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MicroRNAs linked to cancer

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MicroRNAs—the minute noncoding negative regulators of gene expression—could be intimately involved in the development of cancer, according to a trio of papers published in the June 9 *Nature*.

Todd Golub at the Dana-Farber Cancer Institute and the Broad Institute of the Massachusetts Institute of Technology and Harvard and coauthors report that they could accurately classify human cancers with an novel assay that they say could become a powerful diagnostic tool. In a second paper, the groups of Gregory Hannon at Cold Spring Harbor and Scott Hammond at the University of North Carolina describe elevated levels of miRNAs in human lymphoma samples and cell lines. Experimental overexpression of those miRNAs caused cancer in a mouse model.

The highly conserved miRNAs and their link to cancer has been in people's minds for many years, Paul Meltzer at the National Human Genome Research Institute told *The Scientist*. "Previous works have reported changes in miRNA expression associated with cancer, but this new constellation of papers provides very strong support for that idea. Golub's paper provides a very nice database in terms of the pattern of expression of the 217 annotated miRNAs in human cancers," said Meltzer, who wrote an accompanying News and Views commentary.

A third paper by Joshua Mendell at The Johns Hopkins University School of Medicine and colleagues unravels the connection between miRNA and c-Myc, a transcription regulator known to be overexpressed in human cancers. Most importantly, they identify an elusive miRNA target.

To study miRNAs expression, Golub and his colleagues developed a bead-based flow cytometric profiling assay that first amplifies the miRNAs in the cell and then captures them on fluorescently labeled beads. "This method enabled us to measure the expression of a great number of miRNAs from samples including several human cancers," Golub told *The Scientist*. "We found a highly informative pattern of miRNA expression that varied across tumor types and reflected the developmental lineage as well as the differentiation state of the tumors. The patterns of which miRNAs are turned on and off in a cell can be diagnostic for whether that cell is cancerous and what kind of cancer it is."

Golub's work on miRNAs is the most comprehensive analysis to date, according to Leonard Augenlicht at the Albert Einstein College of Medicine and Cancer Center, who was not involved in the study. "It's also the first really convincing evidence that the expression profiles of miRNAs that can tell us something clinically," he told *The Scientist.*

Hammond's and Hannon's teams examined a fragment of human chromosome 13 that is amplified in various tumor types, including B-cell lymphoma. The fragment contains a gene that encodes precursors of seven miRNAs. "The fact that those miRNAs are overexpressed in human tumors and that when we introduce them into mice they develop tumors strongly supports the idea that they are also human oncogenes," Hammond told *The Scientist*.

"There are a lot of genetic abnormalities underlying the development of the cancer, and essentially all have been related to protein-coding genes," said Meltzer. "This evidence is pretty convincing that, in this particular case, the target of the gene amplification is a gene that encodes a miRNA cluster."

Mendell's paper is the most mechanistic of all three, said Meltzer. "The authors make a very exciting observation that the well known oncogene c-Myc can directly regulate several miRNAs, providing another connection between a cancer gene and miRNAs. But they also identify a target of miRNA regulation, the transcription factor E2F1. It's pretty interesting."

There are still many questions for the future, Meltzer said. "Can miRNA be useful for diagnostics and therapeutics? From a more mechanistic point of view, you'd like to map miRNAs and understand what they do in various cancer types, what genes they regulate, and what regulates them," he said. "But the most critical question is, What are their targets and which are the pathways they are involved in?"

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