IN BRIEF

METASTASIS

Seeding and propagation of untransformed mouse mammary cells in the lung

Podsypanina, K. *et al. Science* 28 Aug 2008 (doi:10.1126/science.1161621)

The metastatic growth of tumour cells is often thought of as a late event in tumour progression. However, Harold Varmus and colleagues have found that mouse mammary epithelial cells that express tetracycline-regulated forms of *MYC* and oncogenic *Kras* can form lung metastases without having previously been part of a primary tumour. Specifically, the authors intravenously injected these cells into *Rag1*-null mice that had been fed doxycycline so that the oncogenes were only expressed once the cells were circulating within the mice. They found that these cells could form lung metastases. They confirmed and extended these results using cells that have regulated expression of polyoma middle T (PyMT) antigen. These cells could form small mammary foci and survive in the lungs for up to 16 weeks in the absence of PyMT expression. Moreover, induced expression of PyMT 1.5–16 weeks after injection resulted in the formation of metastases within the lungs. Therefore, oncogenic expression is only required to induce the rapid, metastatic growth of mammary epithelial cells residing in the lung and not for earlier stages of metastasis after intravasation.

ONCOGENES

Kras regulatory elements and exon 4A determine mutation specificity in lung cancer

To, M. D. *et al. Nat Genet.* 31 Aug 2008 (doi:10.1038/ng.211)

The oncogenic capacity of the individual Ras genes seems to be tissue-type-dependent. To investigate why, Allan Balmain and colleagues used *Kras4b* and *Hras* knock-in (KI) mice. Importantly, both transgenes were knocked into the *Kras* locus, such that homozygous *Hras* KI mice express no KRAS. Surprisingly, the homozygous *Hras* KI mice developed ~10-fold more lung tumours than wild-type controls after treatment with the carcinogen urethane. Further investigation showed that the mutation of *Hras* was dependent on its expression from the *Kras* locus and that tissue-specific mutation preferences involve *cis*-acting regulatory elements specific to each gene rather than the functional properties of the proteins.

Interestingly, they also found that KI mice expressing only *Kras4b* (the dominant KRAS isoform) were largely resistant to urethane-induced lung cancer. Further analyses indicate that the 4A isoform is important for lung carcinogenesis. However, KRAS4A has limited expression within the lung, although it is potentially expressed in lung stem cells. Further investigations are needed to understand the implications of these findings.

SIGNALLING

Oncogenic MAPK signalling stimulates mTORC1 activity by promoting RSK-mediated raptor phosphorylation

Carrière, A. *et al. Current Biol.* **18**, 1269–1277 (2008)

Raptor, a scaffolding protein, regulates substrate recruitment to mammalian target of rapamycin (mTOR) complex 1 (mTORC1). This paper shows that raptor is phosphorylated by p90 ribosomal S6 kinase 1 and 2 as a result of mitogen-activated protein kinase (MAPK) signalling. This finding suggests a mechanism through which MAPK-dependent signalling can activate mTORC1 in the absence of phosphoinositide 3-kinase–Akt activation, and has implications for resistance to rapamycin-based drugs.