Cnn, PCM still gathered at the centrioles, but the centrioles refused to stay put. Instead, they "rocketed" through the cytoplasm, trailing PCM. Microtubules powered the centrioles' escape.

These travels can foul up mitosis because the centriole often loses connection with the spindle poles. Such poles lack asters and can become entangled with neighboring spindles.

Loss of Cnn had a similar effect in larval somatic cells. Centrioles strayed during mitosis, and cells sometimes ended up with extras. The work suggests that Cnn helps tie the centrioles to the PCM. The molecular mechanism is uncertain, but the researchers speculate that Cnn restrains centrioles in the middle of the centrosome by strengthening the PCM. JCB

To make a nuclear pore, just relax

Staying limber is crucial not just for yoga enthusiasts, but for cells installing nuclear pores, as Scarcelli et al. report on page 799. They identify a protein that helps the passageways assemble by boosting the flexibility of the nuclear membrane.

Every molecule that enters or exits the nucleus passes through a nuclear pore complex. How cells build these channels remains murky, however. Scarcelli et al. chanced on a key contributor because of their interest in how cells export RNA from the nucleus. That process goes awry in yeast missing the protein Apq12.

Cooling Apq12-lacking cells inhibited their growth, the researchers found, in part because mutant cells can't assemble nuclear pores. Instead, many of their pore proteins, particularly those from the filaments, clustered in the cytoplasm. Warming the cells allowed them to fashion complexes again and sent the mislocalized proteins back to become part of new pores.

One way that cells cope with lower temperatures is to alter the composition of the nuclear membrane to maintain its flexibility. Scarcelli et al. hypothesized that Apq12-deficient yeast can't make that adjustment. To test the idea, the researchers exposed the cells to benzyl alcohol, which slips into the membrane and loosens it up. The alcohol spurred the out-of-place pore proteins to return to their normal locations. The work indicates that Apq12's job is to maintain membrane flexibility. The researchers now want to determine how the protein performs that task. JCB