# In This Issue

## Heart-shaped clones

The intricate shape of the heart is formed by oriented cell growth patterns, according to Meilhac et al. on page 97.

The heart is formed during embryogenesis from a simple tube-like structure. As it grows, the tube morphs into the complicated but familiar shape of our four-chambered heart. How one set of cells in the tube expands to acquire the shape of a ventricle while others become the atrium, for example, is unclear. Recently, oriented cell growth was shown to be the main factor in shaping the fly wing and the petals of the *Antirrhinum* flower. Meilhac et al. now find that directed growth patterns similarly affect the shaping of the heart.

Using clonal analyses of embryonic cardiac cells, the authors were able to trace the patterns of cell growth in the developing heart. They find that new cells are not randomly scattered around their progenitors. Rather, growth is oriented in a pattern specific for each area of the heart, and that pattern reflects the final shape of its region. For instance, in the outflow tract of the heart, which is a tubular region, the clones grew longitudinally along the long axis. In contrast, in the rounded ventricle, the clones were oriented like the spokes of an umbrella.

A computer simulation revealed that similar clone shapes could be formed by simply restricting the plane of cell division. Thus, as long as daughter cells continue to divide along the original mitotic orientation, outside signaling among cardiac cells may not be necessary to attain the clonal shapes seen in vivo. It remains to be determined how each region of cells chooses its mitotic plane.

Other mammalian organs, such as the brain or kidney, may also be shaped by oriented cell divison. Cruder shapes might be formed by variances in proliferation rates, but the group suggests that fine shaping is more easily accomplished by oriented cell division. ■

**Cells in the future right ventricle grow in an oriented pattern resembling the final shape of the ventricle.**

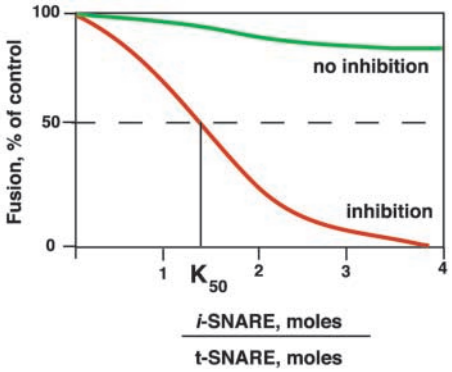
## Membrane fusion SNAREs an inhibitor

Two membranes fuse into one through the action of SNARE proteins. As only particular combinations of t-SNAREs (on the target membrane) and v-SNAREs (on the vesicle) will cause fusion between bilayers, restricting their localization promotes fusion in the right place. On page 79, Varlamov et al. add a new layer to the regulation by showing that some SNAREs actually block fusion that would otherwise occur in the wrong place.

SNARE specificity forms two mutually exclusive systems in the Golgi—one enriched at the cis and one at the trans face of the Golgi. The concentration of cis t-SNAREs at the cis face of the Golgi, where trans t-SNAREs are scarce, helps prevent vesicles bearing trans v-SNAREs from fusing there and vice versa. But even an imperfect distribution of t-SNAREs may be offset by inhibitory SNAREs (i-SNAREs), based on the new results.

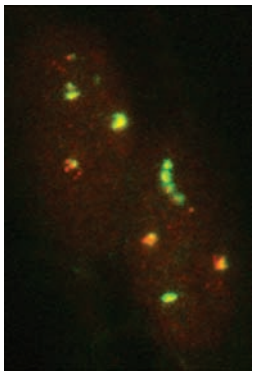
The authors found that some trans-Golgi SNAREs inhibit fusion reactions by cis-Golgi SNAREs and vice versa. At least some of these iSNAREs block fusion by substituting for one of the SNARE subunits of the fusion-competent complex. Most SNARE combinations that will not cause fusion do not form a complex. However, a few nonfusogenic complexes have been seen to form in vitro. Varlamov et al. suggest that these unusual complexes are insurance against unwanted fusion events.

To test their theory, the group recreated the SNARE composition of the Golgi compartments in vitro using liposomes and yeast versions of mammalian SNAREs at concentrations mimicking those seen in vivo. Vesicles containing either cis- or trans-Golgi SNAREs accurately fused with the cis- or trans-Golgi liposomes, respectively. But if the authors removed i-SNAREs from the recreated Golgi, vesicle targeting was less faithful, and the likelihood that vesicles with a cis v-SNARE would fuse with trans-Golgi liposomes increased from 3% to 40%. The group expects that i-SNAREs also work elsewhere, such as at the ER or the plasma membrane, to direct trafficking. ■




**The addition of iSNAREs (red) inhibits normally active SNARE complexes.**

Text By Nicole LeBrasseur
lebrasn@rockefeller.edu



**Stress granules containing HSF1 (red) produce satellite III transcripts (green).**

## Awakening heterochromatin

Sites in the human genome once thought to be inert structural material are brought to life in response to stress, according to results from Jolly et al. (page 25).

