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Stay dynamic to slow aging

On page 803, Gourlay et al. report the first evidence that the actin cytoskeleton can affect release of reactive oxygen species (ROS) by mitochondria, and thus life span in yeast. Certain mutant Saccharomyces cerevisiae strains with alleles that reduce actin dynamics possess defective mitochondria. The team went on to show that such strains display increased levels of mitochondrially-derived ROS and die early compared with wild-type yeast.

In an exciting contrast, mutant yeast with increased actin dynamics live longer. Cells with increased actin dynamics live longer.

The function of the actin–ROS connection is unknown. But actin, as a relatively abundant protein with an intrinsic ATPase activity, may be a convenient indicator of cellular excitement. Thus, cells that are metabolically active, producing a lot of ROS, and in need of a vigorous ROS-suppressing machinery may pick up on the dynamics of actin as a proxy for cellular metabolism and respond by dampening pathways that cause ROS release. Alternatively, actin may directly bind to and regulate the opening of mitochondrial channels involved in ROS release.

Binding to the basement

Cancer metastasis is often more deadly than the primary tumor. Wang et al. report on page 935 that exposed basement membrane may offer a docking site when tumors spread to the lung—the most common site of metastasis.

Some existing metastasis studies have used long time points that may mask several sequential events. Wang et al. targeted the point of initial cell attachment by developing an ex vivo lung perfusion model. After injecting fluorescent tumor cells into rat renal vein, they immediately isolated the lungs allowing them to measure arrest of cells in pulmonary tissue. Prior treatment with a range of integrin antibodies revealed that integrin—whose most common ligand, laminin 5, is widely expressed in cancerous cells—is the key player in tumor cell attachment. This was confirmed by genetic deletion and restoration of the distinct α3 and β1 subunits in a variety of cells.

Having found the anchor, the team then needed to know where it came to rest on the blood vessel wall. And here, perhaps, is the most fascinating part of their discovery: they found that the basement membrane of pulmonary vessels contains "bald patches" where laminin 5, α3β1's most common ligand, is exposed. The authors believe that many other organs don’t have such patches. There is, however, exposed basement membrane in the liver, and laminins 5 and 10 are exposed in the bone marrow. Both of these are strong sites of metastasis.

Keratins make you regular

Spending your days examining mouse diarrhea is not most people’s idea of a worthwhile endeavor; but, at least for Toivola et al. (page 911), the activity has proven highly productive. By doing so, they have uncovered a possible protein sorting function for intestinal keratin 8 (K8), the major keratin of the digestive system.

Keratin knockouts are more famous for leaky skin than soft stools. But removal of these intermediate filament proteins has myriad effects, and loose stools is one consequence of removing K8. The team exploited this phenotype to investigate the cellular mechanisms associated with intestinal keratin function. Through a series of electrophysiological, immunofluorescence, and biochemical studies, they concluded that a lack of keratin filaments in the colon leads to defects in electrogenic transport—such as chloride secretion instead of absorption and altered anion exchanger expression—due to protein mistargeting. This is followed by hyperproliferation and inflammation of the colonic epithelium.

Given that transporter redistribution occurred long before inflammation and hyperproliferation, the group proposes that transporter defects give rise to changes in pH1 leading to hyperproliferation. It remains to be determined whether K8 possesses a similar targeting function in other tissues such as the liver and pancreas, or whether its function depends on the epithelial tissue involved.

Colons from mice lacking keratin 8 (bottom) are distended.