Nature Reviews Cancer | AOP, published online 15 July 2010; doi:10.1038/nrc2898

SMALL RNAS

Pseudogenes act as microRNA decoys

A recent study revises our view of pseudogenes as non-functional relics of evolution by showing that transcripts produced from pseudogenes regulate the effects of microRNAs (miRNAs).

Poliseno, Salmena *et al.* investigated *PTENP1*, a pseudogene of the tumour suppressor gene *PTEN*. They found several binding sites for miRNAs that target *PTEN* in the 3′ UTR of *PTENP1* mRNA.

IMAGE SOURCE

Furthermore, in prostate cancer cells, expression of *PTEN*-targeting miRNAs led to downregulation of both *PTEN* and *PTENP1* mRNAs, confirming that *PTENP1* is subject to miRNA-mediated regulation.

Does miRNA binding by *PTENP1* affect the tumour suppressive activities of PTEN? Overexpression of the *PTENP1* 3′ untranslated region (UTR) led to increased levels of *PTEN* transcripts and protein and to growth inhibition in prostate cancer cells. This derepression of *PTEN* by the *PTENP1* 3′ UTR was abrogated in *DICER*-null colon carcinoma cells, which are defective in miRNA processing. These findings suggest that mature miRNAs are needed for *PTENP1* to regulate PTEN levels.

The authors also identified focal copy number losses at the *PTENP1* locus associated with downregulation of *PTEN* expression in samples from patients with sporadic colon cancer. They suggest that *PTENP1* could be considered a tumour suppressor gene and that there might be selection for loss of *PTENP1* during tumorigenesis.

How widespread is this mechanism of regulating cancer genes? The authors found miRNA-binding sites in pseudogenes of other cancer-related genes. They also demonstrated a similar relationship between the oncogene *KRAS* and its pseudogene *KRAS1P* to that between *PTEN* and *PTENP1*. Because each miRNA has multiple targets and because genes can often have several related pseudogenes, complex networks of regulation may exist. This decoy mechanism may not be limited to pseudogene transcripts, so the next steps will be to investigate whether other gene-coding and non-coding RNAs can act as *trans*-regulators by miRNA binding and how generally this mechanism applies outside of cancer genes. The insights from this study may also help to identify new therapeutic targets in cancer.

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ORIGINAL RESEARCH PAPER Poliseno, L. *et al.* A coding-independent function of gene and pseudogene mRNAs regulates tumour biology. *Nature* **465**, 1033–1038 (2010)