Research Roundup

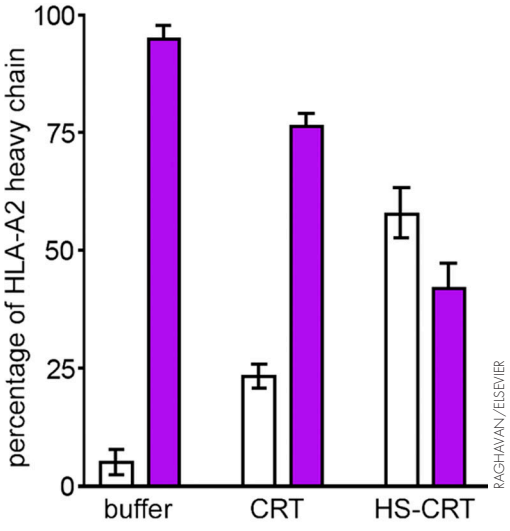
A chaperone feels the heat

A chaperone is supposed to keep its cool when temperatures get hot. But Syed Rizvi, Laura Mancino, Malini Raghavan (University of Michigan, Ann Arbor, MI), and colleagues show that calreticulin—a glycoprotein chaperone—starts to melt in the heat. The resulting structural changes actually improve its chaperone activity and may also occur transiently under normal conditions.

Calreticulin is a stress-induced chaperone that helps glycoproteins such as MHC Class I molecules fold properly in the ER by binding to the target proteins' sugar groups. The new results show that at high temperatures or low calcium levels, calreticulin can also bind independently of sugars and thus more effectively inhibit protein aggregation.

Protein binding was accompanied by structural changes in calreticulin, including oligomerization at high temperatures. "It has remarkable conformational lability for a chaperone," says Raghavan. "Its stability is like [that of] the substrates themselves." The COOH-terminal tail was found to be necessary to inhibit the oligomerized form, but its effect may be overcome at high temperature or low calcium so that the protein can help out when the ER is overwhelmed. JCB

Reference: Rizvi, S.M., et al. 2004. *Mol. Cell.* 15: 913–923.



Heat-shocked calreticulin (HS-CRT) is better able to prevent protein aggregation (purple bars).

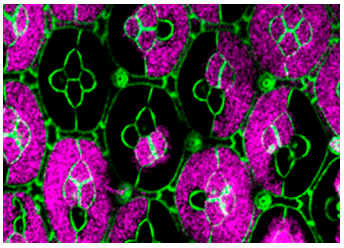
Cells have a bubbly look

A century ago, scientists noted a similarity between the patterns that cells and soap bubbles adopt. Now, this nearly forgotten parallel is recalled by Takashi Hayashi and Richard Carthew (Northwestern University, Evanston, IL). Their results show that the same physical mechanism that drives bubbles to coalesce in forms that minimize their total surface area (and thus their surface free energy) also governs cell patterning.

Like bubbles, cone cells in the fly eye assembled in shapes that minimize surface area. Parameters that help specify this minimization include the number of intersection points between cells or bubbles, the number of interfaces that link these points, and the angles between them. Ommatidia containing abnormal numbers of cone cells still retained these minimizing characteristics. But those that lacked cadherins, and thus intercellular adhesion, did not. Presumably the lack of adhesion makes these cells act as independently energy-minimizing units rather than a single unit.

As well as controlling cone cell packing, cadherins and surface mechanics also organize cone cells within an ommatidia. Only cone cells expressed N-cadherin; other ommatidial cell types, such as pigment cells, expressed E-cadherin. Cone cells thus aggregated in the midst of the other cells to minimize contact between cells of different adhesion strengths (N-cadherin adheres more strongly than does E-cadherin). By altering the adhesion differential through misexpressed or mutant cadherins, the authors perturbed the shape of the cone cell group and thus increased its area of contact with other cells. JCB

Reference: Hayashi, T., and R.W. Carthew. 2004. *Nature.* 431:647–652.



Mutant cone cells (purple) that lack N-cadherin show patterning defects.

Uncooperative immune cells

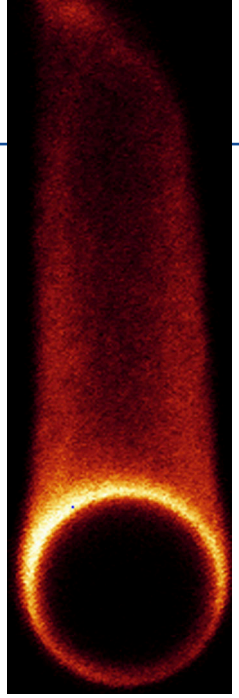
It's hardly *The Art of War*. In what seems like a counterproductive effort, the immune system's first line of defense sets up a barricade to block the next wave of defenders, as shown by Ravi Rao, Francis Luscinskas (Harvard Medical School, Boston, MA), and colleagues.

The first immune cells to arrive at injured tissues are usually neutrophils. These cells transmigrate through the endothelial cells lining the vessel wall and release granules full of proteases that chew up the damaged tissue or infectious agents. Now, one of these proteases, called elastase, is shown to act on endothelial cells to deter the entry of later-arriving T cells.

