Flexible tumor metabolism

Tumor cells can survive the hypoxia in the center of tumor masses by using glycolysis, rather than oxidative phosphorylation, to generate energy. Most tumor cells also stick to glycolysis when normally oxygenated. Valeria Fantin, Julie St-Pierre, and Philip Leder (Harvard Medical School, Boston, MA) now report that some tumor cells, despite their preference for glycolysis, nevertheless retain the ability to use oxidative phosphorylation.

The Boston team reached this conclusion by inhibiting lactate dehydrogenase A (LDH-A). This enzyme converts NADH and pyruvate, the products of glycolysis, into lactate and NAD\(^+\). The lactate is exported and the NAD\(^+\) used to keep glycolysis going.

Therefore, when LDH-A is shut off and oxygen is limited, NAD\(^+\) runs low and glycolysis alone cannot continue. When oxygen is around, however, the pyruvate can be converted to acetyl-CoA to feed the Krebs cycle, which in turn feeds oxidative phosphorylation to regenerate NAD\(^+\).

It was unclear whether tumor cells were capable of switching back to oxidative phosphorylation. It now seems that some are: some cells inhibited for LDH-A got their mitochondria going and grew almost as well as wild-type cells if oxygen levels were normal. The inhibited cells did poorly in low-oxygen and in tumor models, however.

A preference for glycolysis in normoxic conditions, even by cells perfectly capable of oxidative phosphorylation, is somewhat of a surprise given the greater efficiency (per glucose molecule) of oxidative phosphorylation. But in fact oxidative phosphorylation is slower than glycolysis. This difference may be critical for fast-growing tumor cells.

The bias toward glycolysis is probably driven by HIF-1\(\alpha\), which is induced by both hypoxia and oncogenes, and by oncogenes that increase glucose uptake. Normal cells rely far less on glycolysis and LDH-A, however, so anticancer therapies targeting LDH-A should be nontoxic.

Reference: Fantin, V., et al. 2006. Cancer Cell. 9:425–434.

Seeing tube formation

Makoto Kamei, Brant Weinstein (NIH, Bethesda, MD), and colleagues have visualized in vivo tubule formation. As in previous in vitro experiments, large vacuoles fuse to form a tubule lumen that passes through an individual cell. Many such cells adhere in a line to form a blood vessel.

The researchers took advantage of the transparency of zebrafish to look at vessels emerging from the dorsal aorta. Initially, they saw highly dynamic vacuoles that appeared and disappeared. The vacuoles then fused together and enlarged to take up most of the cell volume, thus forming the lumen.

Quantum dots injected into the circulation got into the lumen formed by each cell in turn. Preliminary evidence suggests that vacuoles form independently in each cell, but enlargement may be a progressive process: the cells nearest to established vessels may help out their more distal neighbors.

The tubulating vacuoles formed in vitro are pinocytic in origin. Given the visual similarities, the same may be true in vivo. Weinstein suggests that these vacuoles may mature by establishing their identity as apical membranes, as the inside of a tube is ultimately defined as apical. He now plans to track apical markers in transgenic zebrafish.

Reference: Kamei, M., et al. 2006. Nature. doi:10.1038/nature04923.

Mixed kinetochore fiber

The action of a single kinetochore fiber appears unified—it is either pulling or pushing its attached chromosome at any given time. But underlying this unity is diversity, say Kristin VandenBeldt, Bruce McEwen (Wadsworth Center, New York State Department of Health, Albany, NY), and colleagues. They find that the kinetochore microtubules (kMTs) in a single fiber are a mixture of depolymerizing and polymerizing microtubules.

The concept of unified kinetochore action came from light microscopy. But when the New York team used electron microscopy, they saw that the 10–30 kMTs in one fiber had a mixture of morphologies. The kMTs with straight ends at the kinetochore are believed to be polymerizing, whereas those with curved ends are the unravelling depolymerizing kMTs. Surprisingly, two-thirds of kMTs were in the depolymerizing state during metaphase, suggesting that the kinetochore restrains kMTs that are in the depolymerizing state and retards their shrinkage. This restraint should produce the tension that is central to spindle dynamics.

Some kinetochores had fewer depolymerizing kMTs and some had more, but the differences were on a continuum. Thus the kinetochore appears to change direction based on a balance of pulling and pushing forces rather than a discrete, all-or-none switch. How the polymerization bias and kMT detachment are controlled remains largely mysterious.

Reference: VandenBeldt, K.J., et al. 2006. Curr. Biol. 16:1217–1223.