CELL MIGRATION

# From stop to go

Better known for its inhibitory cell-cycle function as a tumour suppressor, $p27^{Kip1}$ is extending its molecular repertoire. In *Genes & Development*, Arnaud Besson *et al.* tell us about its ability to regulate cell migration by modulating the small GTPase Rho.

Earlier work from other groups had shown that the motility of mouse embryonic fibroblasts (MEFs) from $p27^{-/-}$ mice was impaired compared to MEFs from wild-type animals, and that increased expression of cytoplasmic $p27^{Kip1}$ stimulated cell migration. Besson *et al.* confirmed the effect of $p27^{Kip1}$ on cell migration, and went on to show that this could not be overcome by adding known motility factors, or Ras, a potent inducer of motility. Moreover, glioblastoma cells that were treated with antisense oligonucleotides targeted against $p27^{Kip1}$ showed a similar migration defect.

The activity of Rho must be carefully regulated, as it promotes the formation of stress fibres and focal adhesions, both of which inhibit cell migration by promoting too much cell adhesion. So the fact that $p27^{-/-}$ cells had many stress fibres and focal adhesions, and integrin localization to focal adhesions was enhanced, indicated a potential activation of Rho in these cells (Rho also regulates integrin localization at focal adhesions). Indeed, the authors found higher amounts of Rho–GTP in $p27^{-/-}$ cells than in wild-type cells, whereas the small GTPases Rac and Cdc42 were unaffected.

An effector of Rho, Rho kinase (Rock), often influences cell migration, so it was perhaps not surprising that treating $p27^{-/-}$ cells with the Rock inhibitor Y27632 restored normal migration. $p27^{Kip1}$, therefore, seems to function upstream of Rock in controlling cell migration. However, unlike a close relative, $p21^{Waf1/Cip1}$, which directly inhibits Rock activity, $p27^{Kip1}$ had no effect on Rock. Instead, $p27^{Kip1}$ bound directly to Rho irrespective of whether it was GTP- or GDP-bound.

The interaction of $p27^{Kip1}$ with Rho occurred through the carboxyl terminus of $p27^{Kip1}$; its amino terminus binds to cyclins or cyclin-dependent kinases. These separate binding domains are consistent with the finding that a form of $p27^{Kip1}$ that cannot bind these cell-cycle regulators rescued the migratory defect of $p27^{-/-}$ cells; wild-type $p27^{Kip1}$, as expected, restored cell motility in this situation. So the role of $p27^{Kip1}$ in migration is independent of its function in the cell cycle.

The consequence of the direct interaction between Rho and $p27^{Kip1}$ seems to be the inhibition of Rho activation by its guanine-nucleotide-exchange factors. So, depending on the levels of $p27^{Kip1}$, Rho activity will be inhibited and cell migration will be enhanced accordingly. Although the authors are careful to point out that this effect is probably cell-type-specific, $p27^{Kip1}$ is frequently inactivated in many cancers, often correlating with increased invasion. Inactivation can occur by exclusion from the nucleus, which might not only interfere with its inhibitory cell-cycle role, but also place it in a prime position for inhibiting Rho and increasing migration. And migration is probably just one of the ways in which the effect of $p27^{Kip1}$ on the cytoskeleton is manifest — how broadly $p27^{Kip1}$ might influence the many other processes that are controlled by the cytoskeleton remains to be seen.

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**References and links**

**ORIGINAL RESEARCH PAPER** Besson, A. *et al.* $p27^{Kip1}$ modulates cell migration through regulation of RhoA activation. *Genes Dev.* 12 April 2004 (doi:10.1101/gad.1185504)

# IN BRIEF

CELL MIGRATION

## YSK1 is activated by the Golgi matrix protein GM130 and plays a role in cell migration through its substrate 14-3-3ζ.

Preisinger, C. *et al. J. Cell Biol.* **164**, 1009–1020 (2004)

How the Golgi apparatus alters its position in response to extracellular signalling has been unclear. But Preisinger *et al.* have found that the STE20 kinases YSK1 and MST4 interact with the Golgi matrix protein GM130. This induces autophosphorylation of a conserved residue, which, when mutated in YSK1 to alanine, impairs Golgi-apparatus localization, and cell migration and invasion. The adaptor protein 14-3-3ζ, a Golgi-localized target of YSK1, might link YST1 signalling with migratory responses.

DEVELOPMENT

## *FGF8-like1* and *FGF8-like2* encode putative ligands of the FGF receptor Htl and are required for mesoderm migration in the *Drosophila* gastrula.

Gryzik, T. & Müller, H.-A. J. *Curr. Biol.* 1 April 2004 (doi:10.1016/S0960982204002362)

In early *Drosophila melanogaster* gastrulation, the fibroblast growth factor (FGF) receptor Heartless (Htl) is needed for mesoderm cells to migrate. Until now, the ligand of Htl was unknown. Gryzik and Müller have identified two genes that encode FGF homologues. Ectodermally expressed *FGF8-like1* and *FGF8-like2* are required for Htl-expressing mesodermal cells to undergo the cell-shape changes that are required for migration by activating the mitogen-activated-protein-kinase pathway in these cells.

UBIQUITYLATION

## A novel protein-conjugating system for Ufm1, a ubiquitin-fold modifier.

Komatsu, M. *et al. EMBO J.* 8 April 2004 (doi:10.1038/sj.emboj.7600205)

Ubiquitin-like proteins (UBLs), which resemble ubiquitin structurally, have recently been discovered. Komatsu *et al.* now describe a new UBL protein, Ufm1 (ubiquitin-fold modifier-1). They also identified Ubc5 and Ufc1, which function as E1-like (activating) and E2-like (conjugating) enzymes, respectively. Ufm1 is processed to expose a glycine residue that is necessary for its conjugation to a target protein prior to activation by Ubc5.

APOPTOSIS

## The PIDDosome, a protein complex implicated in activation of caspase-2 in response to genotoxic stress.

Tinel, A. & Tschopp, J. *Science* 8 April 2004 (doi:10.1126/science.1095432)

Tinel and Tschopp have identified a protein complex that is responsible for the activation of caspase-2, which is involved in stress-induced apoptosis. Caspase-2 is activated during complex formation with the adaptor protein RAIDD and the p53-induced protein PIDD. Increased PIDD expression causes the spontaneous activation of caspase-2 and enhanced sensitivity to apoptosis in response to genotoxic stimuli.