

Research Roundup



SOCOLOVSKY/PLoS

Red blood cells developing around a macrophage (center) are close enough to touch—and sometimes kill—each other.

Red blood cells have a killer touch

Red blood cells need their space, suggest results from Merav Socolovsky (University of Massachusetts Medical School), Andre Levchenko (Johns Hopkins University), and colleagues. Fetal developing red blood cells, they show, might just kill some of the brethren they are close enough to touch.

During early embryogenesis, red blood cells need to be produced at a high rate to keep the embryo well oxygenated. Their precursors therefore start out growing ten times faster than the fetus as a whole. This fecundity must be shut down at the right time to prevent overgrowth. To determine how growth is limited, the group measured cell numbers at each stage of RBC development and constructed a mathematical model to fit the numerical data. The

model predicted the existence of negative auto-regulation as a result of physical contact between immature red cell progenitors.

Contact-initiated death is well-suited to the FAS system, in which contact between cells expressing FAS and those expressing its ligand, FASL, results in suicide in the FAS cell. With this in mind, the authors found that both FAS and FASL were expressed shortly after red blood cell maturation began, at the same time the model predicted action by the inhibitory component. When FAS/FASL-expressing cell numbers are low, they rarely interact, and death remains rare. As their numbers grow, however, their rate of interaction grows geometrically. It's then, says Socolovsky, that "the brakes come on to prevent overgrowth."

The regulatory system not only keeps the number of cells from growing too large of its own accord, it also protects the system from external perturbations. If a trauma, for example, depletes the body of red blood cells, their new-found personal space will allow for replenishment. **JCB**

Reference: Socolovsky, M., et al. 2007. *PLoS Biol.* doi:10.1371/journal.pbio.0050252.

Enzyme may link inflammation to new cell fate

Gene silencing is the sine qua non of differentiation, and reversal of gene silencing paves the way for a cell to adopt a new fate. In a new study, Francesca De Santa, Giaocchino Natoli, and colleagues (European Institute of Oncology, Milan, Italy) identify a desilencing protein that might let cells find new fates during inflammation.

"Under conditions of chronic inflammation, tissues tend to show altered differentiation," Natoli says. Chronic gastritis, for instance, can lead to the formation of intestinal cells within the stomach lining. And in a rejected kidney transplant, host macrophages turn into endothelial cells, creating new lymphatic vessels.

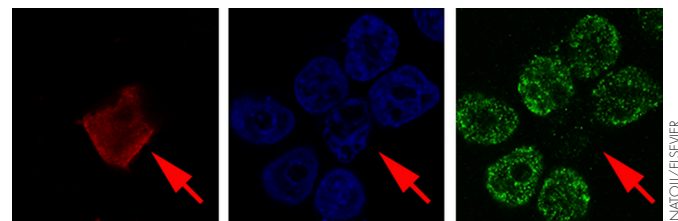
For macrophages to adopt new fates, a lysine in histone H3 must first be demethylated to relieve the silencing of cell fate determinants. One group of enzymes that removes methyl groups is the JmjC domain proteins, which includes JmjD3, whose exact function has been unclear. In the new work, the authors discovered that JmjD3 was up-regulated during inflammation and that it demethylated cell fate genes.

Jmdj3's target genes included late HoxA genes, which are powerful determinants of cell fate. Additionally, knock down of Jmdj3 inhibited the demethylation of bone morphogenetic

protein 2, thus preventing its normal inflammation-induced increase.

The existence of a system to erase controls on terminal differentiation may seem counterintuitive at first, but "it makes a lot of biological sense," says Natoli. In situations in which tissue regeneration is needed, and local stem cells are exhausted, there may be a need to recruit other cell types. New lymphatic vessels, for instance, may be needed to increase the flow of debris out of an injured and inflamed area, Natoli suggests. "Inflammation loosens control over differentiation, and Jmdj3 may be the molecular link between these processes." **JCB**

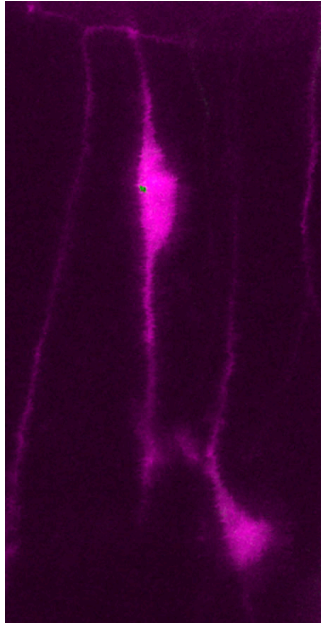
Reference: De Santa, F., et al. 2007. *Cell.* 130:1083–1094.



Jmdj3 (red) removes lysine methyl groups (green) from chromatin and allows macrophages to become new cell types.

