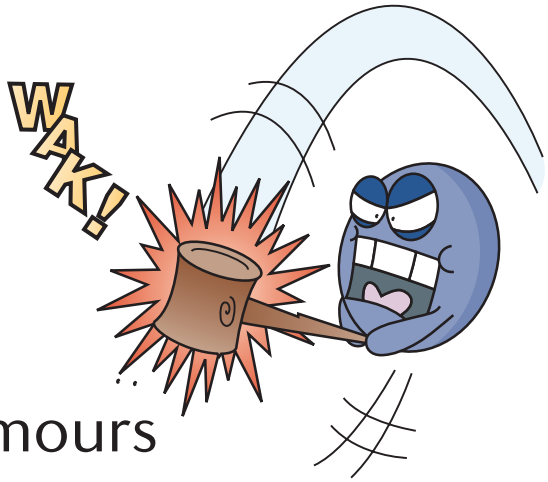

MICRORNA

Let's suppress tumours

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URLs

HMG2A
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=8091

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression by targeting mRNAs, and are often deregulated in tumours. But miRNAs have hundreds of targets, so it is challenging to understand the relevance of a specific miRNA–target interaction to tumorigenesis, especially in mammals, in which it is expected that many interactions need to be disrupted to obtain a tumorigenic phenotype. Now David Bartel and colleagues show that disrupting the miRNA regulation of a single mammalian gene leads to a tumorigenic phenotype.

The authors examined the gene that encodes the high mobility group A2 (HMGA2) protein, which regulates gene expression by altering chromatin structure, and is expressed early during development and in many different cancers. In tumours, *HMGA2* is often the target of chromosomal rearrangements that cause the loss of the C terminus of the protein and the 3′ untranslated region (3′ UTR) of the mRNA. Interestingly, the mouse *Hmga2* 3′ UTR contains seven conserved sites complementary to the *let-7* miRNA, which is expressed late during development, suggesting that *let-7* might control *Hmga2* expression.

The authors showed that the introduction of *let-7* into F9 mouse embryonic carcinoma cells was able to repress HMGA2 expression, whereas inhibiting endogenous *let-7* increased HMGA2 expression in NIH3T3 cells. They then generated mutants of the *Hmga2* 3′ UTR, disrupting two, four or all seven *let-7* complementary sites, and tested them in F9 cells. Strikingly, the level of *Hmga2* downregulation induced by *let-7* co-transfection correlated with the number of intact sites, and repression was restored by the co-transfection of a *let-7* mutant that was able to bind the mutated 3′ UTR.

So, *let-7* is able to directly repress *Hmga2*, but is disrupting this interaction sufficient to transform cells? The stable expression of a vector containing the wild-type *Hmga2* open reading frame but mutated *let-7* sites led to the anchorage-independent growth of NIH3T3 cells. These cells also generated tumours in immunocompromised mice, indicating that *let-7* miRNA functions as a tumour suppressor through the direct repression of an oncogenic gene.

These findings suggest that loss of miRNA-mediated gene regulation is likely to be a common mechanism of tumorigenesis, and should be considered when investigating cancer-associated mutations.

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ORIGINAL RESEARCH PAPER Mayr, C., Hemann, M. T. & Bartel D. P. Disrupting the pairing between *let-7* and *Hmga2* enhances oncogenic transformation. *Science* 22 February 2007 (doi:10.1126/science.1137999)
FURTHER READING Calin, G. & Croce, C. M. MicroRNA signatures in human cancer. *Nature Rev. Cancer* **6**, 857–866 (2006)