CELL MIGRATION

A move away from death

It's not uncommon for proteins to have more than one job — it's probably a cell's way of maximizing efficiency. Joining the list of moonlighting proteins, at least in *Drosophila melanogaster*, is the inhibitor of apoptosis (IAP) protein DIAP1, as Geisbrecht and Montell report in *Cell*. Better known for its anti-apoptotic abilities, DIAP1 also functions independently of this role, in Rac-mediated cell motility.

In egg chambers of wild-type *D. melanogaster*, a cluster of cells migrates from the anterior of the chamber to the border between the oocyte (which is at the posterior) and the nurse cells. These migrating 'border cells' express Rac — a protein with a well-established role in regulating the actin cytoskeleton — and negatively interfering with Rac function blocked border-cell migration. The authors' quest to identify other components in the Rac pathway that mediate border-cell migration involved screening for genes that, when overexpressed, overcame the migration defect of dominant-negative (N17)Rac. Wild-type Rac, as predicted, rescued the effect, but so, too, did actin5C and DIAP1.

Focusing on DIAP1, the authors found it to be expressed in border cells. Both BIR (baculoviral inhibitor of apoptosis repeats) domains, which mediate the anti-apoptotic function of DIAP1, were required for cell migration, whereas the so-called RING domain was dispensable. Without DIAP1, which is encoded by the *thread* (*th*) locus, there were extra nurse cells, defects in follicle cells and in the polarity of egg chambers, and impaired border-cell migration. Some mutant cells also expressed lower levels of actin-binding proteins and labelled poorly with phalloidin, which binds to actin. Together with the identification of actin5C in the screen, this implied that Rac might affect actin polymerization in border cells.

A pool of ATP-bound, monomeric actin — which is required for actin polymerization — is maintained by profilin, an actin-monomer-sequestering protein. Geisbrecht and Montell noticed that overexpressing profilin rescued the N17Rac-mediated border-cell-migration defect. Furthermore, 10% of egg chambers from females that were mutant for *chickadee* (*chic*), which encodes profilin, had defects in border-cell migration. And *chic* and *th* interacted genetically in a dosage-sensitive manner, such that the figure of 10% rose to 50% when a mutant allele of *th* was combined with the *chic* mutant.

So what's the connection between DIAP1 and Rac? DIAP1 had no obvious effect on Rac activation, so the genetic interactions between *Rac*, *th* and *chic* prompted the authors to investigate whether the proteins might associate biochemically. Profilin and Rac interacted, as did profilin and DIAP1, and DIAP1 and Rac, so there seemed to be a physical complex between the three proteins. When DIAP1 was transfected into *D. melanogaster* S2 cells that were already expressing constitutively active Rac, the proportion of cells that showed filamentous-actin-rich 'serrate' or 'stellate' protrusions increased from 10% to >50%. This adds further weight to the possibility of a functional link between DIAP1 and Rac that influences the actin cytoskeleton.

Finally, Geisbrecht and Montell confirmed, using TUNEL assays, that the N17Rac-mediated border-cell-migration defect was not a result of increased cell death, as might have been the case. IAPs function by inhibiting the action of caspases, one of which, in *D. melanogaster*, is Dronc. When the authors expressed a dominant-negative form of Dronc, or its activator Dark, it rescued the N17Rac-mediated border-cell-migration defect. This indicates that Dronc seems to negatively affect migration. Dronc is a protease, and so it might well exert its inhibitory effect by cleaving proteins that affect Rac-mediated adhesion. There is a handful of candidate substrates, including Rac itself, but only further studies will uncover the real culprit.

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References and links

ORIGINAL RESEARCH PAPER Geisbrecht, E. R. & Montell, D. J. A role for *Drosophila* IAP1-mediated caspase inhibition in Rac-dependent cell migration. *Cell* **118**, 111–125 (2004)

IN BRIEF

CELL ADHESION

Activation of Cdc42 by *trans* interactions of the cell adhesion molecules nectins through c-Src and Cdc42-GEF FRG.

Fukuhara, T. *et al. J. Cell Biol.* **166**, 393–405 (2004)

As well as mediating intercellular adhesion, the *trans* interactions of nectins induce Rac and Cdc42 activation, which increases the speed at which cell–cell adherens junctions form. The authors found that these immunoglobulin-like, Ca^{2+}-independent molecules recruited Src to sites of cell–cell adhesion. Here, Src was activated and induced the formation of filopodia and lamellipodia by phosphorylating and activating the guanine nucleotide-exchange factor FRG, which, in turn, activated Cdc42.

CELL PROLIFERATION

Compensatory proliferation induced by cell death in the *Drosophila* wing disc requires activity of the apical cell death caspase Dronc in a nonapoptotic role.

Huh, J. R., Guo, M. & Hay, B. A. *Curr. Biol.* **14**, 1262–1266 (2004)

Up to 60% of cells in the wing discs of *Drosophila melanogaster* die. Despite this, the remaining cells undergo compensatory proliferation so that the adult wings develop normally. By uncoupling signals that induce cell death from the death process itself, the authors found that the activation of death signals, such as Hid, activated the caspase Dronc, which stimulated compensatory proliferation in neighbouring cells. How Dronc might carry out this non-apoptotic role is a focus for future investigation, but increased expression of the mitogen Wingless was observed in Hid-expressing regions of the wing disc.

TELOMERES

Closed chromatin loops at the ends of chromosomes.

Nikitina, T. & Woodcock, C. L. *J. Cell Biol.* **166**, 161–165 (2004)

Telomeres are specialized DNA structures that 'cap' the ends of linear DNA to protect them against shortening. Telomere chromatin has been notoriously difficult to study because it is tightly embedded within the nuclear matrix. But Nikitina and Woodcock used the nuclei from chicken erythrocytes and mouse lymphocytes, which contain fewer non-histone chromosomal proteins, to prepare telomere chromatin and study its structure. Electron microscopy showed that telomere chromatin formed closed terminal loops, which correspond to 't-loop' structures in which single-stranded-DNA ends insert into duplex DNA.

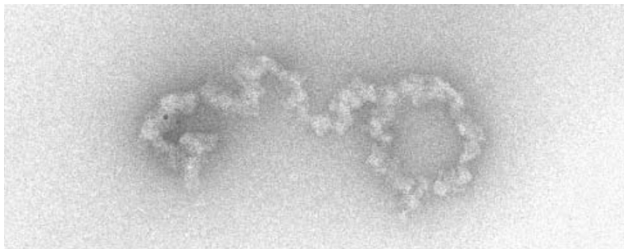

Image courtesy of Christopher L. Woodcock, University of Massachusetts, Amherst, Massachusetts, USA.