

# Micro enhancement

## DOI:

10.1038/nrg2116

## URLs

## Entrez

## DGCR8

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gen&cmd=Retrieve&dopt=full\\_report&list\\_uids=54487](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gen&cmd=Retrieve&dopt=full_report&list_uids=54487)

## Dicer1

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gen&cmd=Retrieve&dopt=full\\_report&list\\_uids=23405](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gen&cmd=Retrieve&dopt=full_report&list_uids=23405)

## Drosha

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gen&cmd=Retrieve&dopt=full\\_report&list\\_uids=29102](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gen&cmd=Retrieve&dopt=full_report&list_uids=29102)

## Kras

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gen&cmd=Retrieve&dopt=full\\_report&list\\_uids=3845](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gen&cmd=Retrieve&dopt=full_report&list_uids=3845)

## Myc

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gen&cmd=Retrieve&dopt=full\\_report&list\\_uids=17869](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gen&cmd=Retrieve&dopt=full_report&list_uids=17869)

MicroRNAs (miRNAs) have been implicated in many biological processes, and a wide range of functions has been attributed to them. For example, individual miRNAs have been ascribed oncogenic function. A new study now shows that global repression of miRNA maturation *in vitro* and *in vivo* promotes cellular transformation and tumorigenesis.

It has previously been shown that levels of mature miRNAs are reduced in cancer cells in comparison with normal tissues. To investigate this further, Kumar *et al.* knocked down *Drosha*, *DGCR8* and *Dicer1* — all known regulators of miRNA processing — in mouse lung adenocarcinoma cells. Although the knockdown was not absolute, it did have striking effects: cells with impaired miRNA processing formed larger colonies and foci *in vitro* — both hallmarks of enhanced transformation, which results from

increased proliferation. Similar results were seen in three independent human cancer cell lines.

Moreover, injecting the knocked-down mouse cells into immunocompromised mice revealed that impaired miRNA processing increased the tumorigenic potential of these cells — although the histology of these tumours was similar to controls, the tumours formed faster and, unlike the controls, invaded the surrounding tissue, consistent with the enhanced cell migration seen in knocked-down cells. Nevertheless, the authors show that impaired miRNA processing alone is not sufficient to transform non-cancerous cells.

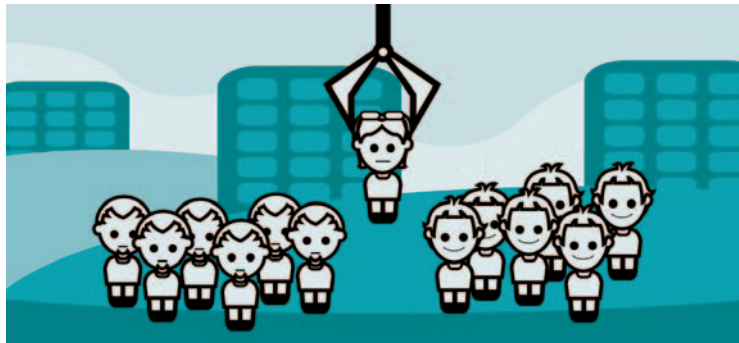
Looking for the basis of the effects they saw in the knocked-down cells, Kumar *et al.* found that protein levels of *MYC* and *KRAS*, but not other oncogenes tested, were significantly elevated. The authors suggest that

miRNAs directly regulate *Myc* expression at the post-transcriptional level. Using a miRNA target prediction programme, Kumar *et al.* found that 3' UTRs of both *Myc* and *Kras* harbour targets of *let-7* family miRNAs; a finding that they subsequently verified experimentally.

Extending their *in vitro* findings to a mouse model, the authors turned to mice that carry a conditional, activatable *Kras* allele, *LSL-Kras<sup>G12D</sup>*, in which non-small-cell lung carcinoma can easily be induced. When these mice are also homozygous or heterozygous for a conditional allele of *Dicer1*, they develop more tumours that are also larger than those in the other litter mates.

Together with other reports that global repression of miRNAs in human cancers is not associated with reduced levels of primary miRNA transcripts, this study implies that miRNA processing machinery is likely to be deregulated in some human cancers. The authors stress that their work does not directly contradict the previously reported oncogenic nature of individual miRNAs.

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**ORIGINAL RESEARCH PAPER** Kumar, M. S. *et al.* Impaired microRNA processing enhances cellular transformation and tumorigenesis. *Nature Genet.* 1 April 2007 (doi:10.1038/ng2003)

**FURTHER READING** Calin, G. A. & Croce, C. M. MicroRNA signatures in human cancers. *Nature Rev. Cancer* 6, 857–866 (2006)