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RNA

A new layer of regulation

Recently, Pandolfi and colleagues postulated that RNAs can communicate with each other by competing for binding to microRNAs (miRNAs), thereby regulating each other's expression. Four papers now provide support for this competing endogenous RNA (ceRNA) hypothesis and reveal roles for this type of regulation in development and cancer.

Three of the studies focused on the tumour suppressor phosphatase and tensin homologue (PTEN), the expression of which is altered in many human cancers, and examined how it might be regulated by ceRNAs. Using a range of approaches, the authors identified RNAs that may be interacting with *PTEN* RNA, some of which were co-expressed with *PTEN* in cells from patients with prostate cancer (Tay *et al.*), glioblastoma (Sumazin *et al.*) or melanoma (Karreth *et al.*). Interestingly, in all three studies, a subset of these transcripts positively modulated the expression of *PTEN* RNA, as their knockdown was accompanied by a significant reduction in *PTEN* RNA levels. This regulation was reciprocal, with depletion of *PTEN* RNA leading to a decrease in the levels of the studied transcripts.

> "a whole new level of regulation in gene expression"

Up the Resolution

The ceRNA hypothesis postulates that interactions between RNAs are mediated by competitive binding of these RNAs to miRNAs — this was in fact one of the principles used by Sumazin *et al.* to identify candidate miRNA-mediated interactions, including more than 500 *PTEN*-regulating RNAs. Consistently, Tay *et al.* and Karreth *et al.* showed that, in the absence of miRNAs, depletion of ceRNAs does not affect the expression of *PTEN* RNA, indicating that the RNA–RNA interaction is miRNA dependent.

So what is the physiological role of the *PTEN* RNA–ceRNA interaction? All three studies show that, by binding miRNAs that normally inhibit *PTEN*, ceRNAs enhance *PTEN* expression and thereby have tumour-suppressive properties. This may be caused, at least in part, by the increased availability of PTEN to inhibit the oncogenic phosphoinositide 3-kinase pathway, its canonical target, as shown by Tay *et al.* and Karreth *et al.*

But it is not just coding transcripts that can act as ceRNAs — Cesana *et al.* describe a similar interaction between a long non-coding RNA (lncRNA) and coding transcripts in the context of muscle development. The authors identified a lncRNA within the genomic region encoding miRNAs that are known to regulate myoblast differentiation. This lncRNA, which they termed linc-MD1, was muscle specific and was induced upon myoblast differentiation. Furthermore, Cesana *et al.* found that linc-MD1 interacted with miR-133 and miR-135, two miRNAs with roles in muscle physiology. Interestingly, miR-133 and miR-135 were also found to bind to, and regulate the expression of, two proteins involved in myoblast differentiation, myocyte-specific enhancer factor 2C (MEF2C) and Mastermind-like 1 (MAML1). Importantly, the levels of MEF2C and MAML1 increased in the presence of linc-MD1 and decreased following its depletion. Together, these findings indicate that linc-MD1 acts as a ceRNA by binding miR-133 and miR-135 and preventing them from binding to, and blocking the expression of, MAML1 and MEF2C.

These four studies show that RNAs compete for binding to miRNAs and can thereby regulate each other's expression. This reveals a whole new level of regulation in gene expression, controlled by an extensive interacting network of both coding and non-coding RNAs, which will have implications beyond the examples discussed above. Further work is now required to start unravelling this complex network and understanding its involvement in both normal and pathological conditions.

Rachel David

ORIGINAL RESEARCH PAPERS Tay, Y. *et al.* Coding-independent regulation of the tumor 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. A. *et al.* *In vivo* identification of tumor-suppressive PTEN ceRNAs in an oncogenic BRAF-induced mouse model of melanoma. *Cell* **147**, 382–395 (2011) | Cesana, M. *et al.* A long noncoding RNA controls muscle differentiation by functioning as a competing endogenous RNA. *Cell* **147**, 358–369 (2011)
FURTHER READING Salmena, L. *et al.* A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? *Cell* **146**, 353–358 (2011) | Poliseno, L. *et al.* A coding-independent function of gene and pseudogene mRNAs regulates tumour biology. *Nature* **465**, 1033–1038 (2010)