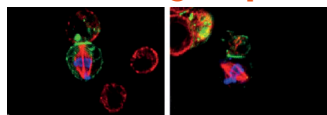


Ran drags spindles through the Mud



Compared with control cells (left), the spindle (red) doesn't orient towards Pins (green) in cells lacking Canoe (right).

The Ran GTPase orients the mitotic spindle by controlling the recruitment of a motor adaptor protein to the cell cortex, Wee et al. report.

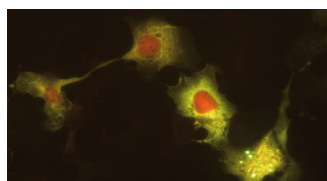
Spindle orientation can determine the fate of daughter cells by affecting the proteins they inherit or the position they occupy within a tissue. A key factor controlling spindle alignment is the protein Pins, which localizes to the apical cortex and recruits both plus- and minus-end-directed microtubule motors to pull the spindle into position. Pins recruits the dynein-dynactin motor complex by binding to the adaptor protein Mud. It also recruits another protein required for spindle orientation, called Canoe, but Canoe's precise function in the process is unclear.

Wee et al. found that Canoe works with Pins to recruit Mud and orient the spindle. Cells lacking Canoe couldn't accurately align their spindles with a cortical patch of Pins because Mud was no longer recruited to the cortex. Although Canoe was found to directly bind to Pins, it doesn't appear to interact with Mud. Instead, the researchers found that Canoe promotes Mud's cortical recruitment by interacting with the GTP-bound form of Ran, a small GTPase that helps assemble the mitotic spindle. Cells expressing lower amounts of Ran, or a version of Canoe unable to bind the GTPase, couldn't recruit Mud to their cortical Pins domains and failed to orient their spindles correctly.

It remains to be seen how Ran and Canoe promote Mud's recruitment to the cell cortex. Wee et al. also want to identify additional proteins that help orient the spindle by performing an RNAi screen.

Wee, B., et al. 2011. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201102130>.

PKA cuts down on HDAC4 signaling



In the presence of PKA and CaMKII, full-length HDAC4 (yellow) is cytoplasmic, but an N-terminal fragment (red) remains in the nucleus.

Backs et al. report that protein kinase A (PKA) may protect the heart from stress by inducing the proteolytic cleavage of a histone deacetylase.

Prolonged stress can induce harmful remodeling of cardiac muscle, eventually leading to heart failure. These pathological changes

and stimulated its cleavage by a serine protease.

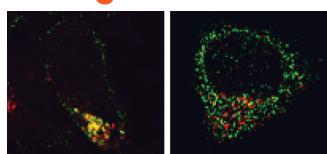
The resulting N-terminal fragment of HDAC4 could still bind and repress MEF2, but it no longer contained the serine residues targeted by CaMKII and therefore remained in the nucleus to inhibit MEF2 even when this kinase was active. The HDAC4 fragment generated by PKA may therefore protect cardiac tissue from stress-induced remodeling.

PKA and CaMKII are both activated downstream of the β -adrenergic receptor. Authors Eric Olson and Johannes Backs think that sustained adrenergic stimulation may favor CaMKII activation and pathogenic cardiac remodeling, whereas shorter bursts of adrenaline (during physical exercise, for example) may activate PKA and promote cardioprotection. The Backs lab now wants to investigate whether HDAC4 cleavage can be manipulated to treat cardiovascular disease, either by targeting the yet-to-be identified protease or by overexpressing the HDAC4 fragment in heart tissue using adenovirus.

Backs, J., et al. 2011. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201105063>.

are partly driven by calcium/calmodulin-dependent protein kinase II (CaMKII), which phosphorylates the histone deacetylase HDAC4, triggering its export from the nucleus so that it no longer inhibits the stress-responsive transcription factor MEF2, thereby inducing the expression of cardiac-remodeling genes. Backs et al. investigated whether other signaling pathways affect HDAC4 activity and found that PKA bound to the deacetylase

PLD gives nutritional advice to mTORC1



PLD1 (green) is delivered to lysosomes (red) in the presence of amino acids (left) but not if hVps34 is inhibited (right).

Yoon et al. describe how two signaling pathways combine to ensure that cells only grow when sufficient nutrients are available.

The kinase complex mTORC1 stimulates protein synthesis in response to various growth factors, as long as

phospholipase D1 (PLD1), an enzyme that activates mTORC1 by generating phosphatidic acid. Amino acids boosted PLD1 activity in cells as long as hVps34 was active. PLD1, in turn, was required for amino acids and hVps34 to stimulate mTORC1. hVps34 activated PLD1 by producing phosphatidylinositol 3-phosphate, which bound to a lipid-binding PX domain in PLD1.

Amino acids and hVps34 also stimulated PLD1's translocation to lysosomes, a necessary step for mTORC1 activation. PLD1 was still delivered to lysosomes in cells lacking Rag GTPases, however, indicating that the two amino acid-sensing pathways—hVps34 and Rag—act in parallel to bring PLD1 and mTORC1 together when nutrient levels are high enough to permit growth. Senior author Jie Chen now wants to investigate where in the cell hVps34 stimulates PLD1 and to determine why lysosomes are the designated site of mTORC1 activation.

Yoon, M.-S., et al. 2011. *J. Cell Biol.* <http://dx.doi.org/10.1083/jcb.201107033>.

the cell's supply of amino acids is plentiful. If enough nutrients are available, the Rag family of small GTPases helps deliver mTORC1 to lysosomes, where the kinase complex is activated. The phosphatidylinositol 3-kinase hVps34 is also thought to promote mTORC1 activity in the presence of amino acids, but how this enzyme controls mTORC1 is unclear.

Yoon et al. found that hVps34 stimulated the activity of