

# Research Roundup

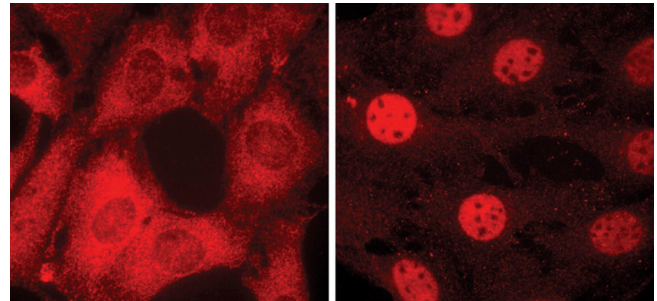
## Actin, the great orchestrator

**C**hanges in cell shape or mobility require changes in gene expression. In a new study, Maria Vartiainen, Sebastian Guettler, Banafshe Larijani, and Richard Treisman (Cancer Research UK, London, UK) reveal how actin coordinates both shape and transcription at once.

Actin rapidly polymerizes into a filamentous (F) form in response to cell growth and motility triggers, such as serum stimulation. Serum stimulation also causes a transcription co-factor called MAL to promote transcription from target genes including *actin*. Reportedly, MAL can bind to monomeric (G) actin. It's possible then that serum-induced polymerization of actin, by lowering the cytoplasmic pool of G actin, frees up transcriptionally active MAL.

Live cell analyses by Vartiainen et al. now reveal that nuclear actin regulates MAL. Fluorescently labeled MAL shuttled back and forth to the nucleus in unstimulated cells, suggesting that G actin binding does not hold MAL in the cytoplasm, as might have been expected. Instead, G actin binding was necessary for rapidly exporting MAL from the nucleus.

Forcing MAL nuclear accumulation (by blocking an export protein) in unstimulated cells was not enough for MAL-regulated transcription, however. The authors therefore con-

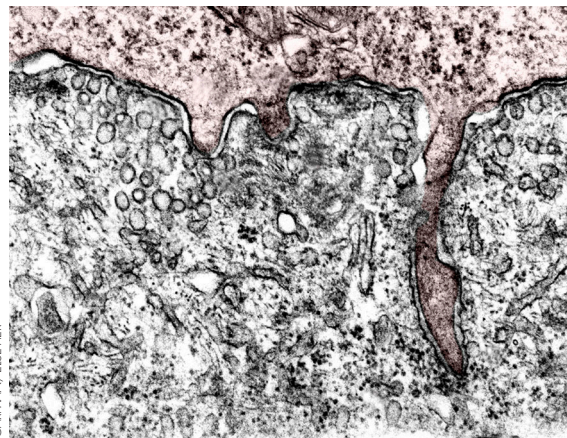


**MAL (red) nuclear export (left) is prevented in serum-stimulated cells (right) by the loss of G actin binding.**

clude that MAL must also dissociate from G actin to activate its target genes.

Through this feedback mechanism, actin is able to activate its own transcription (and that of actin regulators) when G actin supplies are running low. This ensures constant availability of the cytoskeletal building blocks. According to Treisman, there are several other MAL target genes whose functions in actin dynamics are anything but obvious. The team is now trying to determine how these apparent outsiders fit in to the scheme. **JCB**

Reference: Vartiainen, M., et al. 2007. *Science*. 316:1749–1752.



**A leukocyte (pink) palpatates an endothelial cell (gray) with podosomes until it finds a route through.**

## Podosomes push through

**T**o exit the blood, leukocytes must either squeeze past or go directly through the endothelial cells that line the vessels. According to Christopher Carman, Timothy Springer (Harvard Medical School, Boston, MA), and colleagues, to take the latter transcellular route, leukocytes first palpate the endothelial cell with exploratory protrusions called podosomes. The leukocytes then use one, or sometimes several, of these podosomes to push right on through.

The team found that approximately one-third of leukocytes made their way across an *in vitro* vascular endothelial monolayer by transcellular migration. Carman suggests that, *in vivo*, at least in some settings, the proportion might be higher. Transcellular migration might even be favored over the paracellular route, as the latter could potentially weaken cell–cell junctions.

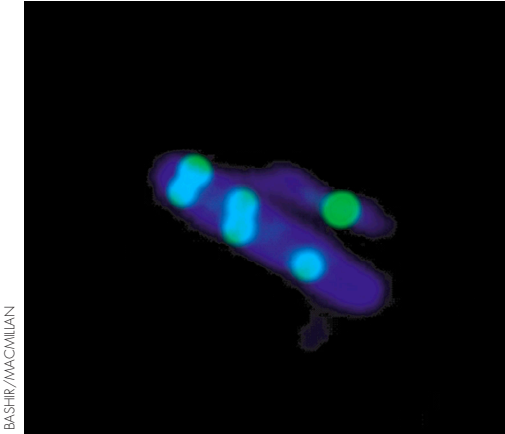
To investigate the mechanism of transcellular migration, the team used a combination of live fluorescence and electron microscopy.

Shortly after leukocytes were added to the monolayer, invaginations in the endothelial membranes appeared coincident with the formation of podosomes by the leukocytes.

