

p66^{Shc} checks the cell's anchor points (yellow) to ensure a good grip.

Tension testing in adherent cells

Like soloing rock climbers, adherent cells need a good handhold to survive. Ma et al. now identify an adaptor protein that monitors the cell's grip and signals death if the grip fails.

Death following detachment, known as anoikis, is a form of programmed cell death that ensures the disposal of displaced adherent cells. Lack of anoikis is thought to give cells metastatic potential.

A number of survival factors have been identified that are activated by integrin attachment to the extracellular matrix. Binding to soluble matrix fragments, rather than to a fixed matrix, does not prevent anoikis. This difference suggests that mechanical tension is also being measured.

Inside the cell, integrins associate with signaling adaptor proteins of the Shc family. One family member, p66^{Shc}, has been suggested to promote apoptosis. The team now shows that an epithelial cell line that resists anoikis does not express p66^{Shc}. Giving these cells back some p66^{Shc} reestablished detachment-induced death. Normal epithelial and endothelial cells express p66^{Shc}. Thus, p66^{Shc} must only trigger death upon cell detachment.

p66^{Shc} did not induce anoikis by the same mechanism as it induces apoptosis. For apoptosis, p66^{Shc} enters mitochondria. But for anoikis, p66^{Shc} associated with integrins and activated the actin cytoskeleton regulator RhoA.

RhoA increases tension between cell attachment points by inducing stress fiber formation. Inhibiting contraction of these fibers, the team showed, curbed anoikis. The authors therefore suggest that the cell continuously checks its tension by contracting its stress fibers—like checking from the inside of a tent whether the pegs are secure. If the cell contracts easily, then p66^{Shc} signals that external anchors are missing and that, for this cell, the camping trip is over. **JCB**

Reference: Ma, Z., et al. 2007. *J. Cell Biol.* 179:23–31.

mRNAs sit out the stress in EGP bodies

In times of stress, cells reduce translation to conserve resources. Hoyle et al. now report that many of the backed-up untranslated mRNAs hang out in a new type of cytoplasmic granule called EGP bodies.

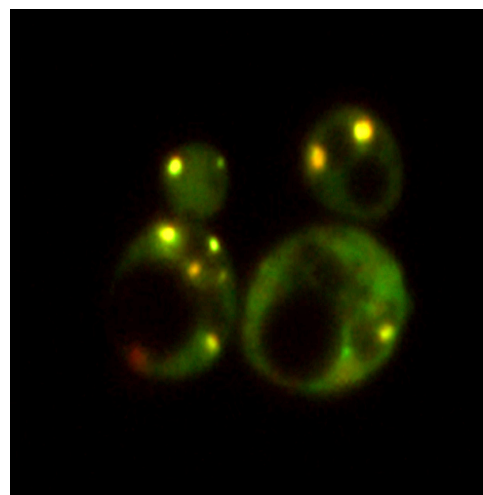
The stress of glucose starvation in yeast abruptly slows translation. So Hoyle et al. wondered what happens to the stalled translation machinery. They discovered that three translation factors, eIF4E, eIF4G, and Pab1p (E, G, and P), huddled together into four or five cytoplasmic foci. The binding of E, G, and P to untranslated mRNAs was thought to commit the transcripts to translation. But when the translation factors formed quiescent foci, the mRNAs went with them.

Two or three of the foci contained an mRNA-decapping enzyme that is found in P bodies—sites implicated in transcript decay. The accompanying mRNAs entering these foci might therefore be degraded. The remaining granules that the authors define as EGP bodies, due to their lack of

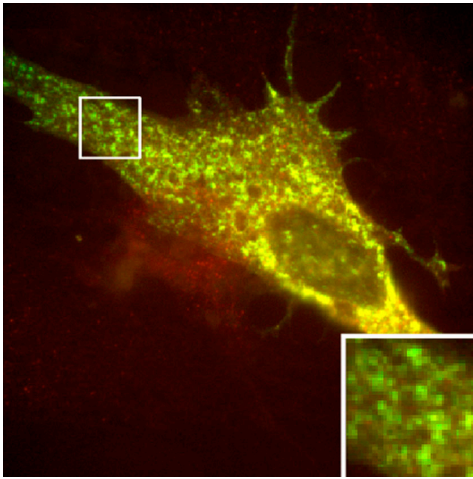
decapper, might instead be sites of mRNA storage. Already bound to E, G and P, the mRNAs would be ready for translation once the tough times are over, say the authors.

Upon glucose starvation, yeast cells start metabolizing ethanol. This switch requires some translation to produce ethanol-metabolizing enzymes. The team is now trying to figure out how the cell decides which mRNAs go to P bodies for possible degradation, and which continue to be translated. **JCB**

Reference: Hoyle, N.P., et al. 2007. *J. Cell Biol.* 179:65–74.



