RNA (1997), 3:1083–1084. Cambridge University Press. Printed in the USA.

BOOK REVIEW

Catalytic RNA, edited by Fritz Eckstein and David M.J. Lilley. 1996. *Nucleic Acids and Molecular Biology, Volume 10.* Heidelberg: Springer-Verlag. 418 pp.

As the preface to the *Nucleic Acids and Molecular Biology* series states, reviewing RNA catalysis is a bit like trying to photograph an express train head-on. This volume does an impressive job of capturing the excitement and highlighting important gains made in this rapidly growing field during the past few years. In contrast to previous books in the series, this tenth anniversary issue focuses on RNA catalysts, enabling in-depth coverage of an expanding area. Knowledge of catalytic RNA structures and mechanisms bears on questions of evolution and enzymology, and is also of potential practical importance as ribozymes are increasingly explored as therapeutic agents.

Naturally occurring classes of ribozymes include group I and group II self-splicing introns, the self-cleaving hairpin, hammerhead, Varkud satellite (VS) and hepatitis delta virus ribozymes, and the *trans*-cleaving RNA of Ribonuclease P. The book covers each of these classes in varying degrees of detail, and also contains chapters on new ribozymes derived by in vitro selection, drug interactions with ribozymes, and applications of ribozymes as therapeutics. The chapters are self-contained and can be read in any order, making this collection ideal for casual readers as well as a useful reference for serious RNA researchers.

In the book's opening chapter, Cech and Herschlag describe some of the breakthroughs in understanding both the catalytic mechanism and structural features that define the conserved core of group I introns. The *Tetrahymena* intron takes center stage here because it is the best characterized of its class, but more recent work on related group I ribozymes has extended our knowledge of how these molecules work. The chapter includes some very concise descriptions and tables of kinetic parameters for two different group I introns, and ends with a discussion of protein-assisted splicing. Building on this discussion, the next two chapters describe the dynamics and structural analysis of group I ribozymes. Turner and colleagues provide a clear exposition on the advantages and shortcomings of fluorescence spectroscopy in the study of ribozyme dynamics. Michel and Westhof discuss the phylogenetically derived model of the group I intron active site. This model has been well-supported experimentally, and has become a paradigm for the use of sequence covariation to predict three-dimensional structure in RNA.

Like group I introns, group II introns and the RNA component of Ribonuclease P (RNase P) typically contain hundreds of nucleotides and fold into complex shapes whose details have yet to be determined. Despite the lack of high-resolution structural information for these ribozymes, rapid progress has been made in understanding their catalytic mechanisms and overall organization. Group II introns have been dissected into domains that can be analyzed independently and assembled in *trans* into active complexes. The chapter by Pyle gives a succinct account of the kinetics of this system, which have led to detailed probing of the functional roles of nucleotides around the cleavage sites and within the highly conserved domain 5 hairpin in the intron active site. For RNase P RNA, as for group I introns and ribosomal RNAs, sequence covariation analysis has been extremely useful in defining the secondary structure and identifying potential three-dimensional interactions within the RNA. Nolan and Pace describe the use of comparative sequence analysis together with experimentally derived crosslinking data to derive a three-dimensional model of RNase P RNA that provides a framework for interpreting mechanistic data.

The small size and deceptively simple cleavage mechanism of the hammerhead ribozyme have attracted the attention of numerous laboratories interested both in ribozyme chemistry and in the use of ribozymes as human therapeutics. Nine of the 22 chapters in *Catalytic RNA* are devoted to the hammerhead, covering topics ranging from the crystal structure to the kinetic pathway to the use of modified hammerhead ribozymes to cleave parts of the HIV genome. As the only complete ribozyme whose crystal structure is known, the hammerhead system reveals principles of RNA folding and chemistry that will likely characterize other RNAs. McKay describes the wishbone-shaped structure succinctly, and includes some effective color stereo figures and line drawings. As discussed in the chapters by Thomson et al. and by Kumar et al., the structure is consistent with data from biophysical studies including fluorescence resonance energy transfer (FRET), transient electric birefringence, and chemical crosslinking. This data is summarized clearly and concisely. Unanswered questions about the possibility of structural changes during the hammerhead cleavage reaction are presented and discussed in some detail.

The kinetics of hammerhead ribozyme cleavage have been analyzed thoroughly, and all of the conserved nucleotides in the ~30-residue core have been modified to 2′ deoxy and numerous more exotic analogues. The chapters presenting this work do an excellent job of making sense of this huge agglomeration of data, while providing a comprehensive review of the work. Similar strategies have been used to study the hairpin ribozyme, reviewed by Burke et al., which has a similar cleavage mechanism to the hammerhead, but an apparently unrelated global structure.

Six chapters are devoted to the use of hammerhead ribozymes for cleaving cellular RNAs, such as HIV and α-lactalbumin. The chapter by Usman and Stinchcomb discusses issues of delivery to target tissues, stability of RNA in vivo, and target site selection that will need to be addressed before ribozymes will be practical as therapeutics. Unfortunately, some of the material presented in this section is repetitive. Furthermore, the descriptions of ribozyme targeting and cleavage ignore alternative approaches to ribozyme engineering, including the use of self-splicing introns to replace defective sequences by *trans*-splicing. Nonetheless, a picture develops here of an exciting, emerging field facing some major challenges in the years ahead.

The catalytic potential of RNA is not limited to the ribozymes found in nature, a fact demonstrated amply by in vitro selection. Two chapters discuss the strategies and results of experiments whose general design involves selecting from large pools of random RNAs those molecules with specific functional properties. The impetus for this work is both to explore the enzymatic and binding abilities of RNA, and also to design new ribozymes of interest. Although in vitro selection has produced many RNAs with specific ligand binding properties as well as with cleavage and ligation activities, new ribozymes reactive with non-RNA substrates have been harder to isolate. Williams and Bartel provide a comprehensive table and figure summarizing the new and improved ribozymes identified by in vitro selection to date, and they discuss aspects of selection design, including pool size and sequential selections, that can influence selection results.

Excellent chapters on drug–RNA interactions and the use of ribozymes to generate circular RNAs expand the scope of the book and include practical information. Schroeder and von Ahsen outline the modes of aminoglycoside antibiotic inhibition of 16S rRNA, group I introns, the hammerhead ribozyme, and the rev-RRE interaction, and include a description of RNAs selected to bind to these drugs. Been and Puttaraju present methods for the preparation and use of circular RNA molecules.

If the past 10 years of RNA research are any indication, a new edition of *Catalytic RNA* will be needed before long. In the meantime, the current volume provides an excellent overview of the field as well as in-depth discussions that will prove useful both to students and to RNA biologists.

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