CANCER

A deadly combination

There are some cell lines in which epithelial–mesenchymal transition (EMT) occurs as the result of a joint effort between H-ras and transforming-growth-factor-β (TGF-β). How relevant this is to the multistage nature of *in vivo* tumour progression, though, is a burning question.

So Allan Balmain's group studied whether changes in the levels of H-ras and TGF-β are significant during tumour progression. They did this using a series of well-characterized tumour cell lines that arise from initiated cells that carry activating mutations in the *Hras1* gene. And, as they now report in *Nature Cell Biology*, Smad2 (a downstream target of TGF-β signalling) and H-ras surpass discrete thresholds during progression from early-stage papillomas, through squamous carcinomas, to late-stage undifferentiated spindle-cell tumours.

First, the authors studied the molecular changes that occur when squamous carcinomas are converted into spindle-cell tumours. TGF-β-mediated transcriptional activity was very high in the spindle cells, and phosphorylated Smad2 accumulated in the nucleus, which indicated that the TGF-β pathway was activated in these cells. Furthermore, in primary material from spindle-cell tumours, but not from differentiated tumours or squamous carcinomas, Smad2 was phosphorylated and predominantly localized in the cytoplasm.

Although Smad2 alone induced changes in the migration of squamous carcinoma cells, only in the presence of increased levels of mutated H-ras did changes in cell shape and the expression of genes such as α-smooth-muscle actin (a mesenchymal marker) occur, resulting in EMT.

The authors then investigated whether, once this stage has been reached, TGF-β signalling through Smad2 is still necessary for tumour progression. Expression of a dominant-negative form of Smad2 showed that this is indeed the case; spindle cells that expressed this construct reverted to a more epithelial phenotype and took on many features of epithelial gene expression. Notably, surface expression of αvβ3 integrin was lost, and this coincided with the loss of collagen-matrix invasion. *In vivo*, this correlated with an inability to form tumours. By contrast, parental spindle cells or spindle cells that express a dominant-active form of Smad2 formed tumours, and those that were formed by dominant-active Smad2 were particularly invasive. Expression of dominant-active Smad2 also promoted extravasation into the target tissue, and a subsequent increase in lung metastases.

As the ability of a tumour to metastasize is the main determinant of whether or not cancer patients die, these findings that different thresholds of H-ras and TGF-β activity — intermediate levels of Smad2 that cooperate with H-ras to induce EMT and invasiveness, and even higher levels of Smad2 that are required for metastasis — are crucial for metastasis offer the opportunity for the design of small-molecule inhibitors to prevent the spread of tumours.

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References and links

ORIGINAL RESEARCH PAPER Oft, M., Akhurst, R. J. & Balmain, A. Elevated levels of activated Smad2 and H-ras control epithelial–mesenchymal transformation, tumour cell extravasation and metastasis. *Nature Cell Biol.* **4**, 487–494 (2002)

IN BRIEF

DNA REPAIR

Involvement of human polynucleotide kinase in double-strand break repair by non-homologous end joining.

Chappell, C. *et al. EMBO J.* **21**, 2827–2832 (2002)

The efficient repair of double-strand breaks in DNA — by homologous recombination or by non-homologous end joining (NHEJ) — is vital to maintain genome stability. Chappell *et al.* now show that human polynucleotide kinase has a direct role in NHEJ. Acting specifically in the context of the NHEJ apparatus, this enzyme restores ligatable 5′-phosphate groups by catalysing the phosphorylation of 5′-OH termini.

DEVELOPMENT

Sensory nerves determine the pattern of arterial differentiation and blood vessel branching in the skin.

Mukouyama, Y. *et al. Cell* **109**, 693–705 (2002)

In this report, Mukouyama and colleagues studied the effect of the nervous system on blood-vessel development in the embryonic mouse limb skin. They found that arteries, but not veins, specifically align with peripheral nerves, and that arteries fail to differentiate in mutant embryos that lack sensory nerves. In addition, they showed that arteries align with misrouted axons in mutant embryos containing disorganized nerves. Their results indicate that peripheral nerves provide a template that determines the organotypic branching pattern of blood vessels and arterial differentiation in the skin through the local secretion of vascular endothelial growth factor.

TRANSCRIPTION

Crystal structure of a bacterial RNA polymerase holoenzyme at 2.6 Å resolution.

Vassylyev, D. G. *et al. Nature* **417**, 712–719 (2002)

In bacteria, binding of the initiation factor σ to the RNA polymerase core enzyme produces the active holoenzyme that initiates transcription. Here, Vassylyev *et al.* describe the crystal structure of this holoenzyme, which provides insights into both the structural organization of transcription intermediate complexes and the mechanism of transcription initiation.

DNA SEGREGATION

Prokaryotic DNA segregation by an actin-like filament.

Møller-Jensen, J. *et al. EMBO J.* **21**, 3119–3127 (2002)

The mechanisms that underlie prokaryotic DNA segregation are not well defined. The *Escherichia coli* plasmid R1 *par* locus encodes a repressor (ParR), a *cis*-acting centromere-like region (*parC*) and an ATPase (ParM) — the function of which has been unclear. Here, the authors show that ParM forms actin-like filaments along the length of *E. coli* cells and this generates the force for plasmid segregation to opposite ends of the cell. Meanwhile, the ParR–*par*C complex functions as the point of nucleation for filament polymerization.