Aspase cleavage of nuclear lamin proteins was thought to be sufficient to cause disintegration of the nucleus during apoptosis. Now, Croft et al. (page 245) show that the actin-myosin cytoskeleton generates a pulling force required to tear apart the structure.

When studying the role of actin and myosin in plasma membrane blebbing and cell contraction during apoptosis, the team noticed that if they inhibited ROCK I, a kinase that increases actin contractility and is activated by caspase cleavage, DNA was efficiently fragmented but did not end up in the expected biochemical fractions. The team hypothesized that ROCK I and the actin cytoskeleton might be involved in apoptotic nuclear breakdown.

In the current study, Croft et al. found that after blocking ROCK I activity and thus myosin light chain (MLC) phosphorylation, the nuclear envelope remained intact. Thus, the actin-myosin cytoskeleton is required for apoptotic nuclear breakdown, even though it is microtubules that do the similar job of nuclear envelope breakdown during mitosis. Furthermore, transfecting cells with a mutant form of MLC that prevents actin bundling and contraction prevented both plasma membrane blebbing—as expected from previous results—and nuclear envelope breakdown. The team also found that myosin ATPase activity, which catalyzes shortening of actin filaments, was required for nuclear breakdown.

When the team blocked caspase cleavage of nuclear lamin proteins, ROCK I activity altered nuclear morphology but wasn't sufficient to cause nuclear breakdown. Conversely, in cells lacking intact lamin proteins, ROCK I activation was enough to break apart the nucleus.

The team concludes that nuclear breakdown requires two cellular processes: contraction of the actin-myosin cytoskeleton, which results from ROCK I activation, and caspase cleavage of lamin proteins. What isn't yet clear is how the actin cytoskeleton links to the nuclear membrane. JCB

Einrich and Rapoport (page 271) have used mathematical modeling to generate the first explanation of how a bidirectional transport system can generate unique compartments, such as the ER and Golgi, despite constant vesicle movement between them. The model provides testable predictions about the vesicle transport system in cells.

In modeling a two-organelle system, the team found that they only needed to include two molecular components of the vesicle transport system: the coat proteins for budding; and the SNARE proteins for fusion. Coat proteins regulate budding from distinct compartments: COPI from the Golgi (to the ER); and COP II from the ER (to the Golgi). Meanwhile, SNARE proteins work in pairs, with a v-SNARE localized in the vesicle membrane and the t-SNARE in the target membrane. Different SNAREs direct vesicle fusion to specific organelles.

The new model only worked when it incorporated differential affinity of one coat protein for one set of SNARE proteins versus the other. If both coat proteins bound all SNAREs with equal affinity, then bidirectional vesicle transport would result in two uniform organelles. If the model assumed that one coat protein bound one pair of SNAREs with at least a 10-fold preference over the other SNARE pair, then the model accurately maintained two unique compartments.

One nonintuitive aspect of the model is that it predicts that both members of a SNARE pair, the v- and t-SNAREs, accumulate in the target compartment, a prediction borne out by experimental observations from other groups.

COP II is known to have high affinity for SNAREs that target the Golgi, and the model predicts that COPI should preferentially bind to ER SNAREs. If, however, the coat protein’s binding affinity for a SNARE pair is too strong, then all of those SNARE proteins would accumulate in the target compartment, leaving vesicles to bud from the other compartment without any SNAREs that would allow it to fuse to the target membrane. The model also predicts that if one SNARE pair is overexpressed, then the size of its target compartment would increase. JCB