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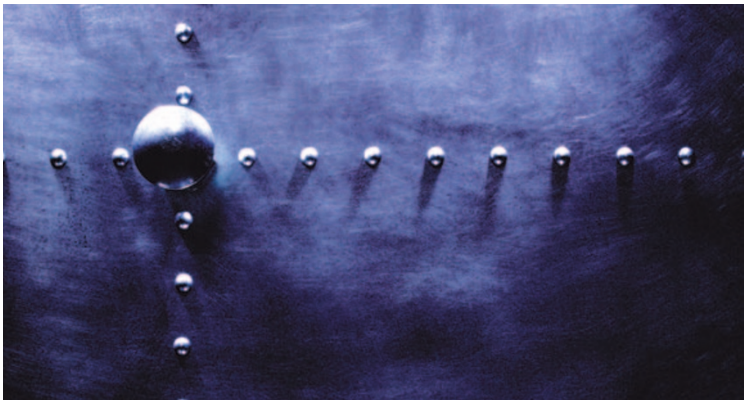

P53

A signalling integration node

Little is known about the mechanisms by which cells coordinate the many spatial and temporal signals they receive during development and tissue homeostasis. Stefano Piccolo and colleagues now show that the tumour-suppressor protein p53 links receptor Tyr kinase (RTK)–Ras–mitogen-activated protein kinase (MAPK) signalling and transforming growth factor-β (TGFβ)-mediated transcriptional activity to drive mesoderm differentiation in *Xenopus laevis* embryos and to arrest growth in adult mammalian cells.

During mesoderm specification, TGFβ-activated SMADs physically interact with p53 to regulate the transcription of mesoderm markers. Piccolo and co-workers found that depleting p53 in animal cap cells from *X. laevis* embryos blocked TGFβ-induced mesoderm differentiation. Ectopic expression of p53 in these cells induced TGFβ target genes, and this effect was abrogated by inhibiting Ras–MAPK signalling. This indicates that the RTK–Ras–MAPK pathway activates p53 to induce TGFβ-mediated gene responses.

The SMAD-binding domain of p53 is localized in its N-terminal region, which contains several Ser and Thr residues, phosphorylation of which is important for p53 activation. Site-specific mutations revealed that N-terminal phosphorylation on Ser6 and Ser9 is required for p53 to interact with SMADs. RTK–Ras–MAPK signalling also promoted phosphorylation of these residues. Fibroblast growth factor (FGF), which activates the RTK–Ras–MAPK pathway, is highly expressed in the marginal zone (the future mesoderm), but not in the animal pole. In accordance, FGF signalling downregulates Ser6 and Ser9 phosphorylation in the marginal zone, whereas phosphorylation of other residues is constitutive. This indicates that FGF defines the phosphorylation status of p53 spatially by restricting its activity to the prospective mesoderm.

In adult human cells, TGFβ activity induces growth arrest during tissue homeostasis. *p53*-null H1299 lung cancer cells (which are defective for TGFβ-induced growth arrest) could be rescued by wild-type p53 but not by N-terminal mutants of p53. This indicates that N-terminal phosphorylation of p53 is also required for temporal activation of the TGFβ cytostatic programme. Inhibition of the CK1ε and CK1δ kinases in p53-reconstituted H1299 cells revealed that these kinases are responsible for Ser6 and Ser9 phosphorylation of p53 in response to RTK–Ras–MAPK signalling.

Together, these data illustrate a previously unknown mechanism through which p53 controls cell proliferation, by functioning as a link between two pathways that are involved in cell fate.

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ORIGINAL RESEARCH PAPER Cordenonsi, M. *et al.* Integration of TGF-β and Ras/MAPK signaling through p53 phosphorylation. *Science* **315**, 840–843 (2007)