These inactive DNA stretches are binding sites for HSF1, a transcription factor that activates individual heat shock genes and accumulates in nuclear granules after heat shock. These granules were, like HSF1, expected to activate heat shock genes. So their recent localization to heterochromatic satellite III regions, which do not contain the major heat shock genes, was surprising. Jolly now shows that the stress granules activate transcription even in these repeat sequences.

The stress granules on satellite III repeats were found to contain RNA polymerase II and acetylated histones, which together produced large transcripts in response to heat shock. Heat stress has also been shown to induce RNA pol III–mediated transcription of repeat sequences in both human and mice. Together, the results suggest that transcription of many heterochromatic regions might be revealed given the right stress conditions.

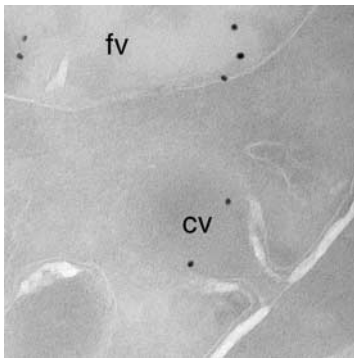
The function of the human satellite III transcripts remains an unanswered question. Most of the transcripts remained associated with the DNA long after their transcription, so the authors hypothesize that they might maintain the architecture of the chromosome at high temperatures. ■

## Malaria protease takes an indirect route

The bug that causes malaria feeds by gobbling up chunks of hemoglobin from the red blood cells it resides in. On page 47, Klemba et al. show how the parasite brings together this food source with its own enzymes that will degrade it. The results offer insight into how to treat this deadly disease.

The parasite breaks down hemoglobin for nutrients in its specialized organelle called the food vacuole, using proteases such as plasmepsin II (PM II). Hemoglobin gets to the food vacuole in vesicles that pinch off from cytostomes—openings through the parasite plasma membrane that lead to the blood cell cytoplasm. But how the endogenous protease reaches the food vacuole to meet its substrate had not been defined, leading some researchers to wonder whether a direct targeting pathway exists from the ER to the food vacuole. The new results suggest this is not the case.

Instead, the group sees that an inactive precursor form of the protease hitches a ride with hemoglobin in cytostome-derived vesicles. GFP fusions of the PM II precursor were seen to be secreted from the ER to cytostomes. From there, the fusions traveled in vesicles shared by hemoglobin to the food vacuole, where the precursor was processed to its active form.



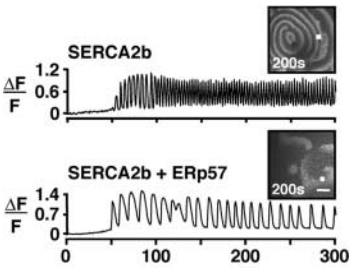

**PM II (labeled) is brought to the food vacuole (fv) in cytostomal vacuoles (cv).**

It is not clear whether PM II is sent directly to cytostomes or simply diffuses laterally once at the plasma membrane. If the former is true, a cytostome-targeted trafficking pathway might be a pathogen-specific target for drug treatments. ■

## Calcium pumps need a chaperone

ER chaperones need calcium to help them in their folding duties. Work on page 35 by Li and Camacho shows that some chaperones take a proactive stance on $Ca^{2+}$ levels by regulating an ER $Ca^{2+}$ pump.

Calcium must be pumped into the ER from the cytoplasm to maintain high levels for $Ca^{2+}$-needy chaperones. This function is performed in many cells by the SERCA 2b pump. The authors show that some chaperones, in addition to helping newly synthesized proteins fold correctly, also inform SERCA 2b of the ER $Ca^{2+}$ status. And what they have to say can alter pump activity.




**SERCA's calcium pumping ability is reduced by the ERp57 chaperone.**

High $Ca^{2+}$ levels lowered pump activity by promoting an interaction between SERCA 2b and the chaperone ERp57, which catalyzed disulfide bridge formation in the lumenal portion of SERCA 2b. But the SERCA–ERp57 interaction was lost at lower ER $Ca^{2+}$ concentrations. This reduced the disulfide bridge and converted the pump into its most active form. The ER is naturally an oxidizing environment, suggesting that a reductase may act on SERCA 2b unless ERp57 gets in the way.

Another chaperone, calreticulin (CRT), was needed for the ERp57–SERCA 2b interaction. CRT binds to both ERp57 and SERCA 2b, and SERCA 2b mutants that did not bind to CRT were not inhibited by ERp57. Thus, it is possible that CRT may be the actual calcium sensor—bringing ERp57 to SERCA only when $Ca^{2+}$ levels are high enough and removing ERp57 when $Ca^{2+}$ levels are lowered so that the stores are rapidly refilled. ■