MIT reports new twist in microRNA biology

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MIT scientists have found a new way that DNA can carry out its work that is about as surprising as discovering that a mold used to cast a metal tool can also serve as a tool itself, with two complementary shapes each showing distinct functional roles.

Professor Manolis Kellis and postdoctoral research fellow Alexander Stark report in the January 1 issue of the journal *Genes & Development* that in certain DNA sequences, both strands of a DNA segment can perform useful functions, each encoding a distinct molecule that helps control cell functions.

DNA works by complementarity: paired DNA strands serve as a template for each other during DNA replication, and ordinarily only a single DNA strand serves as a template to produce RNA strands, which then go on to produce proteins. The process is similar to the way each bump or dent in a mold is paired with a corresponding dent or bump in the resulting molded object.

While many RNAs are eventually translated into proteins with specific functions, some RNA molecules instead act directly, carrying out roles inside the cell. Certain RNA genes, known as microRNAs, have been shown to play important regulatory roles in the cell, often coordinating important events during the development of the embryo. These microRNAs fold into relatively simple hairpin structures, with two stretches of near-perfect complementary sequence folding back onto each other. One of the two 'arms' of a hairpin is then processed into a mature microRNA.

The surprising discovery is that for some microRNA genes, both DNA strands, instead of just one, encode RNA, and both resulting microRNAs fold into hairpins that are processed into mature microRNAs. In other words, both the tool and its mold appear to be functional. Kellis and Stark found two such microRNA pairs in the fruit fly, and eight more such pairs in the mouse.

The idea that there could be such dual-function strands, where both DNA strands encode functional RNA products, "had never even been hypothesized," Kellis says. But followup work confirmed that they did indeed function in this way. The work suggests that other such unexpected pairings, with both DNA strands encoding important functions, may also exist in a variety of species.

This discovery builds on a similar, earlier surprising finding about microRNA regulation. In December, Stark and Kellis reported that both arms of a single microRNA hairpin can also produce distinct, functional microRNAs, with distinct targets. Together, these two findings suggest that a single gene can encode as many as four different functions - one hairpin from each of the two DNA strands, and then one microRNA from each of the two arms of each hairpin.

These recent papers are the latest example of the power of using computational tools to investigate the genomes of multiple species, known as comparative genomics. The Kellis group has used this approach to discover protein-coding genes, RNAs, microRNAs, regulatory motifs, and targets of individual regulators in diverse organisms ranging from yeast and fruit flies to mouse and human.

"This represents a new phase in genomics-making biological discoveries sitting not at the lab bench, but at the computer terminal," Kellis says.

Kellis is the Karl Van Tassel Career Development Assistant Professor in

the Department of Electrical Engineering and Computer Science and an associate member of the Broad Institute. He grew up in Greece and France and earned his B.S., M.Eng., and Ph.D. from MIT, and he was appointed to the faculty here in 2004. At 30, he has already earned numerous awards and accolades, including a place on the list of the 35 top innovators under 35 by Technology Review magazine in 2006.

Source: MIT