The leukocytes used these podosomes to prod and poke the endothelial cell until they find a route of least resistance. Organelles other than the nucleus were then pushed out of the way as one large, invasive podosome created a transcellular pore. Leukocytes that were deficient for an actin regulatory protein called WASP formed podosomes poorly and were thus inefficient in forming transcellular pores. Paracellular migration continued as normal, however.

Endothelial cells survived despite this continuous puncturing by migrating leukocytes. Indeed, multiple leukocytes were able to pass through a single endothelial cell—Carman has spotted up to eight at a time—lending further evidence that this could be the predominant route for transendothelial leukocyte migration *in vivo*. **JCB**

Reference: Carman, C., et al. 2007. *Immunity*. 26:784–797.



BASHIR/MACVILIAN

**Bacteria (blue) carrying nanoparticle cargos (green) are efficient DNA dwellers.**

## Microbots deliver the goods

By combining two not-so-efficient DNA delivery systems into one, Demir Akin, Rashid Bashir (Purdue University, Indiana), and colleagues have engineered super efficient, DNA-delivering “microbots.”

Viruses, bacteria, and nanoparticles are used to deliver DNA to cells. But when used in the body, each delivery vehicle has its limitations. Nanoparticles have the advantage of delivering large copy numbers of DNA molecules. But because of their size and limited targeting ability, they cannot access tissues effectively and thus have a poor efficiency.

Bacteria, on the other hand, are inefficient DNA carriers that can hold only one copy of the DNA cargo per cell. However, bacteria are active microorganisms and can penetrate solid tumors—particularly tricky tissue for passive viral or nanoparticle vectors to access, explains Bashir.

Now, Akin et al. have developed a system whereby active bacteria carry nanoparticles as cargo, thus yielding the benefits of both previous systems. The team calls them microbots.

Microbots delivered DNA-covered nanoparticles with high efficiency into a variety of cancer cell lines in culture and into mouse organs in vivo. Microbot-managed gene expression was much stronger than that achieved by either system alone, and the efficiency of transfection in cell lines was found to be twice as high.

The team is now planning to knock out the pathogenic genes of the carrier bacteria they use to make these microbots safe and to limit their infectivity to specific tissue locations, such as tumors. **JCB**

Reference: Akin, D., et al. 2007. *Nat. Nanotech.* doi:10.1038/nnano.2007.149.

## Eat to compete

If two cell types in a chimeric animal are unevenly matched, the stronger cell type may take over. How do they do it? Wei Li and Nicholas Baker (Albert Einstein College of Medicine, New York, NY) report that the big brutes eat their weakling competitors alive!

Cell competition, in which one cell type has a growth advantage, exists in chimeric animals. Until recently, it was assumed that the weaker cell died due to an inability to compete for nutrients and/or growth factors. In fact, as Li and Baker now show, the stronger cell type actively kills the weaker by eating it.

In fly chimeras that consisted of wild-type cells together with weaker mutant “minute” cells, Li and Baker spotted that dying minute cells were almost always inside wild-type cells. To see whether this apparent engulfment was necessary for competition, the researchers examined flies that lacked known engulfment genes. Sure enough, in chimeras with larger cells that lacked these genes, both engulfment and competition were prevented the minute cells survived.

The next step is to decipher what characterizes minute cells, such that wild-type cells recognize them as dinner. **JCB**

Reference: Li, W., and N. Baker. 2007. *Cell.* 129:1215–1225.

## Migrating neurons keep their limbs tucked in

Neurons with overly long axons and dendrites can't migrate, report Inma Cobos, Ugo Borello, and John Rubenstein (University of California, San Francisco, CA).

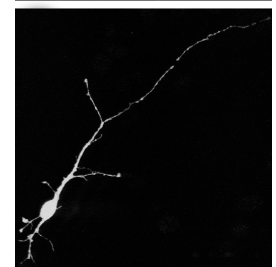
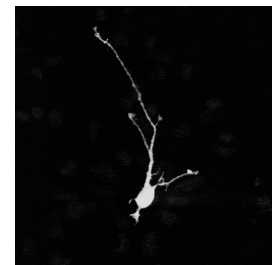
Cortical interneurons migrate to their adult location in the cortex during embryogenesis. It has been known for some time that the transcription factors *Dlx1* and *Dlx2* control this migration, but just how they manage it was unclear.

*Dlx1/2* are normally expressed at high levels in new interneurons and gradually reduce to low levels in postmigratory cells. Cobos et al. show that young interneuron precursors taken from mice lacking *Dlx1/2* have much longer neurites (axons and dendrites) than their wild-type counterparts. The overly long neurites were associated with increased expression of several cytoskeleton regulatory genes.

The team showed that PAK3 kinase, one of these regulators, was expressed at almost undetectable levels in newborn and migrating wild-type precursor interneurons. Its expression rose to high levels once interneurons reached the cortex. Suppression of PAK3 with siRNA in the *Dlx* mutant interneuron precursors led to shorter neurites and partly restored migratory ability.

In addition to their migratory defects, *Dlx* mutant interneurons were also prone to apoptosis. The researchers are currently investigating other *Dlx* target genes to determine how, if at all, interneuron survival is linked to migration. **JCB**

Reference: Cobos, I., et al. 2007. *Neuron.* 54:873–888.



RUBENSTEIN/ELSEVIER

**With shorter neurites, wild-type interneuron precursors (top) migrate more easily than gangly *Dlx1/2* mutants (bottom).**