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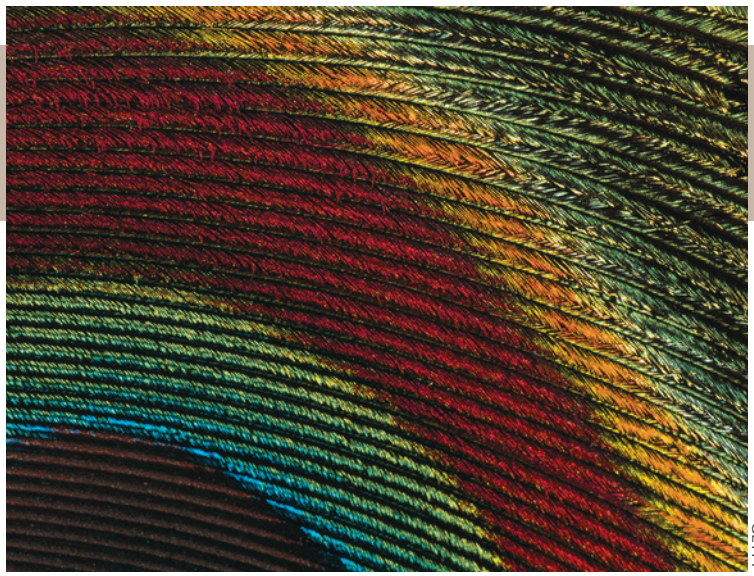
REGULATORY RNA

Layer by layer



GETTY

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Between transcription and translation sits a whole host of regulatory RNAs, chiefly in the guise of microRNAs (miRNAs). Now we can add another regulatory layer: three papers published in *Cell* show that protein-coding and non-coding RNAs influence the interaction of miRNAs with their target RNAs and demonstrate the biological importance of this mechanism in the context of cancer.

Tay *et al.* and Sumazin *et al.* used two different approaches to examine RNA regulatory networks in tumour cells. Tay *et al.* looked at the tumour suppressor *PTEN*, which is known to be regulated by several miRNAs, as well as RNA from the PTEN pseudogene *PTENP1*. Using an integrated computer analysis and an experimental validation process, they identified a set of *PTEN* competing endogenous RNAs (ceRNAs) in prostate cancer and glioblastoma samples. They found that some of these ceRNAs are regulated by the same set of miRNAs that regulate *PTEN* and have similar expression profiles to *PTEN*. For example, knockdown of the ceRNAs VAMP-associated protein A (*VAPA*) or CCR4–NOT transcription complex, subunit 6-like (*CNOT6L*) using small-interfering RNAs (siRNAs) resulted in reduced levels of PTEN. Conversely, expression of 3′UTRs from ceRNAs resulted in increased levels of luciferase protein expressed from a luciferase gene coupled to the PTEN 3′UTR. Importantly, the link between *PTEN*, *VAPA* and *CNOT6L* was lost in cells that had defective miRNA processing, indicating that this regulatory network works by affecting the abundance of miRNAs that are able to bind a specific set of mRNAs.

Sumazin *et al.* investigated the mRNA and miRNA network in glioblastoma cells using data from the Cancer Genome Atlas and a new multivariate analysis method called Hermes. They found a surprisingly large post-translational regulatory network, involving some 7,000 RNAs that can function as miRNA sponges (approximately 248,000 pairwise interactions) and 148 genes that affect miRNA–RNA interactions through mechanisms other than direct sequestration of specific miRNAs. The authors confirmed sponge and 'non-sponge' interactions in the extensive network of RNAs that are linked to *PTEN*. In addition, they presented evidence that deletions of genes in this network can explain the substantial variation in PTEN levels seen in glioblastomas that are wild-type or heterozygous for *PTEN*.

Karreth *et al.* also validated the importance of ceRNA regulation in tumour development. Using the *Sleeping Beauty* transposon system in a mouse model of melanoma, these authors showed that some of the genes that are affected by transposon integration and that accelerate melanoma development are *PTEN* ceRNAs, which include *CNOT6L*. They further characterized one of these genes, zinc finger E-box binding homeobox 2 (*ZEB2*), and demonstrated that *ZEB2* functions as an miRNA sponge for *PTEN* and vice versa.

These results indicate that reduced expression of a specific set of mRNAs can affect other RNAs that form part of an miRNA–RNA network. Moreover, they hint at the subtlety of changes that could be occurring during tumorigenesis, in which a small reduction in the expression level of a few mRNAs could have wide-ranging effects.

Nicola McCarthy, Chief Editor,
Nature Reviews Cancer

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ORIGINAL RESEARCH PAPERS Tay, Y. *et al.* Coding-independent regulation of the tumour suppressor PTEN by competing endogenous mRNAs. *Cell* **147**, 344–357 (2011) | Sumazin, P. *et al.* An extensive microRNA mediated network of RNA–RNA interactions regulates established oncogenic pathways in glioblastoma. *Cell* **147**, 370–381 (2011) | Karreth, F. *et al. In vivo* identification of tumour-suppressive PTEN ceRNAs in an oncogenic BRAF-induced mouse model of melanoma. *Cell* **147**, 382–395 (2011)

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