In This Issue

Mitochondria move in on calcium

Mitochondria aren’t just ATP factories. They serve as important components in intracellular signaling by modulating Ca\(^{2+}\) and act as a relay system in apoptosis. And they are dynamic organelles, moving about the cell at a rapid pace. On page 661, Yi et al. integrate these observations by demonstrating that local Ca\(^{2+}\) concentration controls mitochondrial movement.

Initially, the team was focused on the local interactions between the endoplasmic reticulum (ER) and mitochondria in myoblast cells in culture, but then noticed that changes in Ca\(^{2+}\) induced massive fluctuations in the rate of mitochondrial movement. To quantify these changes, the team labeled mitochondria with YFP fused to a mitochondrial targeting sequence. Stimulating the cells with vasopressin, a Ca\(^{2+}\) mobilizing hormone, or inducing localized Ca\(^{2+}\) release from the ER using IP\(_3\), they found that the mitochondria move most at resting Ca\(^{2+}\) concentrations. The organelles came to a standstill when they reached a region with a high concentration of Ca\(^{2+}\) (1–2 μM range) and moved again as the Ca\(^{2+}\) levels went down.

The mitochondria appear to move along microtubules, yet neither of the known microtubule motors are Ca\(^{2+}\)-dependent. The team hypothesizes that myosin Va, which binds calmodulin and is probably regulated by Ca\(^{2+}\), acts as a bridge between the microtubule motors and the mitochondria. They are currently testing the idea by down-regulating myosin Va.

Mitochondrial arrest in regions of high Ca\(^{2+}\) makes biological sense. The organelles would enhance the cell’s local Ca\(^{2+}\) buffering ability by soaking up the cation. In addition, Ca\(^{2+}\) stimulates ATP production in the mitochondria, so the Ca\(^{2+}\) influx would induce a local rise in ATP that could be used to drive ATP-dependent Ca\(^{2+}\) pumps in the ER and the plasma membrane. Together, the system would help speed the clearance of Ca\(^{2+}\), allowing for rapid, short signaling cascades. JCB

ES cells without teratomas

The therapeutic use of embryonic stem cells may be hampered by their proclivity to form pluripotent tumors called teratomas. On page 723, Bieberich et al. describe the use of a ceramide analogue, S18, to induce apoptosis in a subpopulation of embryoid body–derived stem cells (EBCs). Cells that survive the treatment express the neural marker nestin and differentiate into neural progenitors when injected into the brains of young mice. They do not form teratomas.

The S18 selectively affects those EBCs that express prostate apoptosis response-4 (PAR-4) protein, an endogenous inhibitor of atypical PKC\(\gamma\). Significantly, the majority of the PAR-4–expressing cells also express Oct-4, a marker for pluripotency. Almost all Oct-4–cells were positive for PAR-4, suggesting that teratoma formation might be prevented via elimination of PAR-4–expressing cells with ceramide-induced apoptosis before injection into animals. Sure enough, after injection into the brains of mice, treated cells differentiated into neural cells and some benign tumors, but no invasive tumors. Untreated cells gave rise to a significant number of teratomas in the same animals.

Bieberich et al. hypothesize that coexpression of Oct-4 and PAR-4 may indicate that the expression of PAR-4 is specifically up-regulated at particular stages during ES cell differentiation. Discovering the function and mechanism behind this up-regulation is the next task the team plans to tackle. JCB

Transport if loaded

Nuclear transporters can be viewed as taxis that move cargo across the nuclear envelope. On page 649, Plafker et al. report that importin-11, a nuclear transport receptor, may be an especially selective cabbie. Importin-11 transports UbcM2, a ubiquitin (Ub)-conjugating enzyme, but it does so only when the enzyme is charged with a Ub at its active site.

UbcM2 is an E2 enzyme, which works with E1 and E3 proteins to polyubiquitinate and tag proteins for degradation in the proteasome. To test whether importin-11 preferentially transports the Ub-charged UbcM2 or the unloaded enzyme, Plafker et al. performed coimmunoprecipitation assays with wild-type UbcM2, a mutant enzyme that is constitutively loaded with Ub, or a mutant that cannot be loaded. Importin-11 selectively bound the Ub-charged forms of UbcM2. Furthermore, in vitro pull-down assays showed that, if ATP or the E1 enzyme that loads Ub onto the UbcM2 active site were depleted, importin-11 did not bind UbcM2. In cell assays, catalytically inactive UbcM2 failed to localize to the nucleus.

Only a subset of E2 enzymes bound to importin-11. This specific interaction may control the enzyme’s access to potential substrates, including some involved in cell cycle progression. Plus, if importin-11 gobbles up all the Ub-charged UbcM2, then the enzyme cannot ubiquitinate cytoplasmic proteins. JCB