EGP bodies (yellow) are mRNA storage sites in times of stress.



Spire (green) and Cappuccino (red) come together to nucleate actin.

Nucleator or not?

Formins are thought both to extend existing actin filaments and to nucleate new ones. Work by [Quinlan et al.](#), however, reveals that one particular formin may not initiate new filaments but instead assist in a nucleation complex.

Actin nucleation and filament assembly are required for, among other things, cell polarity. This polarity fails in fly eggs when either Cappuccino (a type of formin) or Spire (a distinct actin nucleator) are missing. Both can nucleate filaments in vitro, and genetic and biochemical evidence suggest that the two work together to create polarity-inducing actin networks in vivo.

Quinlan et al. now show that Cappuccino and Spire proteins interact in vivo. But within this complex, only Spire seems to be capable of nucleation. When brought together with Spire, Cappuccino's nucleation ability was inhibited. Spire's nucleation activity, by contrast, was boosted.

Loss of Spire might be thought to leave Cappuccino able to nucleate actin, yet the Spire mutant flies still have polarity defects. Without Spire, Cappuccino is diffusely expressed in fibroblasts; but with Spire and its membrane-targeting domain, Cappuccino localizes to membrane-associated puncta. Perhaps, despite having its own nucleating capability, Cappuccino is simply not in the right position to use it without Spire. **JCB**

Reference: Quinlan, M.E., et al. 2007. *J. Cell Biol.* 179:117–128.

Calcium channels SMA

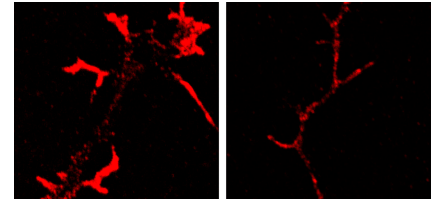
A paralyzing disease might best be treated by exciting motoneurons rather than saving them, report [Jablonka et al.](#)

The paralysis that occurs in patients with spinal muscular atrophy (SMA) stems from defective SMN1, a protein that interacts with mRNA transport factors. Motoneurons seem to be particularly sensitive to the transport problems, perhaps due to their considerable length. In mice with mutant SMN1, β -actin mRNA is not brought correctly to axonal tips, where it normally forms scaffolds needed for vesicle trafficking to the presynaptic membrane.

The scarcity of β -actin scaffolds, the team now shows, severely hinders the delivery of calcium channels to the membrane. Without the usual dense clusters of these channels, calcium influx and thus neuronal excitation were impaired. The excitation defects could be reversed by stimulating the production of SMN protein from a relative of the SMN1 gene, called SMN2.

Although motoneurons die off in SMA, previous analysis of a mouse model indicated that the disease manifested before this death. The findings from [Jablonka et al.](#) confirm that it's not motoneuron death that's to blame and suggest instead that the problem is a lack of motoneuron function. Restoring presynaptic calcium channel clustering and neuronal firing might be a promising therapeutic avenue. **JCB**

Reference: Jablonka, S., et al. 2007. *J. Cell Biol.* 179:139–149.



Calcium channels (red) cluster at presynaptic termini, but not without SMN (right).

How Ire1 senses stress

When demands on the protein folding machinery get too great, how does the cell know? Using a series of yeast mutants, [Kimata et al.](#) now suggest that oligomerization allows an ER stress sensor protein to recognize unfolded protein and signal distress.

Yeast's sole ER stress sensor is Ire1. It sits in the ER membrane and binds a chaperone called BiP on its luminal domain. Upon ER stress—the accumulation of unfolded proteins in the ER—BiP dissociates, and Ire1 autophosphorylates. This starts a signaling cascade that promotes production of a transcription factor that activates ER stress relief genes.

BiP dissociation is not sufficient for activating Ire1, however; removal of the BiP-binding domain does not lead to constitutive activation, although Ire1 can still respond to ER stress. As the authors now show, BiP dissociation serves only to allow Ire1 monomers to oligomerize.

In turn, oligomerization allowed Ire1 to form a domain that recognized unfolded proteins, a step that is necessary for Ire1 activation. In vitro experiments confirmed that this domain of Ire1 directly binds unfolded proteins, although it is not yet clear how binding enables Ire1 activation. Given that certain conformational mutants of Ire1 are constitutively active, the authors suggest that the unfolded proteins probably trigger conformational changes that enable autophosphorylation and action. Why BiP is needed in this equation is yet to be determined. **JCB**

Reference: Kimata, Y., et al. 2007. *J. Cell Biol.* 179:75–86.