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MicroRNAs Can Turn Off Growth of Cancer Cells

Scientists have discovered that the fascinating bits of genetic material known as microRNAs can also shut down the proliferation of cancer cells.

The results of new experiments by Howard Hughes Medical Institute researchers and their colleagues show that microRNAs are part of a network governed by the gene *p53*. This gene, which is mutated in nearly half of all human cancers, also performs critical cellular functions such as regulating the expression of other genes and triggering suicide in damaged cells.

MicroRNAs, which are no more than a couple of dozen nucleotides in length, regulate a broad array of physiological and developmental processes. However, their regulatory roles have remained largely mysterious. Scientists have ascribed functions to only a few of more than 200 known microRNAs. Unlike the larger messenger RNA (mRNA) molecules that code for cellular proteins, microRNAs silence genes by interfering with the messenger RNA that genes use to carry coding information to the protein-making machinery.

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Howard Hughes Medical Institute investigators Gregory J. Hannon, Scott W. Lowe and their colleagues published their discovery on June 6, 2007, in an advance online publication in the journal *Nature*. Lowe and Hannon are at Cold Spring Harbor Laboratory, and other co-authors were from Stony Brook University, Rosetta Inpharmatics and Applied Biosystems.

Researchers had known that microRNA levels decrease in human cancers, but little was known about the significance of that decrease, said Hannon. "In contrast, a great deal was known about p53," he said. "Tens of thousands of

papers had been published on p53, and it is known as the most commonly mutated gene in cancer, with many downstream effects.”

While the regulatory pathways that p53 uses to halt cell growth had been partially mapped, said Hannon, shutting down those pathways did not completely block p53's activity. “The genetics very strongly indicated that there was another arm of the p53 pathway for stopping cell growth that we knew nothing about,” he said.

In their experiments, Hannon, Lowe and their colleagues initially sought to understand how the patterns of activity of microRNAs genes reflected the genetic composition of tumor cells. They used microarrays to compare gene activity in normal and cancerous mouse cells in which they had knocked out p53 activity.

“We saw that microRNA expression profiles really did reflect the genetic background of the tumor cells,” said Hannon. “But most strikingly, we found that the activity of one particular set of microRNA genes reflected the cell's p53 status. This made us think that p53 might regulate these genes.” Those microRNAs belonged to a family called miR-34.

Further studies revealed that p53 directly targets and switches on the genes for the miR-34 microRNAs. The researchers also found that various types of DNA damage and cancer gene activation that switched on p53 also triggered miR-34 genes.

When the researchers switched on the miR-34 genes in cells, they saw an increase in cell suicide, called apoptosis, as well as cell senescence, a kind of “genetic death” in which cells lose the ability to replicate. Further analysis showed that the miR-34 genes regulate a large number of target genes in the cell that are involved in the progression of the cell division cycle, said Hannon.

“There has always been a hole in the p53 pathway, and people have been looking for genes that code for regulatory proteins to fill that hole,” he said. “In fact, that hole may well be filled by microRNAs.”

There are evolutionary hints that the miR-34 genes may have long played a central regulatory role in the p53 pathway, said Hannon. He noted that the equivalent of miR-34 genes have been found, not only in mammals, but in the fruitfly *Drosophila* and the roundworm *C. elegans*.

Hannon said that the discovery of the role of microRNAs in the p53 pathway represents the beginning of efforts to fill in the holes regarding the p53 pathway's functions. “The p53 pathway is exceedingly complicated,” he said. “It has evolved many ways to respond to different types of cellular stresses—whether to trigger apoptosis or senescence. It is possible that certain elements of these different mechanisms will predominate in different

cell types. And, the output of p53 probably depends on integrating lots of different downstream effector signals and also depends on the genetic background.

“This work extends what we knew about the regulatory role of microRNAs,” he said. “It helps us place microRNAs within the context of known biology,” he said. Hannon emphasized that it remains to be seen whether the genes for microRNAs will ever prove to be useful clinical targets in cancer treatment. “We need to do a lot more work to understand the genetic interactions involved, before it will be possible to give an answer.”