CANCER BIOLOGY

Motion capture

> mutant p53 can promote invasive growth by driving RCP-dependent integrin recycling

The ever more complex story of p53 and its relations took an interesting turn as the decade drew to a close. The function of mutant p53 proteins during tumour development is a hotly debated topic and a recent publication in *Cell* indicates that invasion, integrins and receptor recycling are all important to the tale.

Norman, Vousden and colleagues were intrigued by the fact that p53-mutant proteins seem to be more than just dominant-negative inhibitors of the wild-type protein, given that expression of mutant p53 in mouse models of cancer indicated a role in invasion and metastasis. They expressed two p53 mutants that are often found in human tumours (p53 175H and p53 273H) in p53-null lung cancer cells and untransformed human epithelial cells. Assays in matrigel indicated that the cells that expressed the p53 mutants were more invasive. In addition, cells that expressed mutant p53 produced more invasive tumours in two different mouse models of cancer.

The ability of p53 mutants to induce invasive growth in matrigel required the presence of epidermal growth factor (EGF) and fibronectin, indicating that mutant p53-mediated invasion involves integrin function and EGF receptor (EGFR) expression. Indeed, invasion was negated in the presence of an EGFR inhibitor or an α5 integrin-blocking antibody. Previous work had shown that integrins and EGFR are recycled together to the plasma membrane in cells that show increased invasion, and this co-trafficking requires the RAB11 effector, Rab-coupling protein (RCP). Examination of the cells expressing mutant p53 indicated that they also showed increased recycling of both α5β1 integrin and EGFR, and that this was dependent on the expression of RCP. Indeed, mutant p53 indirectly promoted the interaction between α5β1 integrin and RCP. The authors verified these observations in cell lines that expressed endogenous mutant p53, confirming that these findings were not a result of overexpression in transfected cells.

The gain-of-function phenotypes elicited by mutant p53 have been shown to depend on the amino-terminal domain of the protein and on its interaction with p73 and p63. N-terminal deletion mutants did not alter the capacity of mutant p53 to promote invasion; however, mutations that prevented mutant p53 from inhibiting the activity of the TAp63 isoform also inhibited the ability to promote invasion. Moreover, RNA inhibition of TAp63, but not p73, promoted invasive behaviour in p53-null lung cancer cells and increased the recycling of α5β1 integrin and EGFR.

These results indicate that mutant p53 can promote invasive growth by driving RCP-dependent integrin recycling, and that this requires the suppression of TAp63. However, as the authors note, these findings are likely to be context dependent, and mutant p53 proteins undoubtedly have other functional gains that mediate their positive selection during tumorigenesis.

Nicola McCarthy, Chief Editor
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ORIGINAL RESEARCH PAPER Muller, P. A. J. *et al.* Mutant p53 drives invasion by promoting integrin recycling. *Cell* **139**, 1327–1341 (2009)
FURTHER READING Brosh, R. & Rotter, V. When mutants gain new powers: news from the mutant p53 field. *Nature Rev. Cancer* **9**, 701–713 (2009) | Caswell, P. T *et al.* Integrins: masters and slaves of endocytic transport. *Nature Rev. Mol. Cell Biol.* **10**, 843–853 (2009)

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