If this hypothesis is true, some tumour cells must persist after MYC inactivation, so the authors crossed the LAP-tTA/tet-off-MYC mice with mice transgenic for luciferase, so that the liver tumour cells transplanted into SCID mice could be tracked by measuring light emitted by luciferase activity. Eight months after MYC inactivation, luciferase activity was still detectable in tumour cells, whereas normal liver cells were undetectable 5 days after MYC inactivation.

Serial transplantation of liver tumours with inactivated MYC only rarely led to relapse — the relapsed tumours had compensatory increases in L-MYC and N-MYC. The authors conclude that targeted inactivation of MYC might be an effective treatment for some liver cancers.

Ezzie Hutchinson

References and links

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WEB SITE

Dean Felsher's lab:
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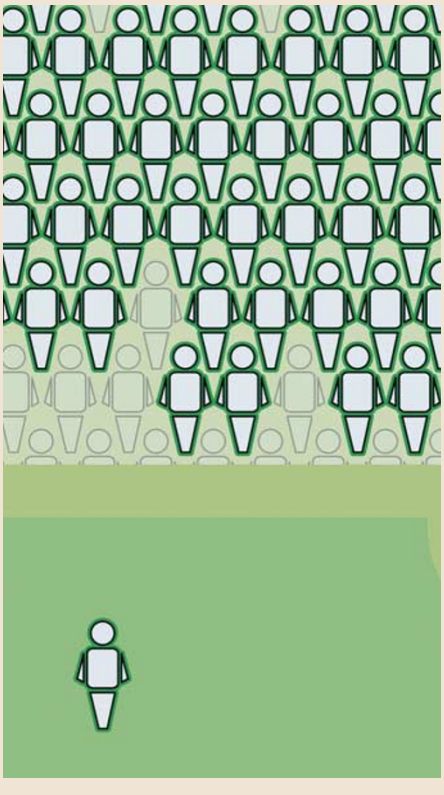

TUMORIGENESIS

Divining forks for developing tumours

In the past 20 years, there has been little progress in identifying improved chemotherapy regimens for children with metastatic rhabdomyosarcoma. Of the two subtypes, alveolar tumours have a worse prognosis than embryonal tumours. Much of the cell and molecular biology of alveolar rhabdomyosarcoma is unknown, apart from the presence of the paired box gene 3 (*PAX3*):forkhead (*FKHR*) t(2;13) translocation in most tumours. So Keller, Capecchi and colleagues have generated a new alveolar rhabdomyosarcoma mouse model to further investigate this rare tumour of skeletal muscle, and they present their results in two papers published in *Genes and Development*.

Keller and co-workers have knocked in a version of the *Pax3:Fkhr* fusion gene — believed to result in a gain-of-function mutation affecting muscle development — and at the same time generated the corresponding inactivation of one allele of *Pax3* and one allele of *Fkhr*, carefully re-creating the genetic situation in the human disease. Importantly, the authors have targeted this mutation to be expressed only in terminally differentiating skeletal muscle. Their paper addressing *Pax3:Fkhr* expression in early development shows, through extensive use of different conditional mouse models, that the *Pax3:Fkhr* mutation in early precursor, embryonal and postnatal muscle stem cells seems unlikely to give rise to tumours, because of the presence of significant muscle defects during embryogenesis and the complete absence of tumour development in mice expressing *Pax3:Fkhr* in postnatal muscle stem cells.

The authors followed the development and growth of 228 *Pax3:Fkhr* mice over 29 months and only one animal developed a rhabdomyosarcoma during this time. So, to investigate what might increase the tumour incidence, the authors first examined if loss of the functional allele of *Fkhr* enhanced the tumorigenic process (as loss of *Pax3* is known not to predispose to tumour formation), but no increase in tumour incidence was seen. Human alveolar rhabdomyosarcomas often have mutations in *TP53* or *CDKN2A* (which encodes INK4A and ARF), so *Pax3:Fkhr* mice were crossed with mice that had muscle-specific loss of one allele of either gene. Again, no increase in tumour incidence was seen, so the authors started to breed homozygotes for each gene. Their results show that rhabdomyosarcomas arise more frequently in these animals only in the absence of functional p53 pathways and mostly require *Pax3:Fkhr* homozygosity. Importantly, these mouse alveolar rhabdomyosarcomas were largely immuno-histologically similar to those found in humans.

The finding that rhabdomyosarcomas in mice most often arise from *Pax3:Fkhr* homozygotes and not heterozygotes differs from the human disease and might reflect that either the *Pax3:Fkhr* fusion gene is not completely identical to that occurring in humans, or might simply be a species-specific difference. However, these results do explain one of the controversies surrounding rhabdomyosarcoma development: that these tumours most likely arise from terminally differentiating skeletal muscle cells that seem to re-express early myogenic markers, and not from early muscle stem cells. Further characterization of this mouse model will hopefully provide novel molecular targets for the effective treatment of childhood alveolar rhabdomyosarcoma.

Nicola McCarthy

References and links

ORIGINAL RESEARCH PAPERS Keller, C. *et al.* Alveolar rhabdomyosarcomas in conditional *Pax3:Fkhr* mice: cooperativity of Ink4a/Arf and Trp53 loss of function. *Genes Dev*. 15 Oct 2004 (doi:10.1101/gad.1244004) | Keller, C. *et al. Pax3:Fkhr* interferes with embryonic *Pax3* and *Pax7* function: implications for alveolar rhabdomyosarcoma cell of origin. *Genes Dev*. 1 Nov 2004 (doi:10.1101/gad.1243904)