EXPANDING THE RNA ROSTER

MOLECULAR BIOLOGY: Chemical screen finds new small molecule-RNA conjugates

ANY 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. Breake, a professor of molecular, cellular, and developmental biology at Yale University. "But a quick glance at transfer RNAs, ribosomal RNAs, or even 5's-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."

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 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 thioester-linked 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 any—these conjugates have, but Liu speculates about a range of possibilities. They could be "evolutionary fossils" that no longer have a role. If they do have a role, they could help control RNA's lifetime or location. Liu's "wildest guess" is that they might participate in some form of templated synthesis.

"The fact that some of these modifications carry coenzyme A derivatives is particularly intriguing," Breake says. More than a decade ago, Breker 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," Breake notes.—CEILIA ARNAUD

PHARMACEUTICALS GSK continues diversification drive with purchase of Stiefel

GlaxoSmithKline has agreed to acquire Stiefel Laboratories, a leading maker of dermatology drugs, for $2.9 billion plus $400 million in debt and a potential $300 million cash payment.

Stiefel, a privately held firm based in Coral Gables, Fla., had sales last year of about $900 million. It mostly sells topical prescription products that treat acne, psoriasis, and other ailments of the skin.

GSK CEO Andrew Witty says the purchase fits with his company's strategy of growth and diversification. GSK already has prescription dermatology drug sales of about $550 million per year. It will combine the two operations into a new business that will operate under the Stiefel name.

GSK is one of several big pharmaceutical makers that are trying to diversify to move away from the boom-and-bust cycle of blockbuster drugs and into more stable businesses, such as generics and drugs for the developing world. In January, for example, the firm spent close to $700 million to buy UCB's drug product line in Africa, the Middle East, Asia, and Latin America.

But stock analysts at Credit Suisse point out that this strategy can come at a price. Dermatology products "tend to be old molecules with limited innovation in formulations," research analyst Luisa Hector wrote in a note to clients. "Historically, the lower level of innovation for dermatology brands means that profitability is lower than normal prescription drugs."

GSK says it can wring out cost savings of up to $240 million per year by combining the two businesses. The British company adds that Stiefel's products will benefit from its global distribution chain.—MICHAEL MCCOY