Research Roundup

Shuffling of neuronal receptors

Local diffusion of neurotransmitter receptors keep a neuron working fast, say Martin Heine, Daniel Choquet (CNRS, Bordeaux, France), and colleagues.

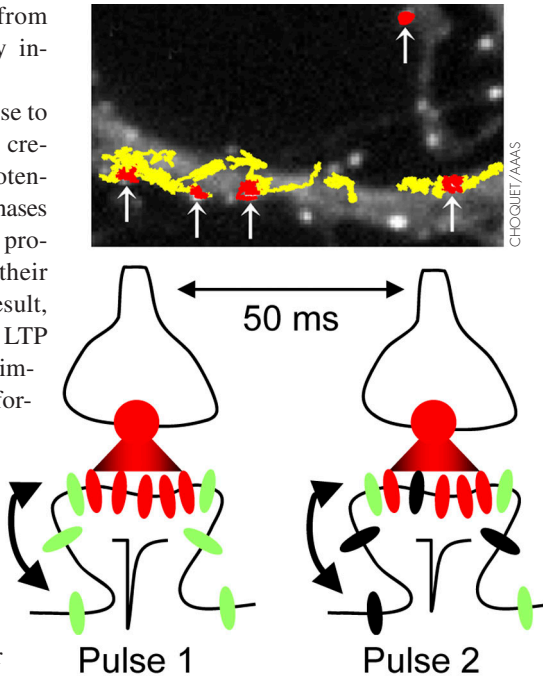
Synapses can become desensitized to quickly repeated stimulations. The receptors that receive signals such as glutamate become structurally altered by their ligands. So if a second stimulus comes too soon, the synapse is unable to react. Recovery from this desensitization—by reversing the structural changes—takes ~100 ms. Yet somehow synapses can decipher two glutamate signals that arrive within just 10 ms of each other.

The findings from Heine et al. suggest that this quick response occurs because nearby receptors that have not yet met glutamate diffuse laterally within the membrane, replacing the desensitized receptors. When the authors limited receptor diffusion via receptor cross-linking or aggregation, the synapses lost their ability to respond to rapid repeated stimulation. Receptor mobility and recovery from desensitization was also blocked by increases in intracellular calcium.

Calcium influx is a normal response to the high-frequency stimulation that creates learning-associated long-term potentiation (LTP). The calcium activates kinases that might phosphorylate scaffolding proteins, perhaps thereby improving their ability to trap local receptors. As a result, synapses that have already achieved LTP mainly respond only to the slower stimulations that accompany typical information processing.

Choquet said his group didn't expect that receptor mobility would curtail desensitization, since diffusion is thought to be too slow. But he explains that it's possible because "smaller areas lead to a faster exchange. The neurotransmitter region is only a few hundred nanometers, so it can create an impact on a short time scale." JCB

Heine, M., et al. 2008. *Science.* 320:201–205.



CHOQUET/AAAS

Glutamate receptors wander (top, yellow lines) in and around synapses (arrows). At synapses, naive receptors (bottom, green) replace desensitized ones (black).

Hungry cells eat ribosomes

Starving cells seem to first gobble up their ribosomes before they start cannibalizing anything and everything, based on results from Claudine Kraft, Matthias Peter, and colleagues (ETH, Zürich, Switzerland). Using a ribosome-specific autophagy pathway, cells might match ribosome number to metabolic needs.

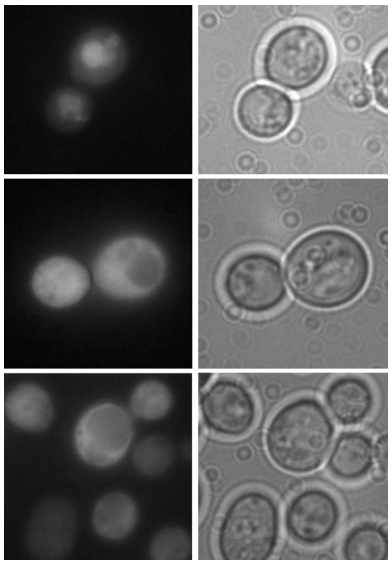
When nutrients are scarce, autophagy allows cells to degrade their internal components and focus on only the essentials. Kraft et al. noticed that one of the first sets of components dumped into vacuoles, where autophagocytosed products are digested, included ribosomes. Their early deposition required several known autophagy genes.

Autophagosomes can engulf either bulk cytoplasm, and anything that comes along with it, or only specific elements, such as mitochondria. According to the new results, ribosomes were taken in selectively by a pathway that the authors dubbed ribophagy, which depended on a ubiquitin-cleaving enzyme called Ubp3p and its cofactor, Bre5p.

Ubp3p mutant cells die upon nutrient starvation, possibly because of their inability to digest ribosomes—an excellent first option for autophagy, according to Peter. "They're rich in protein and RNA, so they provide plenty of building blocks like amino acids. Maybe the starvation response isn't all-or-none. Cells could first get rid of ribosomes and only as a last resort randomly degrade cytoplasm, which can be damaging. You never know what might get destroyed that you might need later."

Peter also imagines that ribophagy is not restricted to starving cells. "Half of a cell's energy goes into ribosome biogenesis and protein synthesis," he says. Autophagy of these very stable organelles might "make sure a cell has only as many as it needs to translate its proteins. Perhaps ribosome number may be adjusted all the time to growth conditions." The pathway might also destroy faulty ribosomes. So far, however, how the organelles are marked as defective or surplus is not known. JCB

Kraft, C., et al. 2008. *Nat. Cell Biol.* doi:10.1038/ncb1723.



PETER/MACMILLAN

Ribosomes (white) end up in the vacuole in starving cells, unless either of the ribophagy proteins Ubp3p (middle) or Bre5p (bottom) is missing.

