Surviving in low oxygen

Randall Johnson (University of California, San Diego, CA) and colleagues have found that cells need a particular transcription factor to survive in the hypoxic interior of developing bones. The critical activity of hypoxia-inducible factor 1α (HIF-1α), they say, is probably its induction of a glycolytic metabolism appropriate to a low oxygen environment. Without this metabolic alteration, the bone-building chondrocytes may well suffer a catastrophic drop in ATP levels that is sufficient to induce their death.

A complete knockout of HIF-1α is lethal in mice, so Schipani et al. used the CRE system to delete HIF-1α only in chondrocytes. The resulting animals had shorter limbs, defective skeletons, and massive cell death in the cartilaginous centers of their bones. In theory these changes could arise because there is no HIF-1α present to induce angiogenesis, but the mutant animals showed few changes in blood vessel growth, suggesting that a HIF-1α-independent angiogenic pathway exists. In contrast, the usual induction of glycolytic enzymes in the hypoxic regions was lost. In vitro studies using different levels of oxygenation will be needed to extend this observation beyond correlation.

The mutant animals also showed dysregulation of a cell cycle inhibitor, p57, and excess cellular proliferation. “It’s quite possible that in this case hypoxia is acting as a developmental switch [to induce differentiation of proliferative cells],” says Johnson. “But that’s certainly not something we have shown yet.”

Reference: Schipani, E., et al. 2001. Genes Dev. 15:2865–2876.

Sigma separation

Symmetry can be broken in a bacterial cell by using the order of genes on the chromosome, according to Jonathan Dworkin and Richard Losick of Harvard University, Cambridge, MA.

The gene whose position is key is an antagonist to the Bacillus subtilis transcription factor σF. Although σF directs the process of spore formation, Losick suspected that the instability of SpoIIAB, the anti-σF, might be the key to asymmetry. An exaggeration of SpoIIAB instability in the developing spore would tip the balance, but there was no clue as to how this might be achieved.

Now Dworkin and Losick show that replenishment of SpoIIAB is temporarily absent in the developing spore because an early cytokinesis leaves the chromosomal region containing the spoIIAB gene stranded in the mother cell. Only later is this part of the chromosome ferried into the spore cell.

As proof of this hypothesis, the authors demonstrate that a spoIIAB gene placed near the chromosome’s origin (the first region to enter the spore) inhibits sporulation. In contrast, cells with a defective DNA translocation apparatus end up superactivating sporulation genes, presumably because the gene for anti-σF never reaches the developing spore.

The anti-σF does not act alone—a redundant mechanism involving a localized phosphatase is also important for formation of a spore at the pole. Dworkin says the research group is attempting to gain a better understanding not only of factors controlling the phosphatase, but of the proteins involved in determining where the initial asymmetric septum forms.

Reference: Dworkin, J., et al. 2001. Cell. 107:339–346.

Pinning down NuMA

Much to their surprise, Ian Macara and colleagues (University of Virginia School of Medicine, Charlottesville, VA) have ended up studying not spindle rotation, but spindle construction.

Their protein of interest, LGN, is the human counterpart of the Drosophila protein Partner of inscuteable (Pins), which helps localize the apical determinant Incscuteable (Insc). Du et al. figured that they could study LGN-mediated spindle rotation using mammalian epithelia, as in these cells the prometaphase spindle rotates to reach its final metaphase orientation. But instead they found that LGN is needed for the construction of the spindle.

Overexpression of LGN appears to disrupt microtubule attachment to spindle poles, whereas a lowering of LGN levels using RNAi results in the formation of multiple poles. Thus, LGN may inhibit spindle pole formation, perhaps via an interaction with NuMA that Du et al. detect using multiple methods. NuMA is normally transported to spindle poles where it anchors and focuses microtubules.

How LGN might affect this process is unknown, but the entry of LGN into the nucleus at the end of prophase (when the nuclear envelope breaks down) may restrict spindles such that they form only two poles.

Reference: Du, Q., et al. 2001. Nat. Cell Biol. 3:1069–1075.