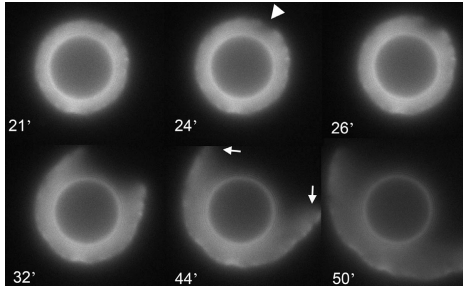


## Breaking down symmetry



VAN DER GUCHT/NAS

**Spontaneous breaking of a symmetrical actin gel surrounding a bead opens up a hole for movement.**

A bead surrounded by a symmetrical actin network cannot move until the symmetry is spontaneously broken, say Jasper van der Gucht, Cécile Sykes, and colleagues (Institut Curie, Paris, France).

Actin machinery *in vivo* typically becomes polarized in response to external cues that trigger directional movement. In the absence of such signals, however, achieving polarization requires breaking part of the actin network. Such is the case for isolated cells at rest or for van der Gucht's experimental system, in which beads coated with actin polymerization proteins are mixed with actin monomers, ATP, and other proteins.

During symmetry breaking, a fracture appeared at the outer actin rim, which then grew inward and expanded to open up a hole within the network. Once the hole was wide enough, the bead escaped through it and was pushed forward by a trailing actin comet.

Using physical models of gel fracturing dating back to 1920, Sykes' group determined that this spontaneous symmetry breaking is caused by the release of elastic stress. Growth of the polymerized and cross-linked actin network moves the network outwards, leading to the greatest tensile stress and stretching at the outer gel surface. Once the stretching stress exceeds the strength of the actin network, a fracture forms and releases stored elastic energy, thereby leading to actin network polarization. As van der Gucht says, "Any elastic material under stress will eventually break." **JCB**

Reference: van der Gucht, J., et al. 2005. *Proc. Natl. Acad. Sci. USA*. 102:7847-7852.

## Weaker is better

Antigenic therapy researchers have long relied on repeated dosing of high-affinity ligands to inactivate select T cells by causing overstimulation that leads to apoptosis. Contrary to this strategy, Bingye Han, Pau Serra, Pere Santamaria (University of Calgary, Alberta, Canada), and colleagues now show that low-affinity peptides targeting autoreactive T cells protect mice more effectively against diabetes than do high-affinity peptides.

Peptides that are similar in sequence to a portion of islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP) that strongly bound to autoreactive T cells nearly completely obliterated this T cell pool in mice. But lurking in the background were smaller pools of autoreactive T cells that were impervious to the high-affinity peptide, yet reactive against other portions of IGRP. Once their competition had been eliminated, these cells emerged to fill in the vacant niche. The high-affinity peptide thus failed to protect against diabetes.

Low-affinity peptides, by contrast, selectively eliminated the most menacing of IGRP-reactive T cells, while maintaining a substantial population of more benign T cells that recognized, but were not harmed by, the peptides. By becoming established as the dominant population, the nonpathogenic T cells effectively blocked more reactive but less prevalent T cells from taking over.

Now with a better grasp on the fine balance between ligand binding and dosage, Santamaria says, "targeting multiple epitopes simultaneously is likely to be more practical than finding the optimal dose for deletion of high-avidity subtypes while preserving low-avidity subtypes." **JCB**

Reference: Han, B., et al. 2005. *Nat. Med.* doi:10.1038/nm1250.

## Putting the pinch on cell division

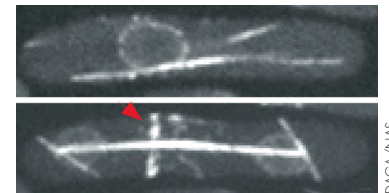
The mitotic spindle sets the division plane in mammalian cells. But fission yeast instead use their nuclei to position the division plane during mitosis, say Rafael Daga and Fred Chang (Columbia University, New York, NY).

Based on previous research implicating the nucleus in plant and fungi cell division, the authors investigated the consequence of repositioning the nucleus to one end of the cell by spinning cells at low speeds. Asymmetric cell division ensued if the nucleus did not migrate back to the center before mitosis.

Moving the nucleus during interphase resulted in a single displaced contractile ring, whereas moving it during early mitosis caused multiple rings or ring fragments to develop. If positioned close enough together, the fragments coalesced before division. Daga and Chang suspect that ring compaction, which normally occurs during ring assembly, may also bring together ring fragments, thus avoiding the formation of multiple division sites.

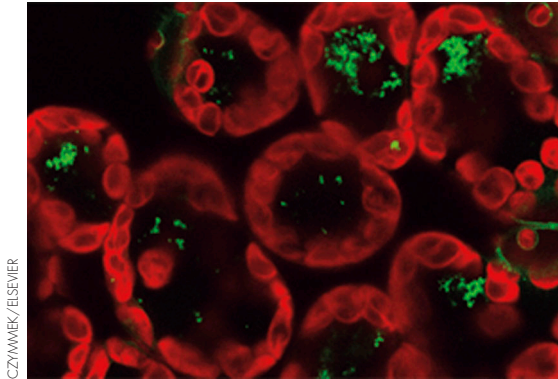
Chang previously observed that the position of mid1 on the cell surface tracks with the movement of the nucleus. As mid1 is required for ring positioning, Chang thinks that the nucleus may use this protein to communicate with the contractile ring. He suspects that "something is physically connecting mid1 to the nucleus." He and his coworkers have already ruled out actin or microtubules as this tethering material, so they are now examining less obvious candidates. **JCB**

Reference: Daga, R.R., and F. Chang. 2005. *Proc. Natl. Acad. Sci. USA*. 102:8228-8232.



