Research Roundup

Pulling backwards

One-cell worm embryos pull harder on their posterior centrosome, thus displacing the spindle toward the posterior and creating a smaller posterior cell. Now Stephan Grill, Joe Howard, Anthony Hyman (Max Planck Institute, Dresden, Germany), and colleagues have tracked centrosome fragments and determined that individual force generators at the anterior and posterior pull with equal strength, but that there are more of them at the posterior.

The fragments were liberated by ablating the central, anchoring portion of the centrosome. The fragments from the posterior centrosome flew out toward the cell cortex faster than did those from the anterior centrosome. They did not, however, fly toward a single focal point, which was a feature of some earlier models.

Dolly, Polly, and friends proved that somatic cells are potentially totipotent, but the reprogramming that a somatic cell nucleus must undergo during cloning remains an error-prone black box. James Byrne, John Gurdon, and colleagues (University of Cambridge, UK) have now shown that the biochemically tractable frog oocyte system can be used to model reprogramming. A modified version of their protocol might allow the isolation of elusive reprogramming factors and, eventually, the reprogramming of somatic human cells for self-transplantation of stem cells.

The Cambridge group chose frog oocytes because, unlike most eggs, oocytes are not at all active in replication but very strongly so in transcription. To see if this transcripcional activity extended to reprogramming, Gurdon microinjected the oocytes with various cells: first mouse fetal fibroblasts, then mouse adult thymic cells, and finally human lymphocytes. All cell types eventually showed robust expression of oct4, whose expression is specific to and preserves the fate of stem cells.

Transcriptional activity not associated with stem cells, such as that of β-actin and the thymus marker thy-1, was reduced or extinguished by the transfer. But the extent of the transformation is not yet clear. "It’s possible that what we are doing is turning everything into an oocyte," says Gurdon. But he believes that oct4 expression is a good sign that the cells are at least headed toward becoming stem cells.

Stem cell characteristics may develop only through sequential inductive events. But the optimists are hoping that there is a single extract that will do the entire conversion. The success of the current experiments, says Gurdon, is "one of the more compelling reasons for believing that to be true." ■

Reference: Byrne, J.A., et al. 2003. Curr. Biol. 13:1206–1213.

Surviving heat through destruction

Canonical heat shock proteins (Hsps) help fold proteins. So it is easy to presume that, when Hsps are compromised, heat shock does its damage by depleting the cell of functional, folded proteins. But now Sylvie Friant, Karsten Meier, and Howard Riezman (University of Geneva, Switzerland) find that it is the toxicity of the denatured proteins that is the death knell for severely heat shocked cells, and that destruction of the damaged proteins via ubiquitination can rescue the cell from death.

The ubiquitination connection arose when the group found the polyubiquitin gene UBI4 as a high copy suppressor of lcb1, a mutant in heat shock induction. UBI4 did not restore Hsp expression to the cells, but did reduce death and protein aggregation at high temperature and bring
The checkpoint of death

Cells that fail to turn on a signaling pathway as instructed go on to commit suicide, according to Olivier Micheau and Jürg Tschopp (University of Lausanne, Switzerland). This checkpoint mechanism may ensure that aberrant signalers do not survive to form tumors or inappropriate cell types.

The mechanism explains how death and differentiation are coordinated from a single receptor, the TNF-receptor I (TNFR1). A host of proteins has been implicated in signaling from TNFR1, but these links have relied on overexpression experiments. On looking more carefully, the Swiss team found that a group of proteins formed complex I with TNFR1, and then peeled away from TNFR1 and the plasma membrane to form the largely cytoplasmic complex II. Only in complex II were death domains available for the binding of other proteins such as FADD, with their recruitment leading to apoptosis.

But if complex I performed its signaling job correctly, the downstream NF-κB pathway was turned on to produce FLIP. This protein shut down the proapoptotic activity of complex II, and thus cells survived.

If the cell has a defect in the NF-κB pathway, says Tschopp, “this cell is probably a dangerous cell, and it needs to be eliminated.” But intact signaling prevents this death, after a delay that allows sufficient time to make sure that the NF-κB pathway is behaving correctly.

References: Micheau, O., and J. Tschopp. 2003. Cell. 114:181–190.

My mother, the wave

Ocean waves continue to wash through our every cell, say Masa Tsuchiya and John Ross (Stanford University, Stanford, CA). They have found that oscillatory metabolism—a more efficient method of creating chemical energy even with constant nutrient inputs—develops faster and more efficiently in response to oscillatory inputs such as the wash of nutrients from seashore waves. Thus such metabolism may have arisen at the seashore and then spread over the rest of the Earth.

Oscillatory metabolism has been seen in reactions such as glycolysis and proton import into mitochondria. The Stanford group earlier showed that oscillatory metabolism can be more efficient than linear metabolism as the oscillations force large amounts of reactants through a reaction when the reactant to product ratio is at its maximum. (This is comparable to the rush of electrical current at the peak voltage of an alternating current [AC] network.)

But how did the oscillations first arise? After staring at waves in a cove in La Jolla, CA, and seeing a paper stating that wave-exposed organisms can grow faster, Ross had his idea: the waves did it. He modeled glycolysis as an evolving genetic algorithm. As the algorithm ran, systems with a constant influx of glucose took about double the number of generations to reach the more efficient oscillatory state than did systems with an oscillatory influx. Furthermore, the algorithms with an oscillatory input reached a higher final efficiency, as measured by the ATP:ADP ratio.

Most biologists continue to focus on linear metabolism. Ross believes that eventually this will change, and that waves will get due recognition for forming not just cliffs but metabolism.

References: Tsuchiya, M., and J. Ross. 2003. Proc. Natl. Acad. Sci. USA. 100:9691–9695.

Ubiquitination rescues heat-shocked lcb1 cells from death.

Where UBI4 succeeded, Hsps failed: Overexpression of Hsps did not rescue lcb1 at high temperature. Thus, although heat shock increases the demand for Hsp action, it is not this folding action but destruction by ubiquitination that keeps the cells alive. “Instead of refolding the proteins,” says Riezman, “the cells simply degrade them.” The cells then hang on until they can make newly synthesized and properly folded proteins.

References: Friant, S., et al. 2003. EMBO J. 22:3783–3791.