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GENOMICS

Distinguishing drivers from passengers

Cancer cells are genetically diverse and contain a range of mutations, including both drivers that actively promote tumorigenesis and passengers that may not confer a selective advantage to a growing tumour, but are nonetheless commonly found. This poses the problem of how to identify the bona fide oncogenes or tumour suppressors in cancer genetic screens. Furthermore, the identification of loss-of-function mutations that contribute to cancer formation has been particularly challenging, especially in the case of finding new tumour suppressor genes. A recent study tackles these problems by elegantly integrating cancer genomics and RNA interference (RNAi) in an *in vivo* mouse model of liver cancer.

Scott Lowe and colleagues previously created a mosaic mouse model of hepatocellular carcinoma (HCC) by introducing genetic mutations into cultured embryonic liver progenitor cells and retransplanting the modified cells into the livers of recipient mice. This allowed them to create HCCs with different oncogenic lesions and thus monitor the contribution of different mutations to tumorigenesis.

Now, the authors describe a new approach that screens this mouse model using an RNAi library that is targeted against putative tumour suppressor genes identified from regions that are commonly deleted in human HCC. Importantly, this method enables rapid and large-scale screening of potential tumour suppressor genes because pools of short hairpin RNAs (shRNAs) that are targeted against many genes can be introduced into liver cells and can successfully knock down a multitude of genes.

The approach was validated by the identification of *Pten*, which is a well-known tumour suppressor gene that is mutated in many kinds of cancer, including HCC. The authors also identified and validated 12 genes that had not been previously linked to cancer. The new candidate genes are associated with a range of cellular activities, and include *Dxd20* (which encodes an RNA helicase), *Gjd4* (which encodes a putative gap junction protein) and the top-scoring gene *Xpo4* (which encodes a nuclear export protein, exportin 4). One known substrate of exportin 4 is SMAD3. SMAD3 modulates the transforming growth factor-β pathway, which plays an important part in tumour progression.

This method could be used to screen other types of cancer, and the shRNA pools could be expanded to target point mutations, large deletions or methylated promoter regions that are associated with cancer, as well as the focal deletions that were targeted in this study. In addition, on the basis of this approach, the libraries of full-length cDNAs that are currently being developed could be used to perform parallel screens to identify and validate potential oncogenes.

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ORIGINAL RESEARCH PAPER Zender, L. *et al.* An oncogenomics-based *in vivo* RNAi screen identifies tumor suppressors in liver cancer. *Cell* 13 Nov 2008 (doi: 10.1016/j.cell.2008.09.061)