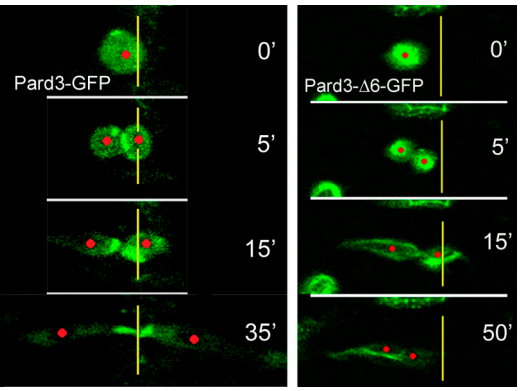
Research Roundup



CLARKE/MACMILLAN

A division that leaves daughters with mirrored allotments of Pard3 (green) causes one cell to cross (left) the midline (yellow line). Cells fail to cross (right) in the presence of a mutant Pard3.

Mirror symmetry in division

By sending apical proteins to the division plane, epithelial cells create mirror image daughters, say Marcel Tawk, Jonathan Clarke (UCL, London, UK), and colleagues. This mirror symmetry helps form the zebrafish neural tube.

Fish form neural tubes by hollowing out a solid rod of cells. Within the rod, cells are elongated and occupy all positions across the rod diameter, including the midline. During tube formation, cells must move away from the midline, where the lumen will form. At the same time, the rod cells become polarized such that their future apical side is adjacent to the lumen.

Tawk et al. examined these changes by fluorescently tagging the apical marker Pard3, whose relatives help to polarize worm and fly embryonic cells. The Pard3 revealed an unusual division in early rod cells that organizes the polarity of apical proteins.

During this division, which occurred ~15 hours after fertilization, Pard3 moved from its ubiquitous cytoplasmic distribution to the cleavage furrow. Upon division, Pard3 was partitioned with mirror symmetry, resulting in daughter cells whose apical sides faced each other.

After division, the daughter cell closer to the midline quickly moved to the opposite side. Loss of Pard3 blocked the cell migration across the midline, but the authors do not yet fully understand how crossing occurs. Until lumen formation, the daughter cells maintained a small area of cell–cell contact where Pard3 was concentrated. Clarke supposes this contact might "stop them from slipping back across one another," thus stabilizing their relative positions.

In mutants in which the rod formed late, the mirrored division took place before rod formation. The authors thus suggest that Pard3 accumulation at the cleavage plane is triggered by a cell-intrinsic mechanism rather than by the rod's environmental influence. But they are still looking for the upstream events that trigger this sudden polarity. They speculate that other developmental cavitations, such as gut formation, might also be preceded by a mirror-symmetric division. JCB

Reference: Tawk, M., et al. 2007. *Nature*. doi:10.1038/nature05722.

Platelets' preset lifespan

Platelets are born with a lit fuse. These clotting cells are set to implode when the fuse—its allotment of Bcl-x_L—is burnt up, based on findings from Kylie Mason, Benjamin Kile, David Huang, and colleagues (Walter and Eliza Hall Institute, Melbourne, Australia).

Life is short for platelets, which survive only about ten days before they are removed from the bloodstream. Platelet numbers are thus set by a balance between their production and removal. Mason et al. found that this balance shifted in mice with mutated versions of the antiapoptotic protein Bcl-x_L: the mice were severely deficient in platelet numbers.

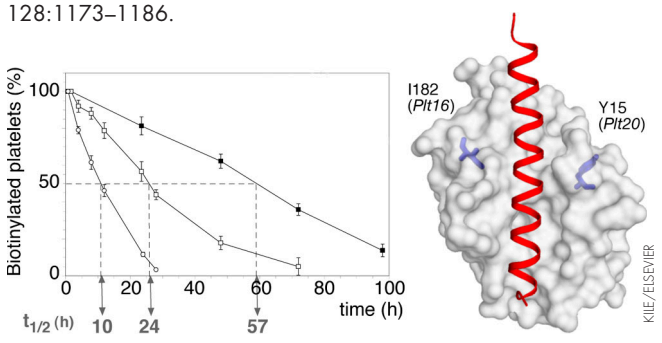
An apoptotic-like mechanism is needed during the birth of platelets, which are shed from bone marrow megakaryocytes. "We thought this would be the problem," says Kile, "but it's not." The platelets were shed normally. "Then we had an exciting thought: what if [Bcl-x_L] is keeping the platelets alive?" Kile and colleagues now show that Bcl-x_L provides "a beautiful dose-dependent regulation of lifespan."

Bcl-x_L protected platelets from death by restraining deadly Bak, which pokes holes in mitochondrial membranes and induces caspase-mediated apoptosis. The authors propose that platelets start out with enough Bcl-x_L to block Bak. But because Bcl-x_L is more labile, Bak eventually wins out. The Bcl-x_L mutants were even more labile than normal, resulting in those platelets' early demise.

Because platelets lack nuclei, they cannot synthesize replacement Bcl-x_L. Their lifespan is thus predetermined by their megakaryocyte-donated allotment even in the absence of an external death signal.

Apoptotic inhibitors might have future use in vivo to boost platelet numbers in clotting-deficient patients. But Kile is excited about a more immediate possibility—that Bak inhibitors might extend the very short shelf life of donated platelets used in transfusions. "Even just a 50% increase would be a huge gain in the clinical setting," he says. JCB

Reference: Mason, K.D., et al. 2007. *Cell*. 128:1173–1186.



