Cell

ceRNAs: miRNA Target Mimic Mimics

In a recent issue of *Cell*, four papers described regulatory interactions among messenger RNAs (mRNAs) that share target sequences for the same microRNAs (miRNAs) (Cesana et al., 2011; Karreth et al., 2011; Sumazin et al., 2011; Tay et al., 2011). The authors state that these mRNAs, dubbed "competing endogenous RNAs (ceRNAs)," define a new layer of regulation of miRNA activity that has only recently been discovered. It may be new for animals and humans, but the principle of this phenomenon had been identified a while ago in plants, where it is known as "target mimicry."

Plant biologists not only played a central role in defining the function of small RNAs in gene silencing, but they also made important contributions to our understanding of miRNA action. In both plants and animals, miRNAs negatively affect their targets through a variety of transcriptional and posttranscriptional mechanisms. In addition, the biogenesis and activity of miRNAs themselves can be regulated at several levels. One of these is through target mimicry. In 2007, we reported that the *IPS1* (*INDUCED BY PHOSPHATE STARVATION1*) RNA altered the protein levels of *PHO2* (*PHOSPHATE2*) by modulating the effects of miR399 on the stability and translation of *PHO2* mRNA (Franco-Zorrilla et al., 2007). The RNAs of both *IPS1* and *PHO2* have highly conserved sequence motifs complementary to miR399, with *IPS1* having additional bases that interrupt the position where miR399 would normally guide cleavage of its target.

A series of experiments supported a model in which noncleavable *IPS1* sequesters miR399 and thus prevents it from inhibiting *PHO2* mRNA accumulation and translation. We coined the term "target mimicry" for this endogenous regulatory mechanism of miRNA activity. Although *IPS1* encodes a noncoding RNA, these early findings already pointed to the possibility that noncleavable target sites in plants could perhaps not only act in *trans*, but also in *cis*, as found to be the case in animals. We subsequently confirmed that artificial target mimic sites in plants could indeed reduce translation efficiency in *cis* (Todesco et al., 2010).

A few weeks after natural and artificial target mimics had been described for plants (Franco-Zorrilla et al., 2007), artificial target mimics were introduced as "decoy targets" for miRNAs in animals (Ebert et al., 2007). Subsequently, a theoretical paper suggested that many natural miRNA target sites could act as miRNA decoys or target mimics in animals. In such a scenario, changes in the expression of some miRNA targets (or mimics) would alter the ability of a miRNA to reduce the activity of other targets (Seitz, 2009).

Last year, Pandolfi and colleagues reported an exciting discovery of a naturally occurring noncoding RNA produced by a pseudogene that acts as a natural target mimic in human tumors (Poliseno et al., 2010). A recent Essay in *Cell* (Salmena et al., 2011) summarized the conclusions from this and some of the prior work, including our initial discovery of "target mimics" (Franco-Zorrilla et al., 2007) and the theoretical prediction by Seitz (2009). The Essay formally enumerated the many ways in which noncoding and coding RNAs with similar miRNA target sites could affect each others' activity. The authors renamed such RNAs with shared and competing target sites as ceRNAs. They also stated that their theory "challenged the notion that a protein-coding mRNA must be translated into a protein to exert function," although there has been ample prior evidence for noncoding functions of protein-coding mRNAs in animals and plants. Such examples include mRNAs that produce small RNAs because they form natural antisense transcripts or are routed through the *trans*-acting siRNA pathway.

In the September 30, 2011 issue *Cell*, three groups described new ceRNAs in animal and human cells (Cesana et al., 2011; Karreth et al., 2011; Sumazin et al., 2011; Tay et al., 2011). The new work goes substantially beyond what was known before and is the kind of research that one is pleased to read about in the pages of *Cell*. However, the impact of these papers would not have been lessened if they had acknowledged that the path for these findings was paved in plants. In our opinion, at the core of these articles is the target mimicry principle, which endows nondegradable miRNA targets with regulatory potential.

Please give credit where credit is due. Plant biologists would rightfully be ridiculed if they claimed to have made new discoveries while equivalent phenomena were already known from animals or fungi. Given that the value of the world's agriculture is more than three times that of the entire pharmaceutical industry and that many more people die each year of hunger and malnutrition than from cancer, it is time that scientists of all stripes paid more attention to plant biology.

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