Center for the Study of Systems Biology

Distinguished Lecture Series in Systems Biology

Martha J. Fedor, Ph.D.

Departments of Chemical Physiology and Molecular Biology
The Skaggs Institute for Chemical Biology
The Scripps Research Institute

"RNA Catalysis: From Folding through Function in Living Cells"

Abstract: Our research aims to generate fundamental insights into catalysis by RNA enzymes and into the pathways through which RNAs form specific functional structures. RNA catalysis remains an intriguing puzzle that has grown in significance since the recent discoveries that the ribosome itself is an RNA enzyme and that human and bacterial mRNAs contain self-cleaving ribozymes. The hairpin ribozyme catalyzes a reversible self-cleavage reaction in which nucleophilic attack of a ribose 2' hydroxyl on an adjacent phosphorus proceeds through a trigonal bipyramidal transition state that leads to the formation of 2',3'-cyclic phosphate and 5' hydroxyl termini. The metal cation independence of activity and the availability of high-resolution active site structures have made the hairpin ribozyme the prototype for nucleobase-mediated catalytic chemistry. A network of stacking and hydrogen bonding interactions align the reactive phosphate in the appropriate orientation for an S_N2-type nucleophilic attack and orient nucleotide base functional groups near the reactive phosphate to facilitate catalytic chemistry. Two active site nucleobases, G8 and A38, adopt orientations reminiscent of the histidine residues that mediate general acid base catalysis in ribonuclease A, a protein enzyme that catalyzes the same phosphodiester cleavage chemistry. However, our biochemical experiments argue against analogous roles for G8 and A38 in hairpin ribozyme catalysis and suggest that these residues contribute to catalysis through positioning and orientation and electrostatic stabilization of the electronegative transition state. Ribozymes are useful model systems for investigations of RNA folding, since self-cleavage reflects the assembly of a precise functional structure. To learn how structure-function principles revealed through in vitro experiments translate to the behavior of RNA in living cells, we devised a way to evaluate RNA assembly in vivo using RNA self-cleavage rates to quantify assembly of functional RNA structures. Results of these studies show that intracellular RNA folding kinetics and equilibria are indistinguishable from RNA folding behavior in vitro, provided that in vitro folding reactions approximate the ionic conditions characteristic of an intracellular environment. These studies contribute basic knowledge of RNA structure and function and provide a framework for developing technical and therapeutic applications involving RNAs as targets and reagents.

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