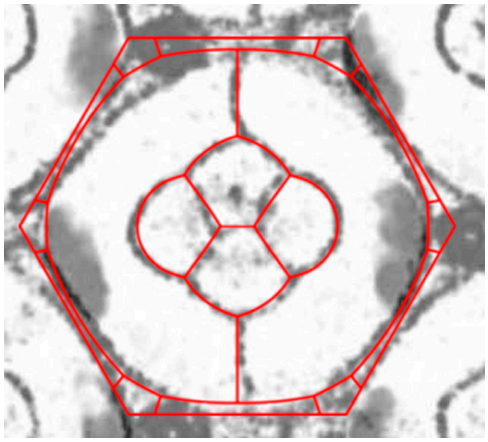
Research Roundup



HILGENFELDT/NAS

Shapes predicted by energy minimization modeling (red lines) match the outlines of cells in the fly eye.

Simple forces, complex shapes

Form follows physics in the fly eye, say Sascha Hilgenfeldt, Sinem Erisken, and Richard Carthew (Northwestern University, Evanston, IL).

The idea that a small set of physical forces governs the shape of tissues goes back at least a hundred years, but there has been little evidence to support it. Now, Hilgenfeldt et al. show that just two parameters—cell elasticity and adhesion strength—can account for the arrangement of cells in the ommatidium, the 20-cell subunit of the fly's compound eye.

The geometry of the cone cells in the center of the ommatidium resembles groups of soap bubbles, says Hilgenfeldt, who studies the physics of bubbles, foams, and other "soft solids." This arrangement suggested that, as in bubble aggregates, adhesion and elasticity might help determine shape. And like bubbles, the cells might be minimizing the surface energy at their interface.

To test this theory, the authors created a computer-simulated model of ommatidium geometry. Adhesion in these structures is supplied by cadherins at the cells' apicolateral surfaces. The elasticity of the cell membrane arises from a number of complex interactions between the lipid bilayer and the cytoskeleton but can be characterized by its resistance to deformation. The team found that beginning with cells of random shapes, and then adjusting the relative strengths of cadherin binding and membrane elasticity to minimize the total surface energy of all the cells, they could precisely reproduce the observed geometries of the eye.

The model also predicted the abnormal cellular arrangements that are found in various cadherin mutants. "Even a small variation in adhesion can alter cell packing dramatically," Carthew says.

Can other tissue geometries be explained as simply? "We think these results stand as an example for less-ordered epithelia," Carthew says, though some element of random variation may be needed in the mix to account for these structures. They also hope to model developmental changes with the same principles.

"You could imagine that tissues undergoing morphogenesis go through a series of minimal energetic states, dictated by changes in a few factors that regulate cell interactions," Carthew says, such as placement and number of adhesion molecules or cytoskeletal alterations. JCB

Reference: Hilgenfeldt, S., et al. 2008. *Proc. Natl. Acad. Sci. USA.* doi:10.1073/pnas.0711077105.

Histone chaperone regulates replication

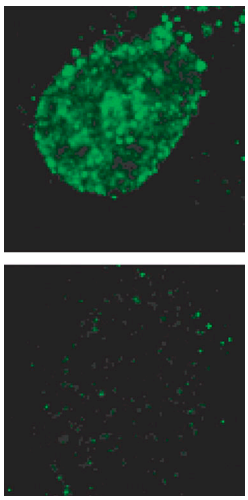
Histone supply and demand are tightly coupled at the replication fork by a chaperone, according to Genevieve Almouzni (Curie Institute, Paris, France) and colleagues. The chaperone, Asf1, passes histones from parental to daughter DNA strands and unwinds just enough DNA to match its transfer activities.

While investigating histone dynamics during replication, the authors found Asf1 in complex with a helicase and two histones. When the group knocked down Asf1, the cells stalled in S phase. Finding no defect in replication initiation and no activated checkpoint to halt replication, the authors suspected that the absence of Asf1 decreased the activity of the helicase, which must first unwind DNA for it to be replicated. They found very little helicase-formed ssDNA at replication sites in cells lacking Asf1, indicating that helicase progression was disabled.

With functional Asf1, but with replication halted by a chemical inhibitor, the number of Asf1/histone/helicase complexes increased. The authors concluded that Asf1 was picking up histones from the parental DNA strand but was unable to offload them in the absence of new daughter strand synthesis. Replication was also stopped by flooding the cell with histones: since Asf1 was loaded with the new histones, it could not remove any more from the parental DNA strand, thus stopping unwinding.

"This system coordinates replication with the packaging of DNA into chromatin," Almouzni says. It also ensures that the charged and sticky histones are chaperoned and prevents DNA from unwinding in the absence of replication. The movements of histone-laden Asf1 during replication are still unclear. Given the large distances involved, Almouzni envisages Asf1 shuttling back and forth from parent to daughter strands, rather than straddling the gap. JCB

Reference: Groth, A., et al. 2007. *Science.* 318:1928–1931.



