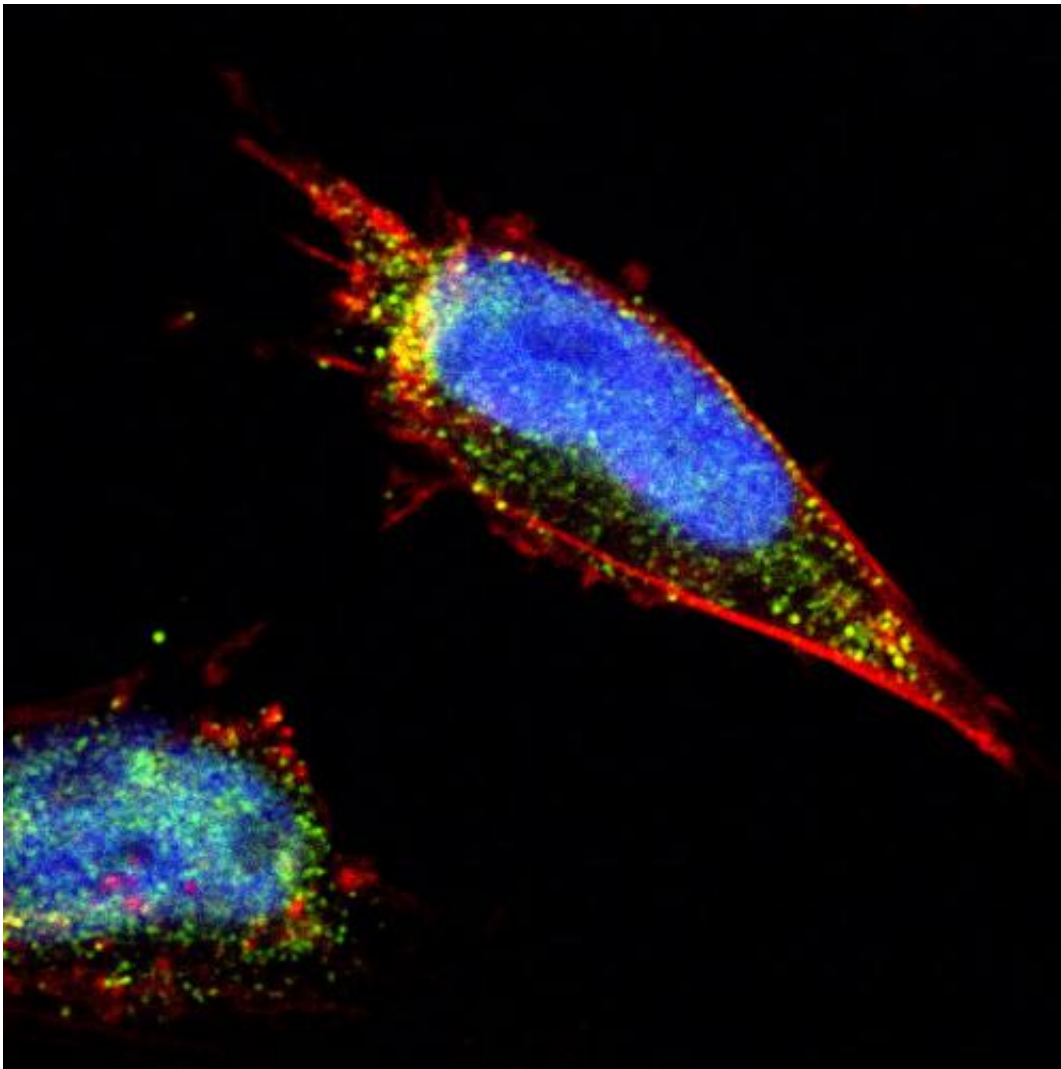


# Chemical tag marks future microRNAs for processing, study shows

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Scientists found the enzyme METTL3 (green) tags a particular sequence within RNA molecules destined to become gene-regulating microRNAs. While this happens within cells' nuclei (blue), METTL3 is also found outside the nucleus in cells' cytoplasm, as shown above. Credit: Laboratory of Systems Cancer Biology

at The Rockefeller University

Just as two DNA strands naturally arrange themselves into a helix, DNA's molecular cousin RNA can form hairpin-like loops. But unlike DNA, which has a single job, RNA can play many parts—including acting as a precursor for small molecules that block the activity of genes. These small RNA molecules must be trimmed from long hairpin-loop structures, raising a question: How do cells know which RNA loops need to be processed this way and which don't?

New research at Rockefeller University, published March 18 in *Nature*, reveals how cells sort out the loops meant to encode small RNAs, known as microRNAs, by tagging them with a chemical group. Because microRNAs help control processes throughout the body, this discovery has wide-ranging implications for development, health and disease, including cancer, the entry point for this research.

"Work in our lab and elsewhere has shown changes in levels of microRNAs in a number of cancers. To better understand how and why this happens, we needed to first answer a more basic question and take a closer look at how cells normally identify and process microRNAs," says study author Sohail Tavazoie, Leon Hess Associate Professor, Senior Attending Physician and head of the Elizabeth and Vincent Meyer Laboratory of Systems Cancer Biology. "Claudio Alarcón, a research associate in my lab, has discovered that cells can increase or decrease microRNAs by using a specific chemical tag."

Long known as the intermediary between DNA and proteins, RNA has turned out to be a versatile molecule. Scientists have discovered a number of RNA molecules, including microRNAs that regulate gene expression. MicroRNAs are encoded into the genome as DNA, then

transcribed into hairpin loop RNA molecules, known as primary microRNAs. These loops are then clipped to generate microRNA precursors.

To figure out how cells know which hairpin loops to start trimming, Alarcón set out to look for modifications cells might make to the RNA molecules that are destined to become microRNAs. Using bioinformatics software, he scanned for unusual patterns in the unprocessed RNA sequences. The sequence GGAC, code for the bases guanine-guanine-adenine-cytosine, stood out because it appeared with surprising frequency in the unprocessed primary microRNAs. GGAC, in turn, led the researchers to an enzyme known as METTL3, which tags the GGAC segments with a chemical marker, a methyl group, at a particular spot on the adenine.

"Once we arrived at METTL3, everything made sense. The methyl in adenosines (m6A tag) is the most common known RNA modification. METTL3 is known to contribute to stabilizing and processing messenger RNA, which is transcribed from DNA, but it is suspected of doing much more," Alarcón says. "Now, we have evidence for a third role: the processing of primary microRNAs."

In series of experiments, the researchers confirmed the importance of methyl tagging, finding high levels of it near all types of unprocessed microRNAs, suggesting it is a generic mark associated with these molecules. When they reduced expression of METTL3, unprocessed primary microRNAs accumulated, indicating that the enzyme's tagging action was important to the process. And, working in cell culture and in biochemical systems, they found primary microRNAs were processed much more efficiently in the presence of the methyl tags than without them.

"Cells can remove these tags, as well as add them, so these experiments

have identified a switch that can be used to ramp up or tamp down microRNA levels, and as a result, alter gene expression," Tavazoie says. "Not only do we see abnormalities in microRNAs in cancer, levels of METTL3 can be altered as well, which suggests this pathway is could govern cancer progression."

Provided by Rockefeller University

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