Home » Latest News » Expanding The RNA Roster

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Molecular Biology

Expanding The RNA Roster

Chemical screen finds new small molecule-RNA conjugates

Celia Henry Arnaud

Many new biological roles for RNA have been discovered in recent years, but discoveries on RNA's chemical diversity have not kept pace with findings on its functional diversity. A team of researchers at Harvard University has now uncovered a new type of small molecule-RNA conjugate—coenzyme A (CoA)-linked RNA—and reports a screening method that offers the possibility of finding many more classes of such RNA structural variations (Proc. Natl. Acad. Sci. USA, DOI: 10.1073/pnas.0900528106).

"The chemical diversity of biological RNA is greater-maybe significantly greater-than is currently understood," says chemistry professor and team leader David R. Liu.

"In the age of genomics, we tend to think that RNAs are made of only the four standard nucleotides," says Ronald R. Breaker, a professor of molecular, cellular, and developmental biology at Yale University. "But a quick glance at transfer RNAs, ribosomal RNAs, or even 5'capped messenger RNAs reminds us how strangely modified some RNAs can become. The work by the Liu lab reveals another collection of RNA modifications and provides the methods to make even more discoveries."



KNOWN CLASSES OF RNA

Standard RNA

BIOLOGICAL ROLE

lifetime extension

Information carrier

(transcription)

The new approach is "unusually broad and not dependent on a particular small-molecule structure, RNA sequence, or class of RNAs," Liu says. First, the researchers isolate RNA from cells and use size-exclusion separation to eliminate molecules smaller than about 2,500 daltons so that all the small molecules they find are bound to RNA. They then cleave small molecules from the RNA. After a second round of size-exclusion separation, they analyze by liquid chromatography-mass spectrometry the small molecules left after discarding the macromolecules.

The mass spectral analysis reveals a number of small molecules associated with RNA. Some of these were previously known, such as the amino acids of aminoacylated tRNAs. But Liu and coworkers also observed some previously unknown conjugates, including CoA- and CoA thioesterlinked RNA. A variety of additional novel small molecule-RNA conjugates uncovered by the work are also being studied by the group.

Liu and coworkers have yet to identify the RNA sequences that are associated with CoA. All they know at this point is that the CoA-linked RNA (or multiple RNAs) contains fewer than 200 nucleotides.

They don't know what biological function—if speculates about a range of possibilities. They longer have a role. If they do have a role, they location. Liu's "wildest guess" is that they mig synthesis.

any—these conjugates have, but Liu could be "evolutionary fossils" that no could help control RNA's lifetime or th participate in some form of templated	3'-Aminoacylated transfer RNA	Protein synthesis
	Base-modified RNA	Unknown
	5'-Capped messenger RNA	RNA stabilization and lifetime exter
	CoA-linked RNA	Unknown

"The fact that some of these modifications carry coenzyme A derivatives is particularly

intriguing," Breaker says. More than a decade ago, Breaker and Gerald F. Joyce of Scripps Research Institute showed that a natural splicing ribozyme could be forced to incorporate coenzymes. "These new findings suggest that modern cells indeed find it useful to covalently link RNA and coenzymes," Breaker notes.

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