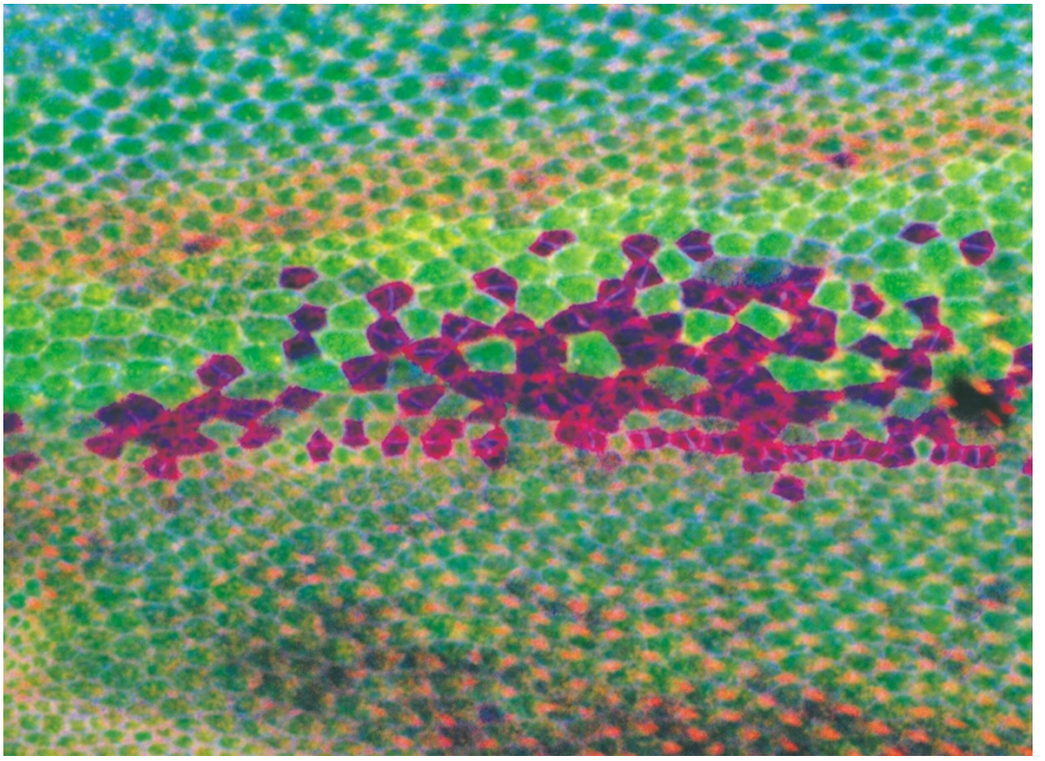

ADHESION

Rap around cells

The small GTPase Rap1 is known to regulate morphogenesis in *Drosophila melanogaster*, but the mechanism by which it does this has remained unclear. Rap1 was originally thought to antagonize Ras1 signalling, but a subsequent study showed that mutations in Rap1 induced abnormal cell shape and disrupted migration, rather than affecting Ras-mediated signalling pathways. Now, reporting in *Science*, Knox and Brown have found that Rap1 probably regulates these properties by regulating the position of adherens-junction proteins.

Studying the behaviour of epithelial cells during *Drosophila* wing development, Knox and Brown found that clones of Rap1-mutant cells spread — often in pairs or groups of four — into surrounding wild-type cells instead of staying together as a group. Combined with the fact that Rap1-mutant cells lacked the typical hexagonal shape and had a reduced apical surface compared with wild-type cells, this indicated that Rap1 might regulate apical cell–cell adhesion.

The authors then studied components of adherens junctions — DE-cadherin, α-catenin and β-catenin — on the apical surface of Rap1-mutant cells and noted that they localized predominantly to one side of the cells, forming 'clusters' of adherens-junction proteins with Rap1-mutant, but not wild-type, neighbouring cells. Interestingly, the cytoskeletal linker proteins AF6/canoe — to which activated Rap1 binds — and ZO-1 — which interacts with both AF6/canoe and α-catenin — were also mislocalized, indicating that ZO-1 might link adherens-junction proteins and Rap1. By contrast, loss of Rap1 function had no effect on septate-junction-associated proteins. Furthermore, as DE-cadherin and β-catenin didn't mislocalize along the apical–basal axis of Rap1-mutant cells, Rap seems to affect the distribution of adherens junctions around the periphery of apical cells specifically.

So, could the mislocalization of adhesion molecules such as DE-cadherin be responsible for the dispersal of the Rap1-mutant cells into surrounding cells? As there are other examples of cell-sorting in response to differential adhesion, the authors proposed that small groups of Rap1-mutant cells could effectively be 'drawn in' to surrounding wild-type tissue as a result of adhesion being stronger between mutant and wild-type cells than between Rap1-mutant cells. Also, because adherens-junction proteins showed mislocalization in undispersed cells, this indicates that the dispersal phenotype occurs as a result of mislocalization, rather than vice versa.

Closer inspection, using a green-fluorescent protein (GFP)–Rap1 fusion protein, showed that GFP–Rap1 was highly concentrated at adherens junctions (consistent with a potential link between Rap1, ZO-1 and AF6/canoe). The authors also noticed that while GFP–Rap1 localized around the cell cortex during cell division, when sister cells subsequently formed it was transiently enriched at the junction between them.

Based on these findings, Knox and Brown propose that the localization of Rap1 at adherens junctions might be necessary for maintaining adherens-junction proteins here, too. Without Rap1, the adherens-junction 'ring' of proteins that surrounds a dividing mother cell might not be resealed during cytokinesis, and as a consequence, it could recoil to one side, causing the proteins to 'cluster'. Rap1, therefore, seems to be able to mediate cell-shape changes through its ability to regulate adherens-junction positioning.

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References and links

ORIGINAL RESEARCH PAPER Knox, A. L. & Brown, N. H. Rap1 GTPase regulation of adherens junction positioning and cell adhesion. *Science* **295**, 1285–1288 (2002)

FURTHER READING Bos, J. L. *et al.* Rap1 signalling: adhering to new models. *Nature Rev. Mol. Cell Biol.* **2**, 369–377 (2001)

WEB SITE

Nick Brown's laboratory: http://www.welc.cam.ac.uk/prospectus/brown_prosp.shtml

IN THE NEWS

Stem cell sagas

The controversy about adult versus embryonic stem cell research continues to rumble on.

On 27 February 2002, a House of Lords committee gave UK scientists the legal green light to carry out experiments on human embryos. The committee decided that objections were insufficient to outweigh the potential benefits to science. This has angered pro-life and religious groups, which claim that recent breakthroughs in adult stem cell research have removed the need for embryo experiments.

But these adult stem cell studies might have serious potential flaws, according to two reports in *Nature*. Previously, when researchers found a genetically labelled bone-marrow stem cell in the brain, they took this as an indication that the stem cell had turned into a brain cell. But Professor Austin Smith of Edinburgh University, and senior author of one of the studies, now believes that these stem cells fused with the brain cells to produce cells with double the number of chromosomes, which could have unknown consequences.

"You are not putting in new cells, but fusing with cells that are already there, so the stem cell you have introduced takes on the character of the resident cell," Smith said (*The Daily Telegraph*, 14 March 2002). "Our study indicates that calls for a halt to embryonic stem cell research are not scientifically justified". (*BBC News*, 13 March 2002).

Professor Smith admits that these results are not the "kiss of death" for adult stem cell research, but stressed that earlier work will need to be re-evaluated.

Rachel Smallridge