# In This Issue

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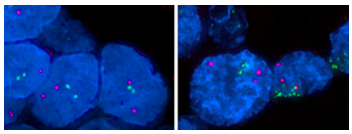
## Genes make their position clear



**Genes including *ERBB2* (green) and *MYC* (red) are positioned differently in normal (left) and cancerous (right) tissue.**

Certain genes switch their nuclear position in tumor cells, offering a potential new method of diagnosing cancer, say Meaburn et al.

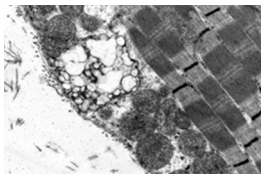
Individual genes preferentially localize to specific points within the nucleus. The reasons for this aren't known, but the positions can be reshuffled during differentiation. Meaburn et al. wondered whether genes might also rearrange during carcinogenesis, when large-scale changes in nuclear morphology 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.

The team analyzed 20 genes and found that most were positioned uniformly in healthy breast tissue from numerous individuals. Eight of these genes consistently relocated in the nuclei of invasive breast cancer cells, including *HES5*, which had an altered localization in all tumors examined. The researchers were able to distinguish between normal and diseased tissue on the sole basis of these genes' nuclear localization with success rates similar to current clinical tests.

The next step, says lead author Karen Meaburn, will be to repeat the study on a larger number of samples. *HES5* is unlikely to be repositioned in all of these, so the authors hope to identify a set of genes that, in combination, can accurately diagnose breast cancer. The approach may be useful for prognosis, too—in vitro studies suggest that gene movements are an early event in cancer development, so gene positions might provide an indication of the cancer's future progress.

Meaburn, K.J., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200909127.

## VCP takes out the trash



**Membranous vacuoles corresponding to nondegradative autophagosomes accumulate in muscle expressing mutated VCP.**

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.

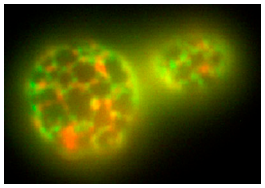
Mutations in VCP, a member of the AAA ATPase family, cause inclusion body myopathy, Paget's disease of the bone, and frontotemporal dementia (IBMPFD), a rare disorder that mainly affects skeletal muscle, brain, and bone. Patient muscle contains aggregates of membrane and proteins called rimmed vacuoles, 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.

Knocking down or expressing mutated VCP in cells increased levels of the autophagy markers p62 and LC3. Microscopy revealed that although autophagosomes containing these two proteins formed, they failed to mature into autolysosomes capable of degradation. VCP mutant mice and IBMPFD patients also accumulated p62 and LC3 in their muscle, and the two proteins localized to rimmed vacuoles, suggesting that the membrane–protein aggregates arise from frustrated autophagosomes. Indeed, injecting wild-type mice with a drug that blocks autophagosome maturation also produced rimmed vacuoles, as well as inducing other markers of IBMPFD myopathy.

The researchers now want to determine the mechanism by which VCP promotes the final stages of autophagy and how this is perturbed in IBMPFD patients. However, senior author Chris Weihl points out that many therapies being developed to treat degenerative diseases attempt to rescue cells by stimulating autophagy. In the case of IBMPFD, this could make matters worse, as autophagy has no problem initiating—it's the failure to finish that causes the problem.

Ju, J.-S., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200908115.

## Membranes enter transfer negotiations



**Osh2p (green) is enriched where the ER (red) is close to the plasma membrane.**

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 $PI(4,5)P_2$. 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.