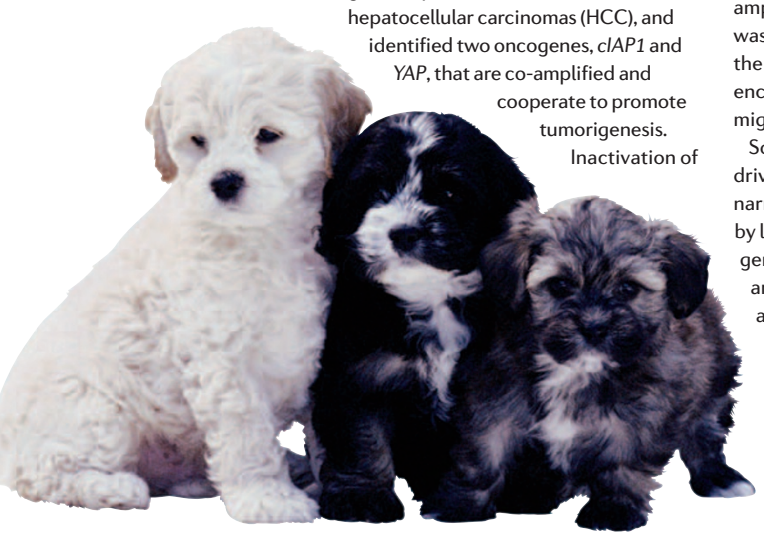
ONCOGENOMICS

Cross-species comparisons



Spontaneously arising human tumours are heterogeneous and often show genomic instability, which makes it difficult to distinguish cancer-causing from bystander mutations. Scott Lowe and colleagues used an integrative oncogenomic approach, comparing gene amplifications in mouse and human hepatocellular carcinomas (HCC), and identified two oncogenes, *cIAP1* and *YAP*, that are co-amplified and cooperate to promote tumorigenesis. Inactivation of p53 and activation of MYC are two important events in HCC. The authors developed a new model of HCC tumorigenesis by isolating liver progenitor cells from *Trp53*$^{-/-}$ mice, expressing *Myc* by retroviral transduction and then transplanting the *Trp53*$^{-/-}$*/Myc* cells into recipient mice, which led to liver tumour formation. They then conducted genome-wide scanning of the resultant tumours and human HCC samples using an approach called representational oligonucleotide microarray analysis (ROMA), which identifies gene amplifications at high resolution. ROMA identified an amplification in human HCCs that was syntenic to a region amplified in the murine *Trp53*$^{-/-}$*/Myc* HCCs. Both encoded many overlapping genes that might have a role in HCC development.

So, which gene on this amplicon is driving tumorigenesis? The authors narrowed down the list of candidates by looking at the expression of each gene that was present on both amplicons, and found that *cIAP1* and *YAP* mRNA and protein were consistently increased in mouse and human HCCs. They then used their mouse model to evaluate the roles of these two genes in liver tumorigenesis. The expression of cIAP1 or YAP in the *Trp53*$^{-/-}$*/Myc* progenitor cells accelerated tumour onset and progression and increased the tumour burden, whereas reducing the expression of cIAP1 or YAP using short hairpin RNAs partially inhibited tumorigenesis. Furthermore, expression of cIAP1 and YAP together synergistically increased tumour growth.

cIAP1 is an inhibitor of apoptosis (IAP) protein, but the role of IAP proteins in tumorigenesis is controversial. YAP is a transcriptional co-activator that has been shown to promote apoptosis, which is inconsistent with an oncogenic role. However, its *Drosophila* homologue, Yorkie, functions in the Hippo–Salvador–Warts pathway to control tissue expansion through the transcription of *cyclin E* and the *Drosophila Iap2* gene, which has functional similarities to *cIAP1*. In addition to identifying the importance of the Hippo pathway in HCC and perhaps other cancers, the work by Lowe and colleagues has provided a new mouse model of HCC and highlighted the potential power of integrating data from appropriate mouse models and oncogenomics.

Sarah Seton-Rogers

ORIGINAL RESEARCH PAPER Zender, L. *et al.* Identification and validation of oncogenes in liver cancer using an integrative oncogenomic approach. *Cell* **125**, 1253–1267 (2006)

MICROENVIRONMENT

Down to a T

Loss of SMAD4 in T cells in the microenvironment is sufficient for the formation of gastrointestinal carcinomas. Letterio and colleagues show that mice that lack SMAD4 in T cells develop carcinomas, whereas those that lack SMAD4 in epithelial cells do not.

SMAD4 is a mediator of transforming growth factor-β signalling and is mutated in about half of patients with familial juvenile polyposis (FJP), a syndrome with a high frequency of gastrointestinal carcinomas. The gastric and intestinal mucosae of these patients are invariably infiltrated with inflammatory cells, which led the authors to suggest that a loss of SMAD4 signalling in the T-cell lineage is responsible for the carcinomas. To test this they created four mouse models, two of which had *Smad4* mutated only in the T cells, and two of which had it mutated only in the epithelial cells. Only in the T-cell models did carcinomas occur, and these models were close phenocopies of human FJP.

These results pose many questions about the mechanism of tumorigenesis. In patients with FJP, loss of heterozygosity (LOH) of *SMAD4* is observed in epithelial cells and has not been seen in lymphocytes. However, this does not preclude a role for LOH in T cells and other lineages. The authors also showed that in mice with T-cell disruption of SMAD4, those T cells produced more cytokines such as interleukin 4 (IL4), IL5, IL6 and IL13, which are known to promote proliferation.

To fully understand the significance of these data, further experiments are needed that combine the T-cell SMAD4 defect with defects in epithelial cells. However, they clearly illustrate the potential importance of the microenvironment in tumorigenesis.

Patrick Goymer

ORIGINAL RESEARCH PAPER Kim, B.-G. *et al.* Smad4 signalling in T cells is required for suppression of gastrointestinal cancer. *Nature* **441**, 1015–1019 (2006)
FURTHER READING Siegel, P. M. & Massague, J. Cytostatic and apoptotic actions of TGF-β in homeostasis and cancer. *Nature Rev. Cancer* **3**, 807–820 (2003)