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NATOLI/ELSEVIER



KENGAKU/NAS

The nucleus of a cell can pass in front of the centrosome (green) as it migrates downward.

Nucleus runs ahead of centrosome

The nucleus is not pulled by the centrosome in migrating neurons, according to a new direct imaging study by Hiroki Umeshima, Tomoo Hirano, and Mineko Kengaku (RIKEN Brain Science Institute, Wako, Japan).

Previous studies showing the centrosome leading the nucleus in migrating neurons led to the suggestion that the centrosome provides the motive force for nuclear migration. “Our results clearly argue against this accepted model,” Kengaku says.

The imaging study in mouse cerebellar slices indicates that the nucleus sometimes passes in front of the centrosome—a phenomenon not seen previously in isolated cells. While the nucleus spent part of its time behind the centrosome, it also jumped ahead. Neither the dynamic microtubules enveloping the nucleus or the stable microtubules extending from nucleus to leading edge converged at the centrosome.

Disruption or excess formation of the stable microtubules interrupted nuclear movement. One possibility is that the stable filaments form a track along which the nucleus is pulled by the dynamic microtubules.

Inhibition of LIS1, which regulates the microtubule motor dynein, prevented migration of the nucleus without interfering with the centrosome, indicating the two use different mechanisms to migrate. What, then, is the centrosome’s role in nuclear migration? “That’s the next question we have to answer,” Kengaku says. “We think the centrosome is important for microtubule organization,” perhaps in preparing microtubules during the cyclic pauses in nuclear migration for future movements, “but we haven’t proven it yet.” **JCB**

Reference: Umeshima, H., et al. 2007. *Proc. Natl. Acad. Sci. USA*. doi:10.1073/pnas.0708047104.

Forward walk with a random twist

Myosin-V makes a random twist as it traverses hand over hand along its actin filament, according to a study by Yasunori Komori, Atsuko Iwane, and Toshio Yanagida (Osaka University, Osaka, Japan).

The transport molecule myosin-V, which bears two actin-binding heads each linked by an arm to a central stalk, carries cargo along the cytoskeletal network. The hydrolysis of ATP drives the lagging head off of actin, but how that head swings around the leading head to rejoin the actin was unknown.

In the new experiments, fluorescently labeled actin filaments bound to an immobilized myosin-V were seen to twist randomly clockwise or counterclockwise during each clamp-release-reclamp cycle. The finding indicates that in the cell, where actin is fixed and myosin is free to twist, the trailing myosin head can swing in either direction as it searches out its next forward binding site.

Yanagida thinks the ability to twist in either direction gives the motor better mobility. “The cell is very crowded by the many kinds of proteins within,” he says. “It’s probably not easy to transport cargo along the complex actin meshwork.” In addition, unlike a twist in a fixed direction, a random twist allows multiple myosin-V molecules on a single cargo to avoid twirling each other around as they move. **JCB**

Reference: Komori, Y., et al. 2007. *Nat. Struct. Mol. Biol.* doi:10.1038/nsmb1298.

Hand it to the nucleolus

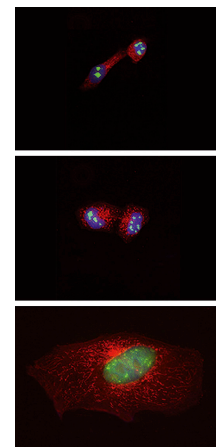
Long viewed as merely a biofactory for ribosomes, the nucleolus has recently come to be seen as a multifunctional and dynamic subnuclear organelle. New support for this view comes from a study by David Martindill, Paul Riley (UCL Institute of Child Health, London, UK), and colleagues, who show that a cell fate regulator is held inactive in the nucleolus until phosphorylation releases it to trigger differentiation.

Differentiation of mouse trophoblast stem cells into a specialized cell type called giant cells requires Hand1, a bHLH transcription factor. Hand1 interacts with a wider variety of other bHLH partners than do others of its class. The authors thus wondered whether it might also interact with unrelated partners that help it time giant cell differentiation. Using a yeast two-hybrid approach, they found that Hand1 bound to a nucleolar subunit of a protein called HIC.

While Hand1 hung out with HIC in the nucleolus, trophoblast cells did not differentiate. But Hand1 exited the nucleolus at the time of their differentiation to giant cells. This exit required the phosphorylation of Hand1.

The kinase that phosphorylated Hand1, called Polo-like kinase 4, is evolutionarily conserved. Phosphorylation-dependent release of transcription factors from the nucleolus may turn out to be a widespread mechanism to control their activity. **JCB**

Reference: Martindill, D.M.J., et al. 2007. *Nat. Cell Biol.* doi:10.1038/ncb1633.



RILEY/MACMILLAN

The release of Hand1 (green) from the nucleolus coincides with giant cell differentiation (top to bottom).