In This Issue

Genes make their position clear

Certain genes switch their nuclear position in tumor cells, offering a potential new method of diagnosing cancer, say Meaburn et al. Individual genes preferentially localize to specific points within the nucleus.

The reasons for this aren’t known, but the positions can be reshuffled during differentiation. Meaburn et al. wondered whether genes might also rearrange during carcinogenesis, when large-scale changes in nuclear morphology occur. The researchers previously identified four genes that shift their location in a 3D culture model of early breast cancer, and now turned their attention to human tissue.

VCP takes out the trash

It’s important to finish what you start, say Ju et al., who reveal how a mutant ATPase blocks autophagy partway through to cause a multi-tissue degenerative disease.

Mutations in VCP, a member of the AAA ATPase family, cause inclusion body myopathy, Paget’s disease of the bone, and frontotemporal dementia (IBMPFD), a rare disorder of the brain, and bone. Patient muscle contains aggregates of membrane and proteins called rimmed vacuoles, which accumulate and disrupt cellular architecture. This pileup of membranous trash is inconsistent with VCP’s known involvement in proteasome-mediated protein degradation. Ju et al. thus wondered whether the ATPase might also be involved in garbage disposal via the autophagy pathway.

Membranes enter transfer negotiations

A family of yeast proteins can bridge adjacent membranes and transfer sterol lipids between them, say Schulz et al. The process may allow one organelle to regulate the lipid composition of another.

To maintain the correct level of sterols that they need to function, organelles exchange the lipids through vesicular and nonvesicular pathways. In yeast, the latter mechanism requires the Osh family of sterol-binding proteins and is thought to occur at membrane contact sites, where organelles are positioned extremely close to each other. How Osh proteins facilitate lipid transfer is unknown, however.

Schulz et al. discovered that Osh proteins can bind two different organelles simultaneously, due to the existence of distinct membrane-binding domains on either side of their structure. One of these domains is next to the protein’s sterol-binding pocket, and probably positions the pocket so it can easily extract a sterol molecule or deliver it to a target membrane. But the other site may regulate this process by interacting with phospholipids in another membrane close by. When the second site was mutated in Osh4p, the protein could still transfer sterols between liposomes in vitro but—unlike the wild-type protein—the rate of exchange wasn’t enhanced by the presence of PI(4,5)P2. Moreover, Osh4p lacking the second membrane-binding site couldn’t transfer sterol in cells.

The researchers found that most Osh proteins localize to membrane contact sites, where they likely transfer sterols between closely apposed organelles. The direction of transfer might be controlled by the phospholipids in each membrane, says senior author William Prinz, if the protein prefers to release sterol when its second membrane-binding site is contacting a particular phosphoinositide. Schulz, T.A., et al. 2009. J. Cell Biol. doi:10.1083/jcb.200905007.