In This Issue

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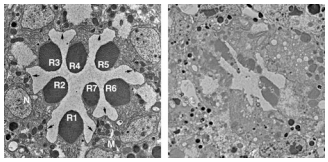
Sphingolipid imbalance can take out an eye



Normal eye receptor cells (left) contrast with degenerating cells (right) in a fly that overproduces an enzyme involved in sphingolipid synthesis.

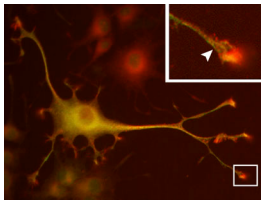
Yonamine et al. report that the relative amounts of two sphingolipids control the breakdown of light-sensing proteins and determine whether eye cells survive.

Sphingolipids aren't just building blocks of membranes. Some of the molecules, such as sphingosine 1 phosphate (S1P) and dihydrosphingosine 1 phosphate (DHS1P), take part in signaling pathways that manage everything from heart development to immune cell migration. Yonamine et al. found that these sphingolipids also control endocytosis of rhodopsin and another light-sensitive eye protein, the transient receptor potential (TRP) channel. After exposure to light, receptor cells in the *Drosophila* eye reduce the levels of these proteins at the membrane. Many of the proteins eventually recycle back to the membrane, but some are diverted to the lysosome for destruction. If too many of these proteins is destroyed, however, photoreceptor cells degenerate.

The researchers found that the balance between recycling and degradation depends on the balance between DHS1P and S1P. When the researchers engineered flies to boost their production of sphingosine kinase 2, which helps synthesize DHS1P, lysosomal destruction of rhodopsin and TRP surged, and large numbers of receptor cells in the animals' eyes perished. Yonamine et al. saw the same effect if they increased the amount of DHS1P in the animals' diet. How the ratio between DHS1P and S1P affects cell survival isn't clear, but the researchers suggest that the excessive breakdown of TRP, which normally lets calcium into the cells, dramatically reduces cytosolic calcium levels, causing the cells to die.

Yonamine, I., et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201004098.

Annexin keeps tau on a short leash



Tau (green) and annexin A2 (red) cohabit at the growing tip of a neural cell (arrow).

Gauthier-Kemper et al. identify tau's membrane tether and show how the protein breaks free in a form of dementia.

Some cases of frontotemporal dementia (FTD) and Alzheimer's disease (AD) have similar symptoms and a common molecular malfunction. Microtubule (MT)-binding tau proteins that normally settle in axons bunch up in the cell body, which can kill the neuron. One difference between the diseases relates to tau phosphorylation. In AD, tau is hyperphosphorylated, which might allow the protein to abscond to the cell body by breaking its connection to MTs. But in one of the most common inherited forms of FTD, mutant tau carries fewer phosphate groups than normal. Researchers haven't explained how this hypophosphorylated form of the protein gets loose.

Tau links to the cell cortex and adjusts MT dynamics during processes such as axonal growth. Gauthier-Kemper et al. found that the extensions that sprouted from neural cells carrying a form of mutant tau from FTD patients were fragile and highly dynamic, rapidly elongating and then collapsing. In the brain, such behavior might cause synapses to disconnect. However, Gauthier-Kemper et al. showed that this version of tau can still attach to MTs, ruling out one possible explanation for its mislocalization to the cell body.

Instead, the problem appears to be tau's connection to the cell cortex. The researchers determined that the protein annexin A2 normally fastens tau to the plasma membrane. But mutant tau didn't bind annexin A2 and could thus escape from the axon tip, perhaps because the mutant's reduced phosphorylation prevents it from making the connection.

Gauthier-Kemper, A., et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201007161.

Natural killer cells commute death sentence

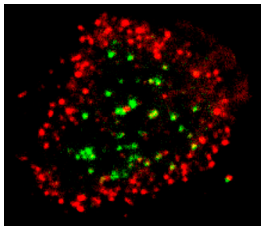


IMAGE COURTESY OF PREENI ABEYWEERA

A ring of inhibitory receptors (red) surrounds activating receptors (green) on the surface of a natural killer cell.

Natural killer (NK) cells sometimes target a friend instead of a foe. Abeyweera et al. reveal how healthy cells call off a misdirected attack.

An NK cell hunts down and destroys tumor cells and cells infected by viruses. Once it detects the characteristic surface proteins that betray one of these abnormal cells, an NK cell delivers the kiss of death, glomming onto its target and forming a cytolytic synapse. But the killer checks for an additional form of ID—the class I MHC protein, which is mainly expressed by healthy cells. A mystery is how an NK cell's inhibitory receptors, which halt an attack in response to class I MHC, override the activating receptors that spur the cell to kill.

Abeyweera et al. crafted an HLA protein—the human version of the class I MHC molecule—that fit a specific inhibitory receptor on NK cells only after exposure to UV radiation. Thus, the researchers could switch on the attack-canceling mechanism with a flash of light.

Contact with a would-be victim triggers a series of responses in an NK cell. Actin polymerizes and forms a ring at the edge of the cytolytic synapse. Clusters of activating receptors gather in the synapse, and cytosolic calcium levels rise, enabling the cell to release cytotoxic proteins. Switching on the customized HLA protein reversed all these changes except for the calcium surge, and NK cells let go of the target surface. However, the cells held tight if their inhibitory receptors lacked signaling activity. These results suggest that inhibitory receptors countermand attack signals by undermining the cytolytic synapse.

Abeyweera, T.P., et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201009135.