ALMOUZNI/AAAS

Helicase-induced ssDNA (green) is reduced and replication is halted by depletion of a histone chaperone (bottom).

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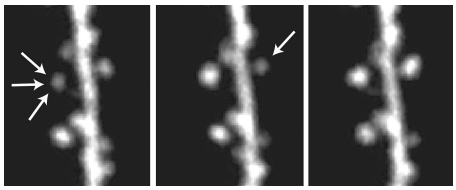

HARVEY/MACMILLAN

LTP induction in response to strong stimuli at one synapse (left, arrows) permits weak stimuli (middle, arrow) to build up nearby synapses.

Learn more when your neighbors do

Synaptic neighbors help each other learn, according to Christopher Harvey and Karel Svoboda (HHMI, Chevy Chase, MD).

Learning and memory, which require a strengthening of synaptic connections known as long-term potentiation (LTP), have traditionally been thought to be synapse specific, with one synapse unable to influence LTP induction in even its closest neighbors. But computational modeling has suggested that this kind of influence could allow individual neurons to store more information.

To test whether brains exploit this theoretical advantage, the authors stimulated individual dendritic spines with the neurotransmitter glutamate. Next, a weaker stimulus was applied to nearby spines. This weak stimulus is too low to trigger LTP on its own, but it caused robust potentiation when following the stronger stimulus.

"It made it easier for [synapses] to learn in the future if their neighbors had learned something in the past," Harvey says. But too far in the past, or too distant a neighbor, didn't help: the subthreshold stimulus had to occur within 10 min and 10 μm of the first. The two synapses also had to be on the same branch, suggesting that the bolstering signal probably travels intracellularly from spine to spine. So far, the group has no leads on this roaming internal signal.

The authors suggest that such "clustered plasticity" may link memories that are laid down in close succession on the same dendritic branch. Whether this neighbor effect increases storage capacity remains to be seen. JCB

Reference: Harvey, C., and K. Svoboda. 2007. *Nature*. 450:1195–1202.

Organelles in parallel

Endocytic organelles in three eukaryotic kingdoms evolved in parallel, according to Joel Dacks, Mark Field (University of Cambridge, UK), and Pak Poon (Dalhousie University, Halifax, Canada).

Unlike mitochondria and chloroplasts, the membrane trafficking system did not arise through endosymbiosis; it evolved from within. When fungi, plants, and animals split off from their last common ancestor, some parts of the system were "caught midstream in the process of becoming discrete organelles," says Dacks.

To track the development of the system, the authors performed phylogenetic analyses of three components: Rab5 and β-adaptins, which help sort cargo into vesicles, and the endocytic syntaxins, which assist vesicle fusion. The team found that in the common ancestor, each was represented by a single molecule that performed multiple functions. After divergence, the components evolved in parallel through gene duplication and specialization. For instance, syntaxin E homologues in each kingdom now include one that drives fusion at the early endosome and another that helps fuse late endosomes to the lysosome. These two sets of syntaxins arose after the eukaryotic split and independently adopted similar functions within each group.

"The distinction among the endosomes was less clear at the start and was firmed up afterward," says Field. The need for increased cargo specificity and sorting efficiency in each group seems to have driven the parallel evolution. JCB

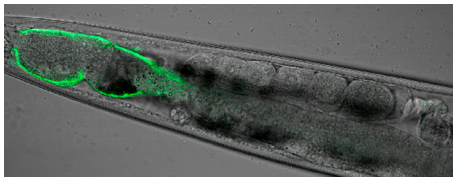
Reference: Dacks, J., et al. 2008. *Proc. Natl. Acad. Sci. USA*. doi:10.1073/pnas.0707318105.

H^+, the tiniest transmitter

Protons make muscles move in the worm gut, making the H^+ ion the newest and smallest chemical transmitter known, according to Asim Beg, Erik Jorgensen (University of Utah, Salt Lake City, UT), and colleagues. The protons are released by intestinal cells and stimulate defecation.

The group discovered the phenomenon while looking for neurons that control defecation. After killing the neurons innervating the posterior body muscles, the authors found that contractions nevertheless continued. To find out how, they screened for mutants in muscle contraction and identified two genes. One was *pbo-5*, which encodes a receptor on the muscle surface. The other was *pbo-4*, whose protein product sends protons out of the intestinal epithelium. Classical neurotransmitters did not activate the PBO-5 receptor or muscle contraction, but the release of caged protons did, even in *pbo-4* mutants, which are unable to release their own gut protons. By contrast, *pbo-5* mutants did not respond to proton release.

"These protons possess all the attributes of a classical transmitter," says Jorgensen, including having a specific receptor. The brain might also use protons to control neuronal signaling. According to him, the gut signaling role for protons "demonstrates the creativity of evolution. Cutting out the middle man—the nervous system—allows direct communication between the epithelia and the muscle." JCB


JORGENSEN/ELSEVIER

The Na^+/H^+ exchanger *pbo-4* (green) is expressed on the basolateral surface of intestinal epithelial cells.

Reference: Beg, A., et al. 2008. *Cell*. 132:149–160.