KILE/ELSEVIER

Normal platelet lifespan (filled boxes) is shortened (circles) by Bcl-x_L mutations (right).

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Early replication for short telomeres

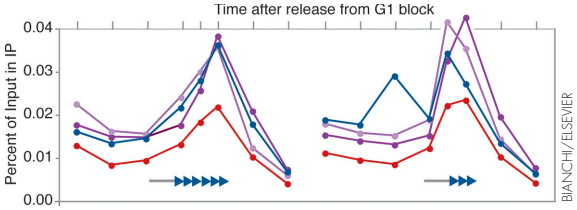
Like first-class airline passengers, short telomeres get preferential treatment. They cut to the front of the line during DNA replication, according to Alessandro Bianchi and David Shore (University of Geneva, Switzerland).

The shortening of telomeres with each cell division is counteracted by telomerase, which extends these repetitive sequences that cap the ends of linear chromosomes. The squeaky telomere gets the grease, however, as shorter ends seem to recruit or activate more telomerase.

Bianchi and Shore set out to examine the basis of this inequality by comparing individual short and long telomeres. "We expected to see a quantitative difference in the binding of telomerase or Cdc13, which activates it," says Bianchi. "But instead we noticed a shift in the replication timing." Shorter telomeres were replicated earlier in S phase.

The early start comes from an earlier firing of replication origins. Origins near long telomeres consistently fired late, but those near short telomeres were more likely to fire early. The mechanistic basis of this difference is still unclear.

The head start on replication corresponded with the creation of longer telomeres. Longer extension may be due to the noted advanced arrival of Cdc13 to early firing origins along with DNA polymerase. Telomerase inhibitors, on the other hand, were not affected by replication timing. JCB



A long telomere (blue, left) is replicated later in S phase than a shortened version of the same telomere (right).

Reference: Bianchi, A., and D. Shore. 2007. *Cell.* 128:1051–1062.

The pore slides open

Structures of a nuclear pore protein, presented by Ivo Melčák, André Hoelz, and Günter Blobel (Rockefeller University, New York, NY), suggest that the pore's central channel expands by an unusual sliding between hydrophilic residues.

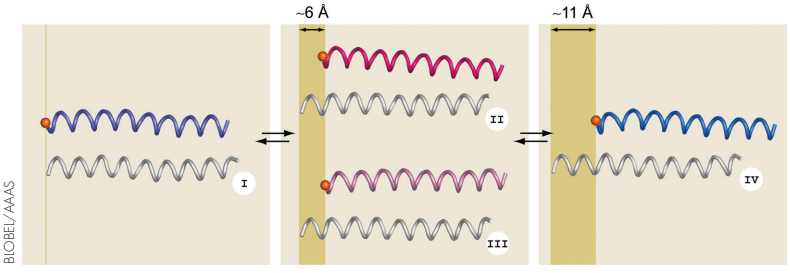
The crystals reveal structures of one of the four nucleoporins that make up the main channel. The authors suggest that the pore is encircled by eight side-by-side tetramers of this nucleoporin, called Nup58/45. The tetramer came in two forms; in one, the dimer–dimer interface was laterally displaced by ~6 Å compared with the other.

Most protein interfaces depend on hydrophobic residues. But in Nup58/45, an electrostatic dimer–dimer interface permits expansion by allowing alternative hydrogen bond pairings. Hoelz describes this interaction as "the opposite of a leucine zipper." Intermediate steps that resemble sliding-like movements are probable.

Because each structure was equally abundant in the crystals, the authors propose that little energy is required to switch between the states. Perhaps only the binding of the cargo complex is needed.

If each tetramer is at full extension, the pore diameter might widen by 30 Å, probably during the export of large cargo such as preribosomal subunits. Perhaps the other core pore proteins have similar sliding mechanisms. How accessory proteins alter the situation will be studied for years to come. "There are so many proteins involved," says Hoelz. "I think that the nuclear pore complex will be full of surprises like [this one]." JCB

Reference: Melčák, I., et al. 2007. *Science.* 315:1729–1732.



Nup58/45 conformations suggest that its tetramerization interface can slide apart (black arrows). Only one of the two N-helical pairs that generate this interface is shown.

Plant hormone is human cytokine

Human hormones don't arouse plants' desires. But plant hormones can be stimulating to humans—or at least to their immune cells—based on new work from Santina Bruzzone, Elena Zocchi (University of Genova, Genoa, Italy), and colleagues. The authors identify the plant hormone abscisic acid (ABA) as a human cytokine.

In plants, ABA triggers stress responses such as seed dormancy and stomatal closing. Zocchi previously found that very simple animals such as sponges also use ABA-driven pathways to respond to light and heat. She now finds that ABA's reach extends to mammals.

For humans, the first cells to be exposed to environmental stresses are often immune cells. The group's results show that phagocytosing immune cells called granulocytes synthesize ABA in response to high temperature, like that of a fever.

The ABA calls in more granulocytes, and possibly other immune cell types, by activating chemokinesis. It also stimulates phagocytosis and the production of reactive oxygen species (which help kill pathogens) and nitric oxide (another cytokine).

As in plants, the biochemical pathway that activates granulocyte ABA responses induced intracellular calcium increases via cyclic ADP–ribose. "The capacity to respond to environmental stimuli through biochemical events is really at the heart of life," says Zocchi. It's no surprise then that it has been so highly conserved. JCB

Reference: Bruzzone, S., et al. 2007. *Proc. Natl. Acad. Sci. USA.* 104:5759–5764.