Calcium goes nuclear

A fine reticulum that pokes its fingers across the nucleus is capable of storing and releasing calcium, according to Wilhelma Echevarría, Michael Nathanson (Yale University, New Haven, CT), and colleagues. The physiological activators of the compartment remain obscure, but they could potentially induce localized signaling in the nucleus.

Intracellular extensions of the ER have been described previously, but the Yale group is the first to show that the compartment both contains and can release calcium. Localized photorelease of inositol 1,4,5-trisphosphate (InsP3) in the nucleus resulted in a gradient of calcium that spread from the site of photorelease across the nucleus. The effects of nuclear calcium release were distinct from those of cytosolic calcium release: nuclear calcium caused translocation of a labeled protein kinase C (PKC) to the nuclear envelope, whereas cytosolic calcium triggered PKC translocation to the plasma membrane.

Several growth factor receptors are known to translocate to and signal in the nucleus. And several transcription factors—signals of signal transduction pathways—rely on calcium as one of their stimulatory inputs. As yet there is no obvious candidate pathway that combines both of these characteristics. But, if such a pathway is identified, two important factors—the site of calcium release and the proximity of target genes to this site—may help control the strength of the pathway’s output.

Reference: Echevarría, W., et al. 2003. Nat. Cell Biol. 5:440–446.

Metastasizing in search of oxygen

Metastatic growth can start when suffocating tumor cells go hunting for oxygen, according to a report from Selma Pennacchietti, Paolo Michieli, Paolo Comoglio, and colleagues (University of Torino, Torino, Italy).

The response appears to be part of a normal program used to create and maintain organs—a process that uses oxygen gradients as one guiding principle. “Mother Nature has given us the invasion program not to promote metastasis but to promote sprouting and branching of epithelial tubes,” says Comoglio.

In hypoxic tumor cells, his team found that binding of hypoxia inducible factor-1 (HIF-1) to two sites in the met promoter-induced expression of the Met tyrosine kinase receptor. This newly abundant Met, after the binding of ubiquitous hepatocyte growth factor (HGF, or scatter factor-1), activates an invasive migration program.

They found that Met levels were dramatically increased in the hypoxic areas of tumors, and that high levels of Met were both necessary for hypoxia-induced branching morphogenesis and sufficient to induce branching morphogenesis in normoxic conditions.

Previous workers have stressed that hypoxia induces angiogenesis and apoptosis resistance. But the new work suggests that treatment with antiangiogenic agents is too simplistic. These drugs increase hypoxia in a tumor, and may thus promote metastasis. A combination therapy that attacks both angiogenic and metastatic pathways may have a better chance of success.

Reference: Pennacchietti, S., et al. 2003. Cancer Cell. 3:347–361.

A graveyard for mRNA

A mother day, another organelle. Cytoplasmic foci of various mRNA processing enzymes have now been confirmed by Ujwal Sheth and Roy Parker (University of Arizona, Tucson, AZ) as functional sites for degrading mRNA. But that confirmation has led to a host of questions about the origins and range of functions of these processing bodies (P bodies).

Sheth and Parker found that mRNA decapping enzymes, activators of decapping, and an mRNA nuclease all clustered in two to three P bodies per budding yeast cell. The P bodies melted away when mRNA turnover was inhibited before decapping (by inhibiting deadenylation), but proliferated when the inhibition was at or after the decapping step. Finally, a decay intermediate was localized to P bodies.

P bodies proliferate when mRNA degradation is blocked (right).

The range of reactions occurring in the P bodies remains to be explored, as does the significance of the structure. “Whether the [degradation] biochemistry requires the macroscopic environment of the P body or can occur in a dispersed fashion is not known,” says Parker.

A full understanding of P body control is also hampered by the field’s poor grip on what controls the switches between different mRNA states: from active translation to storage or destruction. At least one factor implicated in storage is found in the P bodies, so these bodies may do double duty in storage and destruction. At the very least, says Parker, the P bodies sequester mRNAs that are being degraded, so they do not compete for factors with mRNAs that are being actively translated. Determining how much additional regulation is present is work for the future.

Reference: Sheth, S., and R. Parker. 2003. Science. 300:805–808.