Elastase hindered T cell transmigration by cleaving and inactivating the vessel-bound chemokine SDF-1α, which guides T cell migration on the vessel wall to entry sites. "When we started," says Luscinskas, "we thought the neutrophils might enhance chemokine activities at the blood vessel wall, where more white blood cells are destined to transmigrate. But the opposite is true." By closing the door on T cells, neutrophils might prevent potentially dangerous overactive immune responses.

Although protease inhibitors are abundant in the blood stream, plasma did not improve T cell entry. Elastase may be protected from the inhibitors by the neutrophil cell body, which physically seals off plasma inhibitors from accessing the space between the neutrophil and endothelium. JCB

Reference: Rao, R., et al. 2004. *J. Exp. Med.* 200:713–724.



PLASTINO/ELSEVIER

A hollow actin comet is formed by VASP.

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VASP comet sightings

Less is more when it comes to actin-fueled propulsion. Julie Plastino, Stéphane Olivier, and Cécile Sykes (Institut Curie, Paris, France) show that hollow actin comets propel beads faster than a more filament-packed comet.

Actin comets, which drive bead or bacteria movement, are thought to depend strongly on Arp2/3–built, branched actin networks. Now, Plastino et al. show that another actin polymerizer, VASP, builds comet tails that are less dense overall and hollow in the center, but nevertheless led to bead speeds that were seven times that of Arp2/3–built tails. "It's not about having as much polymer as possible," says Plastino. "It's how the geometry of filaments affects movement."

VASP is thought to weaken interactions between actin filaments and the membrane or bead. The first filaments to be detached would be those at the center back of the bead, as these bead-filament attachments produce the strongest pulling force on the moving bead. This hollowing out of the comet reduces friction between the bead and the comet and speeds the bead on its way. This model also supports the idea that actin squeezes the sides of beads to move them forward rather than pushing beads from behind.

VASP-built tails were aligned in the direction of movement, not angled like the branched Arp2/3 networks. The aligned arrangement resembles that of actin in filopodia, where VASP is prevalent. One speculation proposes that the inside surface of membrane invaginations at the leading edge of fibroblasts may be somewhat rounded like beads and similarly squeezed forward by actin filaments. Others have shown that VASP slows overall cell movement but quickens the protrusion of small membrane fluctuations. These bursts of speed are perfect for the exploratory nature of filopodia. JCB

Reference: Plastino, J., et al. 2004. *Curr. Biol.* 14: 1766–1771.

Insulin keeps time

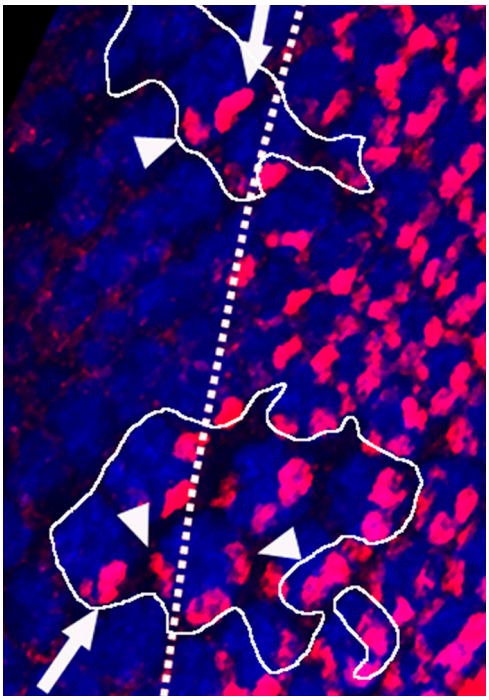
Insulin hastens or delays differentiation so that it keeps pace with growth rates, according to results from Joseph Bateman and Helen McNeill (Cancer Research UK, London, UK).

Insulin is the perfect candidate to decide when cells should differentiate, as it is a well-known growth regulator. Along with the Tor pathway, which senses amino acid levels, insulin turns up ribosome synthesis to match increased nutrient availability. Bateman and McNeill now find that insulin and Tor also control neuronal tissue differentiation. Whereas the identities of cell fates were unaffected by changes in insulin signaling, the fates were acquired at inappropriate times.

The aberrant timings were easily seen in the developing fly eye, whose 800 photoreceptor clusters differentiate in a wave pattern that makes timing mutants easy to identify. While using the eye to find patterning mutants, the authors found that cells lacking TSC1, a negative regulator of Tor, differentiated prematurely compared with neighboring TSC1-containing clusters. Dampened insulin or Tor signaling, in contrast, delayed differentiation. Thus, when growth was delayed by factors resulting in low insulin levels, differentiation was also delayed appropriately.

The altered timings were measured by changes in the appearance of definitive transcription factors such as Elav and Prospero. But the Ras/MAPK pathway, which turns on these transcription factors, was not affected by *tsc1*. As it does with ribosomal proteins, insulin signaling may activate the translation of a differentiation factor that lies downstream of or parallel to Ras/MAPK.

Insulin's control was independent of absolute cell size, thus allowing cell types of varying sizes to time differentiation via the same mechanism. *Tsc1* had no effect on differentiation timing outside the nervous system, however. Neurons may depend on this insulin system because they are particularly sensitive to timing miscues given the precision required to make distant synaptic connections. JCB



MCNEILL/ELSEVIER

Cells lacking TSC1 (outlined) express Elav (blue) and Prospero (red) ahead of the differentiation front (dotted line).

Reference: Bateman, J.M., and H. McNeill. 2004. *Cell.* 119:87–96.