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Finding the right target

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Because of the frequent mutational activation of Ras in cancer, there is widespread interest in developing Ras inhibitors. However, because Ras has many downstream effectors that regulate complex signalling networks, there has been much debate regarding which effectors of Ras are most important during tumorigenesis. Gupta *et al.* now use mouse models of Ras-mediated tumorigenesis and validate the importance of the phosphatidylinositol 3-kinase (PI3K) pathway in Ras-induced tumorigenesis.

Most of the studies that have analysed the role of Ras effectors in Ras-mediated tumorigenesis have been carried out in tissue-culture cells. Genetically engineered mouse models have also been used to study the relevance of Ras effectors; however, genetic ablation of some Ras effectors results in defective development, therefore complicating the analyses of their functions in Ras-mediated tumorigenesis.

To evaluate the role of the PI3K isoform p110α in normal and mutant Ras signalling, Gupta *et al.* engineered mice in which the endogenous *Pik3ca* gene encodes a mutant p110α protein that is enzymatically active, but cannot interact with Ras. Analysis of mouse embryonic fibroblasts (MEFs) that were treated with various growth factors showed that disruption of the interaction of p110α with Ras attenuates growth factor signalling — in p110α-mutant MEFs, activation of PI3K was reduced in response to epidermal growth factor and fibroblast growth factor-2.

The phenotype of *Pik3ca*-mutant mice also suggests that there is a requirement for the Ras–PI3K interaction *in vivo* for some growth factors to signal correctly. Mutant mice have defective branching of the lymphatic vasculature, which results in accumulation of lymphatic fluid in the abdominal cavity and markedly reduced viability at birth. Although this phenotype recapitulates the phenotype of vascular endothelial growth factor C heterozygous mice, further analysis is required to investigate the mechanisms that are impaired in *Pik3ca*-mutant mice.

But what is the role of p110α in Ras-mediated tumorigenesis? The authors analysed the p110α mutants in two Ras-driven tumour mouse models. In one model, they treated animals with DMBA (7,12-dimethylbenzanthracene), which causes activating mutations in the murine *H-Ras* gene. They also used the K-Ras LA2 model, in which tumorigenesis is driven by endogenous levels of mutant K-Ras expression, resulting in lung adenocarcinomas. A striking 95% reduction in lung-tumour formation was observed in double K-Ras LA2 p110α-mutant mice. Furthermore, DMBA-induced carcinogenesis was almost abrogated in p110α-mutant mice. Transformation assays in mutant MEFs showed resistance to Ras transformation (in contrast to their wild-type counterparts), supporting a cell-autonomous effect on mutant Ras signalling.

Taken together, these findings show that the interaction of Ras with the PI3K subunit p110α is required for both developmental and malignant growth-factor signalling. This study also argues against the perception that the Raf–mitogen-activated protein kinase (MAPK) pathway is of prime importance in Ras-mediated tumorigenesis, and points to targeting of the Ras–PI3K interaction as an effective strategy in the treatment of tumours with a high incidence of Ras mutation. Whether these results from mouse models accurately reflect the mechanisms of Ras-mediated tumorigenesis in human tumours remains to be seen.

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> “…points to targeting of the Ras–PI3K interaction as an effective strategy in the treatment of tumours…”

ORIGINAL RESEARCH PAPER Gupta, S. *et al.* Binding of Ras to phosphoinositide 3-kinase p110α is required for Ras-driven tumorigenesis in mice. *Cell* **129**, 957–968 (2007)
FURTHER READING Der, C.J. & Van Dyke, T. Stopping Ras in its tracks. *Cell* **129**, 855–857 (2007)