MMPs rearrange DNA

Matrix metalloproteases (MMPs) create havoc both outside and inside a cell to pave the way for tumorigenesis, based on findings from Derek Radisky, Mina Bissell (Berkeley Lab, Berkeley, CA), and colleagues.

MMPs are known to support cancer progression by their ability to degrade the matrix metalloproteases (MMPs) create havoc both outside and inside a cell to pave the way for tumorigenesis, based on findings from Derek Radisky, Mina Bissell (Berkeley Lab, Berkeley, CA), and colleagues.

The genomic instability stems from mitochondrial production of the reactive oxygen species (ROS) superoxide, which altered the genotype and phenotype of mammary epithelial cells. The authors show that ROS are sufficient to reproduce the effects of MMP treatment, and that quenching ROS prevents MMP-3–induced genomic rearrangements and cell motility. The authors are now investigating the link between ROS and motility.

Superoxide is made in response to the induction of an overactive splice variant of the Rac1 GTPase in MMP-treated cells. Expression of this variant, called Rac1b, induced ROS in the absence of MMPs. The MMP-induced cell motility that accompanies invasiveness was prevented by silencing Rac1b, which might be a new target for antitumor therapies. It is unclear how MMPs cause the alternative splicing of Rac1. Perhaps β-catenin, which moves to the nucleus upon E-cadherin cleavage by MMPs, affects splicing as well as transcription. JCB Reference: Radisky, D.C., et al. 2005. Nature. 436:123–127.

Need an EGO to escape arrest

Nutrient starvation arrests cell growth by shutting down the insulin-sensitive TOR pathway. How cells get back into proliferation is largely unknown, despite the fact that escape from quiescence is a hallmark of cancer. Now, Frederique Dubouloz, Claudio De Virgilio, and colleagues (University of Geneva, Switzerland) suggest that nutrient sensing from the vacuolar membrane might control the return to proliferation.

A screen for yeast mutants revealed that a vacuolar complex containing the Gtr2 small GTPase and two new proteins, Ego1 and Ego3, were needed for exit from growth arrest. The complex seems to activate microautophagy—the formation and release of vesicles into the vacuolar lumen. This process counteracts macroautophagy-induced vacuole growth, which occurs upon TOR inhibition and growth arrest. In ego or gtr2 mutants, vacuoles thus continued to grow even under conditions that were expected to reactivate TOR.

This vacuolar growth would maintain a low concentration of amino acids, which the vacuole generates during protein degradation. But EGO-activated microautophagy, and the resulting shrunken vacuole, might increase vacuolar nutrient concentration enough to allow TOR reactivation and release cells from growth arrest when external nutrients are also sufficient. “It’s a new way to look at the vacuole,” says De Virgilio, “as an intracellular nutrient pool that may affect cellular growth. Now we need to ask, what kind of signals does EGO respond to?” Genetic interactions suggest that glutamine is a good candidate, although the authors are also considering phospholipids. JCB Reference: Dubouloz, F., et al. 2005. Mol. Cell. 19:15–26.