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# RNA snippets control protein production by disabling mRNAs

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Short pieces of RNA, called microRNAs, control protein production by causing the proteins' RNA templates (known as messenger RNA or mRNA) to be disabled by the cell, according to Whitehead Institute scientists.

Researchers have known that mammalian microRNAs control protein production by causing the mRNAs to degrade but they have wondered how much additional effects microRNAs impart by jamming the process that translates mRNAs into proteins.

For Whitehead Institute Member David Bartel, his lab's genome-wide research helps answer this question and will serve as a foundation for future research.

"These results reveal the ultimate outcome of microRNA regulation of many genes and provide a framework for us to think about how microRNAs are acting," says Bartel. "Also, we're more confident that you can learn which genes are regulated by a microRNA simply by looking at the mRNA levels, which is much easier to do than looking at protein levels."

This is the first time regulation of so many natural targets of microRNAs has been studied in such exacting detail. The Bartel lab's results are published this week in *Nature*.

A cell uses each microRNA to dampen the protein production of

hundreds of target mRNAs, thereby fine-tuning the cell's protein output. To create a protein, a cell uses an RNA template that is copied from a gene. A cellular machine called a ribosome then translates this mRNA template into a chain of amino acids to form the protein. Until now, researchers were unsure where in this process microRNAs act—through elimination of mRNA targets or through interference with mRNA-to-amino acid translation without much change in the mRNA.

To date, some researchers have relied mostly on highly sensitive mRNA assays to study the effects of microRNAs. Because these assays measure only mRNA levels and not protein levels, researchers worried that any microRNA activity that reduced translation without reducing the mRNA would be missed, potentially skewing results.

To determine microRNAs' effects on translation and mRNA levels, Huili Guo, a graduate student in the Bartel lab, performed genome-wide ribosome profiling of human and mouse cells. This test provides a snapshot of whether or not ribosomes are sitting on the mRNA templates. The presence of ribosomes on the mRNA indicates that the mRNA is being translated.

Guo then measured the levels of mRNAs in the cell. By accounting for the change in the amount of targeted mRNAs, she could derive the microRNAs' effects at the translation level.

If microRNAs only disrupt translation, then targeted mRNA levels should be similar to those seen in controls. Also, the ribosome profile should show far fewer ribosomes on the targeted mRNAs as a result of interrupted translation. However, Guo found that the levels of the targeted mRNAs all decreased. Although the ribosome profiling indicated that translation was also slightly reduced on these mRNAs, the overall reduction in protein production was primarily due to the more greatly reduced mRNA levels.

To extend her results, Guo says other cells should be tested.

"I looked at cells that were growing under normal conditions," says Guo. "But microRNAs have been linked to stress responses in some cells, so cells may act differently under those and other conditions."

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