RESEARCH HIGHLIGHTS

MicroRNAs mediate reprogramming

The techniques available to reprogramme somatic cells to a pluripotent state require forced expression of at least one transcription factor. Together with the low efficiency of the process, this drawback has prevented large-scale application of induced pluripotent stem cell (iPSC) technology. MicroRNAs (miRNAs) highly expressed in embryonic stem cells can improve this efficiency, possibly through their effect on the cell cycle, but no miRNA has been described that can completely replace the pluripotency factors.

Morrisey and colleagues (*Cell Stem Cell* **8,** 376–388; 2011) now show that the expression of the mir-302/mir-367 cluster, normally controlled by pluripotency factors Oct4 and Sox2, can directly reprogramme both mouse and human somatic cells with an efficiency two orders of magnitude higher than other methods. The authors find that reprogramming of mouse embryonic fibroblasts also requires inhibition of the histone deacetylase HDAC2 with valproic acid. The miRNA cluster contains five miRNAs and miR-367 is essential for the process, possibly through induction of Oct4 expression, although it is not sufficient to induce reprogramming in the absence of the other miRNAs. In this study, miRNAs were expressed using a lentiviral vector and future work with a therapeutic goal should focus on developing viral-free methods of delivery. NLB

A trigger for extrusion

Squeezing dying cells out of an epithelial cell layer is important for its barrier function. While apoptotic cells are known to initiate Rho-mediated actomyosin contraction in surrounding cells leading to apoptotic cell extrusion, the molecular identity of this trigger was unknown. Rosenblatt and colleagues now show that it is the lipid sphingosine-1-phosphate (S1P) (*J. Cell Biol.* doi: 10.1083/jcb201010075).

The authors had previously developed an assay in which adding dying cells to epithelial monolayers enables the monitoring of actin assembly and cell extrusion. As protease treatment did not inhibit the actin response, the authors speculated that the active trigger was a lipid. Indeed, addition of S1P to epithelial cells induced actin accumulation similarly to the presence of apoptotic cells. Pharmacological inhibition of a S1P-synthesizing enzyme or S1P receptor 2 (S1P2) also prevented extrusion of apoptotic cells. Furthermore, depletion of S1P2 in surrounding cells but not in apoptotic cells blocked extrusion. Using a previously validated zebrafish system, they found that S1P2 is critical for apoptotic cell extrusion from the larval epidermis. Antibody labelling of S1P confirmed that S1P is produced by apoptotic cells and taken up by its neighbours. As S1P is associated with cancer cell proliferation and invasion, the authors suggest that its role as a trigger of extrusion could also be relevant in the context of metastasis. CKR

Modelling cell shape

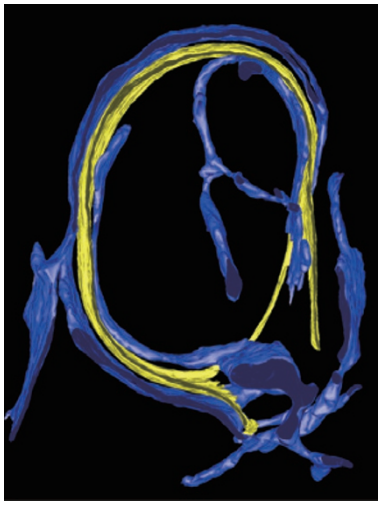
Cell migration depends on the strength of the cell's adhesion to the substrate, myosin contraction and the organization of the actin network, parameters that also impinge on cell shape. Barnhart *et al.* now present a mechanical model of cell shape determination by the adhesion- and myosin-dependent regulation of actin dynamics (*PLoS Biol.* doi:10.1371/journal.pbio.1001059)

Following manipulation of the adhesion strength of fish epithelial keratinocytes to polymer substrates, the authors observed that low adhesion conditions promoted small, round and slow-moving cells, which became larger, fan-shaped and fast-moving under intermediate adhesion strength and decreased in speed but maintained their large size under high adhesion conditions.

To investigate the role of adhesion strength in cell morphology, the authors developed physical models that recapitulated these observations on the basis of the mechanical interplay between adhesion, myosin-mediated contraction, actin treadmilling and the cell membrane. They then experimentally validated a series of simulation-derived predictions of myosin localization and activity, actin network dynamics and adhesion distribution.

Based on experimental findings and modelling, the authors propose that shape change depends on the rates of both actin polymerization and myosin-driven retrograde actin flow at the cell boundaries. Changes in adhesion strength and myosin contraction switch cells between retrograde flow- and actin-polymerization-dependent shape determination mechanisms. AIZ

Regulating autophagosome membrane fusion



In yeast, the ubiquitin-like protein Atg8 contributes to autophagy by regulating elongation of the autophagosome membrane. Previous reports have suggested that mammalian Atg8 orthologues, including $LC3_B$ and GATE-16, are similarly important for autophagosome biogenesis, but their precise contributions to this process have not yet been revealed. Zvulun Elazar and colleagues now show that $LC3_B$ and GATE-16 mediate tethering and fusion of autophagosome membranes (*Dev. Cell* **20,** 444–454; 2011).

$LC3_B$ and GATE-16 both stimulated liposome tethering and lipid mixing *in vitro*; membrane fusion was dependent on each protein's amino-terminal α-helix. The amino-acid composition of the $LC3_B$ and GATE-16 α-helices is divergent, and the authors found that two positively charged amino acids were important for $LC3_B$ activity, whereas GATE-16 function required two hydrophobic residues.

Knockdown of $LC3_B$ or GATE-16 promoted accumulation of Atg16-positive punctae, indicating a defect in membrane fusion. This could be rescued with wild-type proteins, but not N-terminal-domain mutants. Together, these data show that $LC3_B$ and GATE-16 are required for autophagosome membrane fusion, providing compelling evidence for a role for ubiquitin-like proteins in this important biological process. EJC

Written by Emily Chenette, Nathalie Le Bot, Christina Karlsson Rosenthal & Alexia-Ileana Zaromytidou