**The position of the yeast nucleus in early mitosis (top) determines where the contractile ring forms (red arrow; bottom).**

DAGA/NAS



CZYMIK/ELSEVIER

Plant cells generate autolysosomes (green) following viral infection to limit the spread of cell death.

## The death stops here

Plants rely on a sensitive process of programmed cell death to curtail pathogenic infection by selectively executing infected cells. To prevent the death response from spreading to noninfected areas, cells near and at the site of infection activate autophagy, say Yule Liu, S. Dinesh-Kumar (Yale University, New Haven, CT), and colleagues. In virus-infected plants that are unable to turn on autophagy, cell death spreads from the site of infection to surrounding healthy tissues and even to adjacent leaves.

“The programmed cell death response is very discrete, and we were interested in answering the question of what makes death stop,” says Dinesh-Kumar. To that end, the team used RNAi to identify genes involved in disease resistance and the programmed cell death response. They struck death paydirt when they silenced *BECLIN1*, a gene that has been implicated in autophagy based on its abilities to rescue autophagy-defective yeast and to prevent premature senescence in plants.

Whether the plant was attacked by viral, bacterial, or fungal pathogens, *BECLIN1* and other autophagy genes limited pathogen-induced cell death to the infection site and also repressed viral replication. These findings contrast with the situation in mammalian cells, where autophagy genes are required for initiating programmed cell death when apoptotic machinery is compromised. Autophagy may promote cell survival by controlling the production of the pro-death signal, preventing the movement of the signal into uninfected cells, or protecting cells against cellular damage caused in defense against pathogenic invasion.

The group also discovered that the spreading pro-death signal does not arise from the virus itself. Sites of virus infection within leaves did not expand despite extensive cellular death throughout the plant, and plants infected with just the viral protein that elicits the programmed cell death response still showed widespread cell execution despite the viral protein’s inability to move. The big mystery, and a new focus for Dinesh-Kumar’s research, therefore centers on identifying this mobile pro-death signal and its origin. **JCB**

Reference: Liu, Y., et al. 2005. *Cell*. 121:567–577.

## Making mature attachments

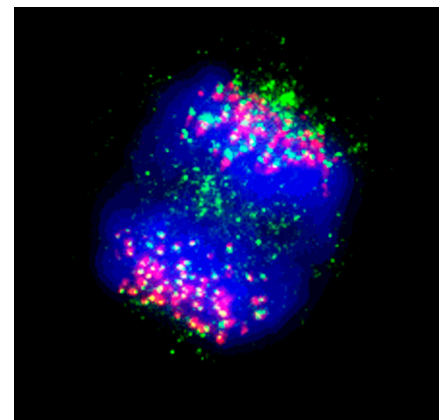
During mitosis, the absence of Ran-GTPase pathway components at kinetochores leads to aberrant attachment of kinetochore fibers, disordered mitotic spindle assembly, and haphazard chromosome segregation at anaphase. To ensure that Ran complex proteins get where they need to be, Crm1—the Ran-GTP-binding nuclear export receptor—goes moonlighting at kinetochores after nuclear envelope breakdown, according to Alexei Arnaoutov, Mary Dasso (National Institute of Child Health and Human Development, Bethesda, Maryland), and colleagues.

Crm1 binds to its export cargo in complexes that also contain Ran-GTP. Blocking the formation of these Crm1-cargo-Ran-GTP complexes, either by preventing cargo binding or by starving cells of Ran-GTP, resulted in no Ran-GAP1/Ran-BP2 kinetochore recruitment, which was bad news for dividing cells. Crm1-blocked cells rarely established mature kinetochore fiber attachments between kinetochores and spindle poles.

The microtubules within kinetochore fibers failed to end discretely and attach to kinetochores at their plus ends. Instead, microtubule bundles that extended far past where they should end lay along centromeric DNA.

Subjecting the Crm1-blocked cells to cold treatment—a common method used to depolymerize microtubules that are not assembled into mature kinetochore fibers—broke down the majority of microtubule attachments to kinetochores, indicating that kinetochore fiber stability had been compromised. These compromised cells still held tension on their kinetochores, however, so force can be exerted on the kinetochores even when the fibers are not properly assembled or stably attached.

How Crm1 binds to kinetochores during mitosis and the function of Ran-BP2 and Ran-GAP1 in mature kinetochore fiber attachment remain to be determined. “Ran-GAP1 and Ran-BP2 can be detected on kinetochores about the time that the kinetochores make their first microtubule



DASSO/MACMILLAN

The movement of Crm1 (green) to kinetochores (red) is essential for proper chromosome (blue) segregation.

attachments,” says Dasso. “We are intrigued by the idea that Ran-GAP1/Ran-BP2 may be important for converting those initial attachments into mature kinetochore fibers. We now want to understand how these fibers are built, and whether Ran-BP2 and Ran-GAP1 [function] in this process.” **JCB**

Reference: Arnaoutov, A., et al. 2005. *Nat. Cell. Biol.* doi:10.1038/ncb1263.