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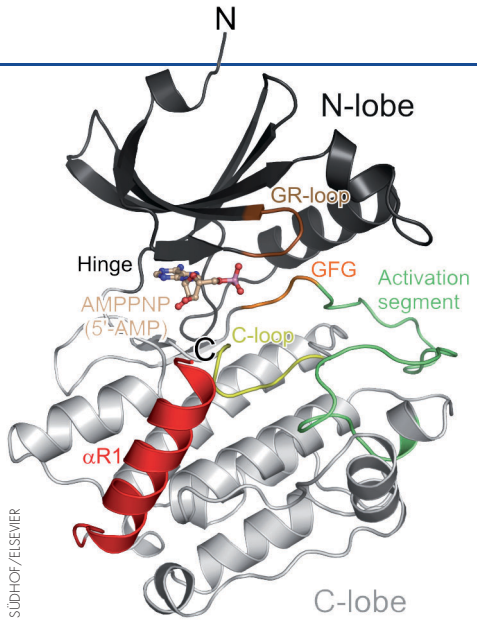


SÜDHOF/ELSEVIER

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.

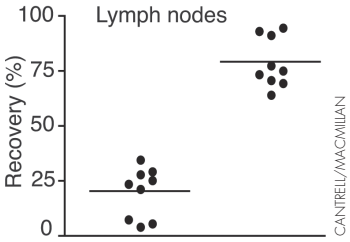
The channel also tweaked its preference for calcium over sodium. When extracellular calcium levels were high, the channel's preference for calcium waned with time. But if calcium levels were low, its calcium preference further increased.

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.



CANTRELL/MACMILLAN

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.