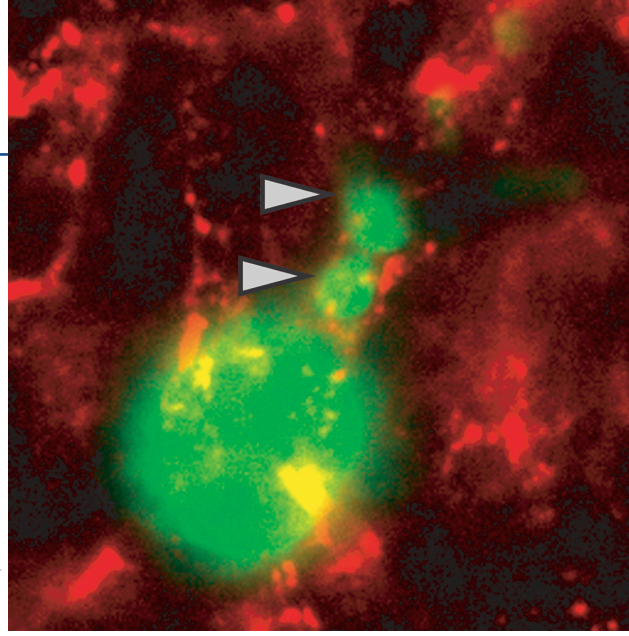
Research Roundup

Malaria undercover

Malaria parasites half kill their liver cell hosts, and then hide out in the shattered remnants, say Angelika Sturm, Volker Heussler (Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany), and colleagues. The disguise allows them to escape from the macrophage-rich liver into the general bloodstream; once there they can invade red blood cells.

This complex bit of subterfuge contrasts with the simple grow-and-burst mechanism that the parasite uses to eventually escape from red blood cells. "People extrapolated from the red blood cell situtation," says Heussler. "But if hepatocytes would burst, [the parasites] would have to individually find their way through the endothelium to the blood vessels and even then they would not be safe—the [liver's] vessels are packed with macrophages."



HEUSSLER/AAAS

Malaria parasites can bud from hepatocytes.

A simple burst was, however, what Heussler first hoped to see in vitro. Instead he saw the infected liver cells detach and float in the medium. These cells were half dead—their nuclei and mitochondria were damaged—but they did not look dead to macrophages observing from outside. The parasites accumulated calcium, and therefore the cell's scramblase enzyme did not flip phosphatidylserine (PS) to face the outside of the cell. Without the tell-tale PS facing outwards, macrophages cannot identify the cell as a target that is dead and should be eaten.

Parasites were also present in membrane-bound vesicles that did not contain nuclei. In vivo, these vesicles (dubbed merosomes) could be seen slowly oozing out of liver cells, with parasites apparently being shuffled into them before the merosomes departed. The merosomes often squeezed through endothelial walls into blood vessels, with macrophage proteases perhaps creating a path for the exit.

The force for merosome movement might be supplied by the uninfected cells, which try to knit together while expelling the dying cells. Merosomes then appear to bide their time until they have escaped the liver, before releasing parasites in a spaced series of volcanic bursts. JCB

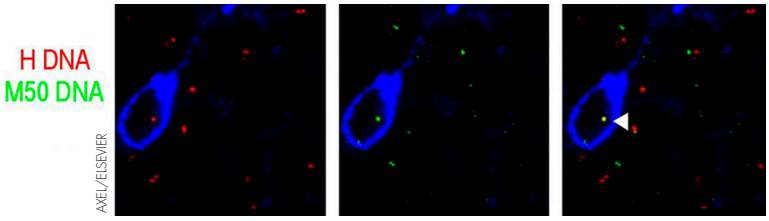
Reference: Sturm, A., et al. 2006. *Science*. doi:10.1126/science.1129720.

Smell genes must wander

Choosing which 1 of 1,300 odorant receptor genes to express depends on a random interchromosomal encounter, acccording to Stavros Lomvardas, Richard Axel, and colleagues (Columbia University, New York, NY). The receptor gene that nestles nearest the single enhancer available in the genome is the single gene that gets expressed in a given cell.

Various other models for odorant receptor choice had already been deemed unlikely or incorrect. A unique set of transcription factors for each receptor sounded too complicated. And irreversible DNA recombination to place a single receptor gene at a single expression site was clearly not happening, as mice cloned from the nucleus of a mature olfactory neuron expressed the full repertoire of odorant receptors.

The Columbia group started with the H enhancer, which was known to be necessary for the expression of at least some nearby receptor genes. They cut and ligated DNA so that DNA regions that were close to each other would now be covalently linked. They found that the H sequence was now linked to one of 22 different odorant receptor genes. In cells expressing a particular receptor, the H region colocalized with the gene for that receptor in ~29% of cells, and with nascent RNA for that receptor in 85% of cells.



AXEL/ELSEVIER

Enhancer (left, red) and M50 receptor gene (middle, green) colocalize in a cell producing M50 protein (blue).

Additional safeguards ensure that only one receptor is expressed. The H enhancer is probably restricted to a single functional copy by the CpA methylation that the group discovered at one of the H alleles. There would still be a risk of olfactory receptor genes latching onto the H enhancer one after another, except that any productively expressed receptor protein represses the production of any other receptor protein. If a pseudogene is the first gene that latches onto H, this previously characterized feedback mechanism will not kick in, and a productive receptor can still be produced.

This model is consistent with the group's findings: introducing an extra H element allowed two receptors genes to be expressed, but only if one was a pseudogene. Deleting the H element will tell the group whether this element rules the production of all 1,300 receptor genes, or just a subset. Clues about what proteins bridge the H element and individual genes may come from flies, which use a process called transvection to bridge enhancers and genes that lie on different homologous chromosomes. JCB

Reference: Lomvardas, S., et al. 2006. *Cell*. 126:403–413.