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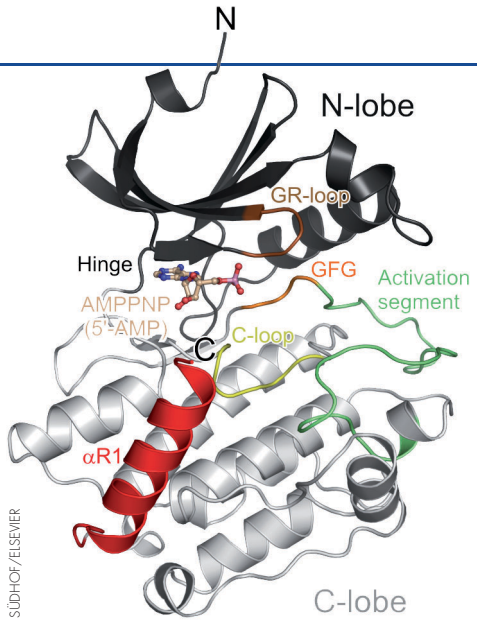


The crystal structure of CASK has an ATP-binding pocket and resembles active kinases.

Pseudokinase is active after all

Don't judge a book—or a kinase—by its cover, based on new findings from Konark Mukherjee, Thomas Südhof (University of Texas Southwestern Medical Center, Dallas, TX), Markus Wahl (Georg-August-University, Göttingen, Germany), and colleagues. The group shows that a kinase predicted to be inactive has plenty of phosphorylation power.

This not-so-disabled kinase is CASK. CASK lacks the residues needed to coordinate magnesium, which was thought to be required to transfer phosphates. But the new findings suggest that CASK works without magnesium.

The group's new crystal structure of CASK adopted a conformation that is characteristic of constitutively active kinases. And it contained a pocket that looks like it should bind very well to ATP. "It would be weird," says Südhof "for CASK to bind ATP and have an active conformation but be inactive." The group thus thoroughly tested its kinase abilities.

Even in the absence of magnesium, CASK phosphorylated one of its known binding partners, a synaptic adhesion molecule called neurexin-1. The biological outcome of the modification is not known. CASK probably has several other substrates, as it is widely expressed and contains a protein-interacting scaffolding domain.

Several pseudokinases similarly lack magnesium coordination centers. At least some of these proteins might have previously overlooked phosphorlyation skills. JCB

Mukherjee, K., et al. 2008. *Cell.* 133:328–339.

Channel changes customers

With the right stimulation, an ion channel changes its stripes, say Man-Kyo Chung, Ali Guler, and Michael Caterina (Johns Hopkins School of Medicine, Baltimore, MD).

Even ion channels that are a little promiscuous have their favorite passengers. Such channels were generally thought to stay true to their preferred customers. But Chung et al. found that the TRPV1 channel of pain-sensing neurons was more fickle.

TRPV1 opens its gates when it binds to the chili pepper compound, capsaicin. The new electrophysiology experiments showed that, upon first opening, the channel mostly let through small cations, such as calcium and sodium. But over time, the channel became more permissive to larger cations.

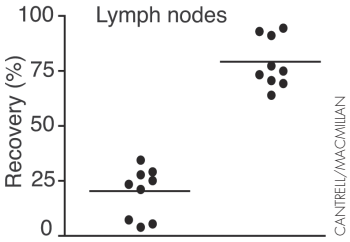
The channel also tweaked its preference for calcium over sodium. When extracellular calcium levels were high, the channel's preference for calcium waned with time. But if calcium levels were low, its calcium preference further increased.

The alterations probably stem from structural changes upon capsaicin binding. Heat and camphor also open the channel, but they did not have such a strong effect on passenger preferences. TRPV1 phosphorylation, by contrast, amplified the selectivity changes. "This is another layer at which the details of ionic flux into the cell can be regulated," says Caterina. It is not clear, however, which large cations that might enter through TRPV1, such as spermidine, are physiologically relevant to neurons. JCB

Chung, M.-K., et al. 2008. *Nat. Neurosci.* doi:10.1038/nn.2102.

mTOR sends T cells on their way

Only well-fed T cells explore the body for intruders, if results from Linda Sinclair, Doreen Cantrell (University of Dundee, Scotland), and colleagues are any indication. T cell trafficking, the group finds, is linked to nutrient-sensing pathways.



More T cells remain in lymph nodes instead of exploring the body in mice when the mTOR/PI3K pathway is blocked (right).

The group connected nutrient status with trafficking when they noticed that stimuli that decrease T cells' cache of nutrient receptors boost levels of CCR7 and L-selectin, which help keep T cells in lymph nodes. When nutrients are plentiful, metabolism is dialed up by the mTOR/PI3K pathway, which the group now shows reduces L-selectin levels via two routes.

In one route, PI3K and its PIP3 lipid product led to the rapid cleavage of L-selectin on the T cell surface. A later-acting path prevented the transcription of CCR7 and new L-selectin.

L-selectin and CCR7 levels are normally turned down when T cells are activated by antigen in the lymph nodes. The loss allows foreigner-fighting T cells to leave the node and head to remote tissues. The new results suggest that this exit does not occur in starved cells, which cannot turn on mTOR; inhibiting mTOR/PI3K in mouse cells restored L-selectin levels and retained T cells in lymph nodes.

"The system ensures that a T cell does not leave the node," says Cantrell, "until it is in a metabolic state to do its job. It's like explorers making a dash for the North Pole. They need to be well fed before they go. And if they're not, they should return to base camp." JCB

Sinclair, L.V., et al. 2008. *Nat. Immunol.* doi:10.1038/ni.1603.