Diverse Catalytic Strategies of RNA Enzymes: Recurring Themes and New Twists

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Ribozymes are molecules of RNA that act as catalysts, and their discovery in 1982 had profound implications into theories of evolution. In biology, ribozymes play important roles in gene regulation, RNA processing and peptide synthesis. However, the function of many ribozymes have yet to be unveiled, and new ribozymes continue to be discovered. In industry, synthetic ribozymes have been engineered that extend the range of their catalytic domain, and have great promise in the design of new biomedical technology and therapeutics.

From a chemical perspective, it is a fascinating question as to how molecules of RNA, with their limited repertoire of building blocks and chemical functionality, are able to fold into three dimensional structures that are able to convey catalytic capability. A detailed understanding of the mechanisms of RNA catalysis, therefore, provides a foundation from which new ribozyme-based technologies or therapeutics can be designed.

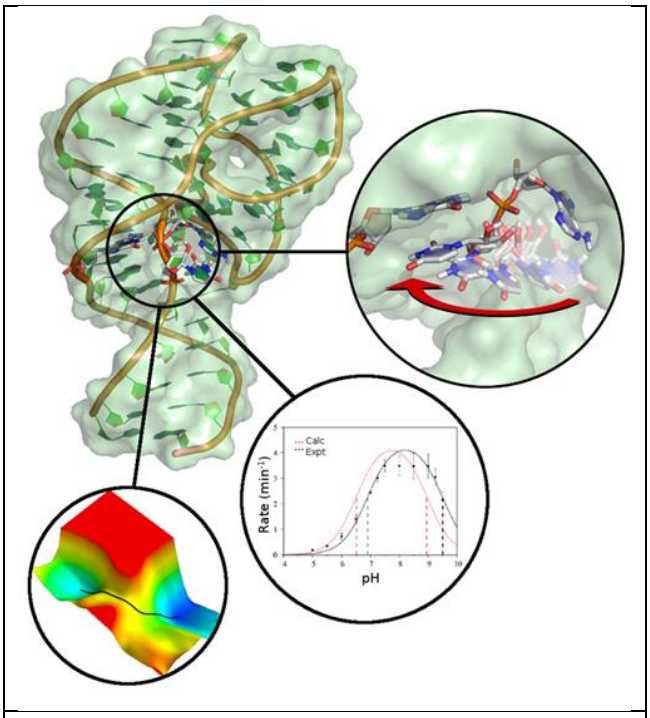

Figure: Mechanism of the twister ribozyme.

Small nucleolytic ribozymes are important model systems in the study of RNA catalysis. Recently, there has been a surge of progress in the identification of new classes of self-cleaving nucleolytic ribozymes that have been revealed by comparative genomics analysis. Following in this wake of this discovery has been intense structural biology efforts to determine crystal structures of these new ribozymes in order to gain insight into the origin of their function. However, crystal structures often are not representative of the active states in solution due to a number of factors, including the inherent conformational heterogeneity exhibited by structured RNAs, combined with artifacts introduced by crystal packing or modifications to inactivate the ribozymes so that they can be crystallized. Further, the inability to directly observe a transition state experimentally inherently eliminates the ability to interpret experimental structural and functional data without recourse into computational modeling.

The present talk will focus on the use of molecular simulation models, including from *ab initio* combined quantum mechanical/molecular mechanical methods, 3D-RISM calculations, and GPU-accelerated free energy methods to study the many facets of RNA catalysis for a series of nucleolytic ribozymes including the hammerhead, HDV, twister, and TS ribozymes. These studies reveal common themes and new twists in the diverse array of catalytic strategies employed by RNA enzymes.