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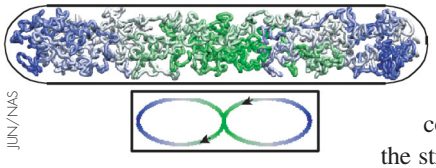
Segregation by entropy

Entropy may be sufficient to drive bacterial chromosome segregation, say Suckjoon Jun and Bela Mulder (FOM Institute for Atomic and Molecular Physics, Amsterdam, Netherlands).

The rapid and abrupt nature of chromosome segregation in bacteria has led researchers to suspect eukaryotic-like mechanisms based on active cytoskeletal proteins. Jun approached the problem from a very different viewpoint: that of a polymer physicist. Polymers tend to repel each other because of the greater conformational freedom, and thus higher entropy that results if they untangle and separate. It is this tendency, which is much stronger in confined spaces such as the cell, that the Dutch group believes is the driver for chromosome segregation.

They devised a mathematical model of bacterial chromosome replication and segregation. In this model, the existing DNA is constrained within a nucleoid, and newly replicated DNA is ejected by entropic forces into a peripheral region. Based purely on a consideration of entropic states, the bacterial chromosomes segregated rapidly after replication. Supercoiling and DNA condensation are expected to increase the structure of a given chromosome and increase the entropic effects.



JUN/NAS

Modeling (top) shows how bacterial chromosome separation can be driven by entropy alone.

To test the model, better visualization of bacterial chromosome segregation is needed. Past studies have suggested that segregation may not occur until much of the chromosome is replicated, but uncertainties remain. Meanwhile, Jun hopes to create an approximation of two segregating chromosomes under controlled conditions in a microchamber. JCB

Reference: Jun, S., and B. Mulder. 2006. *Proc. Natl. Acad. Sci. USA.* 103:12388–12393.

Killers aid a pregnancy

From a mother's perspective, a fetus is a bag full of foreign antigens—invaders against which an immune system might be expected to protect. But, according to Jacob Hanna, Ofer Mandelboim (Hebrew University, Jerusalem, Israel), and colleagues, certain immune cells actually help fetal cells to invade the uterus and ensure an adequate blood supply. Their success is essential to avoid the often fatal condition of preeclampsia.

All this cellular action takes place in the decidua, the outer lining of the uterus during pregnancy. Up to 40% of the cells in this tissue are maternal natural killer (NK) cells—but specifically the NK cells rich in CD56. Unlike the majority of circulating NK cells, these dNK cells are good at excreting proinflammatory cytokines and bad at killing infected cells.

The Israeli group found that dNK cells produce chemokines that can attract embryonic cells called trophoblasts. These trophoblasts form the placenta, in part by invading the decidua and tapping into the underlying blood vessels. Blood vessel growth and remodelling appears to be further aided by the VEGF now found to be secreted by dNK cells.

If this invasion is insufficient, the result is preeclampsia: blood vessels that do not fully penetrate the myometrium result in high blood pressure in the mother and fetus, which can only be relieved by delivering the fetus. In a recent genetic study, preeclampsia risk was greatest for parental gene combinations that inhibited dNK cell activation. Thus, when fetal cells are looking for a foothold, a pacifist subset of killer cells is the critical collaborator. JCB

Reference: Hanna, J., et al. 2006. *Nat. Med.* doi:10.1038/nm1452.

Automatic cell topology

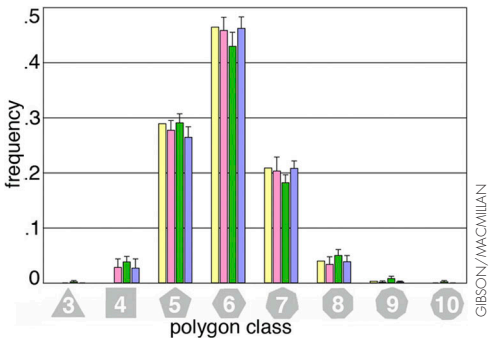
Soap bubbles (and coins pushed together on a tabletop) shift around until they reach an optimal packing state. But epithelial cells are not free to shift, because they maintain a constant grip on their neighbors. Instead, their predictable packing state simply emerges as a consequence of a random cell division process, according to Matthew Gibson and Norbert Perrimon (Harvard Medical School, Boston, MA), and Ankit Patel and Radhika Nagpal (Harvard University, Cambridge, MA).

The Harvard group first confirmed that epithelial neighbors did not easily reassort their contacts, even during a cell division. They then constructed a model that predicted the probability that a daughter cell would have a particular number of sides after assigning a cell division plane randomly.

Where the division plane hit the side of a neighboring cell, that neighboring cell gained an extra side. This gain was balanced in the dividing cell: typically its two progeny had less than twice the number of sides than the parent. This to-and-fro of sides drives the system to an equilibrium with a very specific distribution of cells, with hexagons the most abundant. The relative numbers of these shapes as predicted by the model was matched almost precisely by the shapes seen in real epithelia.

"If it didn't [emerge this way], maybe it would be very difficult for the cell to proliferate rapidly," says Nagpal, because the cells would have to reassort to regain stable topologies. The Harvard group now plans to add assumptions about cell volume and side lengths to the model, which will allow predictions about how changes in cell proliferation can change the shape of a tissue. JCB

Reference: Gibson, M.C., et al. 2006. *Nature.* doi:10.1038/nature05014.



Predicted (yellow) topologies match those seen in various species.