convey growth signals from the cell surface to the nucleus, and their overexpression or aberrant activation is an important cause of cancer. Although activating mutations of RAS are frequent in human cancers, many tumours still retain wild-type copies of the gene, prompting Agami and colleagues to look for genes for which inhibition activates RAS.

They identified the homeodomain gene paired-like homeodomain transcription factor 1 (*PITX1*), which is frequently downregulated in bladder and prostate tumours. Although it is not yet known whether *PITX1* is mutated or deleted in human cancers, the authors present some intriguing evidence that loss of PITX1 can lead to RAS activation and a transformed phenotype. They found that PITX1 transcriptionally activates *RASAL1*, a RAS-GAP gene that belongs to a family of genes that suppress RAS activity.

Although *REST* and *PITX1* are exciting candidates, further studies will be needed before their roles in cancer can be confirmed. However, these studies show how powerful screens using RNAi libraries can be for identifying potential tumour-suppressor genes.

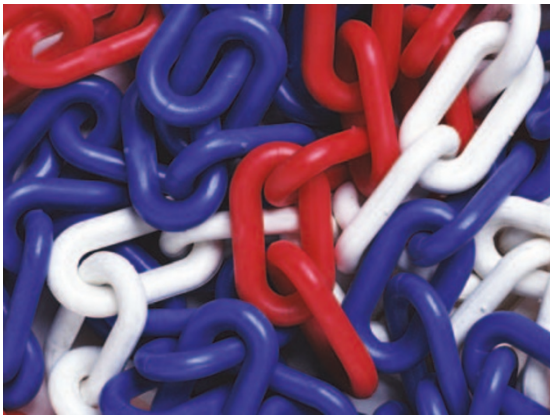
Jenny Bangham

References and links

ORIGINAL RESEARCH PAPERS Westbrook, T. F. *et al*. A genetic screen for candidate tumor suppressors identifies *REST*. *Cell* **121**, 837–848 (2005) | Kolfschoten, I. G. M. *et al*. A genetic screen identifies PITX1 as a suppressor of RAS activity and tumorigenicity. *Cell* **121**, 849–858 (2005)

CHROMATIN DYNAMICS

Repressive links



The regulation of gene transcription relies on the concerted efforts of several proteins, including those that modify the structure of the chromatin. Jan-Herman Dannenberg, Gregory David, Ron DePinho and colleagues looked at the transcriptional networks regulated by the co-repressor mSIN3A in both normal and neoplastic cells using combined genetic, biochemical and computational approaches.

mSIN3A interacts with histone deacetylases (HDACs) and numerous transcription factors to regulate diverse signalling pathways and biological processes. To further investigate the function of this protein, Dannenberg and co-authors engineered mice that harboured a conditional *mSin3A*-knockout allele with embedded Lox-P sites ($mSin3A^{L}$) that delete the gene *in vivo* on crossing to mice expressing Cre recombinase, or *in vitro* on exposure to Cre-encoding retroviruses.

mSin3A-null mice are embryonic lethal, indicating a crucial function for mSIN3A in normal development. As early lethality hampered in-depth dissection of mSIN3A function, additional studies were conducted in $mSin3A^{L/L}$ mouse embryonic fibroblasts (MEFs) that were depleted of mSIN3A following exposure to the Cre-encoding retrovirus. Loss of mSIN3A initiates unscheduled DNA synthesis, triggering an S-phase checkpoint that results in profound growth arrest at G2/M and increased apoptosis — data that might explain the lethal phenotype observed in the null embryos.

As mSIN3A–HDAC has been implicated in regulatory modifications of the p53 tumour-suppressor protein, the investigators assessed the impact of combined deletion of mSIN3A and p53 on these cellular phenotypes. Working with MEFs as well as lymphomas and sarcomas derived from $Trp53^{-/-}$ mice carrying conditional *mSin3A* alleles, loss of p53 was shown to not be enough to overcome mSIN3A-mediated growth arrest or apoptosis. The authors also showed that loss of both p53 and RB tumour suppressors failed to alter the lethal outcome.

So what genes trigger the growth arrest in mSIN3A-deficient cells? To address this question, Dannenberg and colleagues conducted a time course to map the changes in gene expression after mSIN3A deletion. They showed that genes involved in numerous crucial processes were altered, including DNA replication, cell-cycle regulation, apoptosis and mitochondrial metabolism. Computational analysis of the mSIN3A transcriptome, using a knowledge-based database, identified several well-known genes as nodal points, including the *Myc–Mad, E2f* and *Trp53* transcriptional networks.

Loss of mSIN3A expression also changed the expression of many components of the mSIN3A–HDAC complex, consistent with the ability of mSIN3A to regulate its own transcription and that of other members of this complex. In addition, mSIN3A showed novel links to DNA-repair and peroxisome-proliferator-activated-receptor networks. These findings were verified using *in silico* promoter analyses and complemented by chromatin-immunoprecipitation assays that also revealed links to the signal transducer and activator of transcription (STAT) network, and the nucleosome remodelling factor FALZ. However, the authors additionally note that not all MYC, E2F and p53 target genes are upregulated on loss of mSIN3A, indicating that mSIN3A might only regulate a subset of these targets and/or that mSIN3A regulates these genes depending on the physiological conditions or the tissue type.

This integrated approach has produced novel insights into the diverse functions of mSIN3A and has confirmed the importance of mSIN3A in cancer-related pathways and processes. No doubt this approach will be useful to address the function of other components of multi-protein transcriptional complexes.

Nicola McCarthy

References and links

ORIGINAL RESEARCH PAPER Dannenberg, J. H. *et al*. mSin3A co-repressor regulates diverse transcriptional networks governing normal and neoplastic growth and survival. *Genes Dev*. **19**, 1581–1595 (2005)