Preface to Volume 9

Structural and Catalytic Roles of Metal Ions in RNA

This volume is solely devoted to the vibrant research area indicated in the book title. It opens with three general chapters: The first one presents an overview on the binding of metal ions to RNA focusing on monovalent and divalent ions, but providing also information on higher charged cations. The roles of metal ions in the formation of RNA structures, in RNA function, and in RNA catalysis are closely intertwined; therefore, precise knowledge on metal ion-binding motifs is required to understand these processes. In Chapter 2 methods to detect and to characterize metal ion-binding sites in RNA are discussed. Spectroscopic methods encompassing X-ray crystallography, NMR, EPR, lanthanide(III) luminescense, etc. as well as chemical and biochemical methods including sulfur-rescue experiments, nucleotide analogue interference mapping (NAIM), hydrolytic and Fenton cleavage experiments to probe metal ion-binding sites are considered. The importance of computational methods involving databases as well as the calculation of binding constants are emphasized. The chapter highlights the advantages, but lists also the caveats and possible difficulties associated with each method. The majority of metal ions surrounding nucleic acids are used for charge screening of the phoshate-sugar backbone, yet an estimated 10% of the divalent metal ions are bound more specifically, taking over structural as well as catalytic roles. In Chapter 3 the importance of 'diffuse' metal ion binding to RNA is pointed out. This binding type provides a significant stabilizing force and is critical in the folding kinetics of RNA.

The following chapters are devoted to specific RNAs, like RNA quadruplexes, which are dealt with in Chapter 4. The quadruplexes involve four

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Metal Ions in Life Sciences, Volume 9 Edited by Astrid Sigel, Helmut Sigel, and Roland K. O. Sigel

Published by the Royal Society of Chemistry, www.rsc.org DOI: 10.1039/9781849732512FP007

guanine residues leading to four-stranded nucleic acid conformations. K^+, due to its size, fits most suitably into the center of the G-quartet. These higher order nucleic acid conformations have been proposed to be involved in various biological functions, such as gene regulation, nucleosome positioning, recombination, and genomic maintenance. The roles of metal ions in gene regulation by riboswitches are discussed in Chapter 5. Classes of signal-responsive RNA elements have been discovered recently to function as metalloregulating agents. This suggests that RNA-based regulatory strategies exist which precisely tune the intracellular metal ion level.

Nearly 30 years ago several small RNA motifs capable of chemical catalysis have been discovered. They play vital roles in the replication of subviral and viral pathogens, gene regulation in prokaryotes, and have recently been found in non-coding eukaryotic RNAs as is reviewed in Chapter 6. Although the interactions between small ribozymes and metal ions are relatively non-specific, the activity of these ribozymes is quite sensitive to the types and concentrations of metal ions present in solution, suggesting a close evolutionary relationship between cellular metal ion homeostasis and cation requirements of catalytic RNAs. Chapter 7 describes the multiple roles of metal ions in large ribozymes, that is, in group I and group II introns as well as in ribonuclease P (RNase P). Metal ions affect RNA folding and catalysis; regarding the last point in particular, the 'two-metal-ion mechanism', which has been confirmed repeatedly, is emphasized

The spliceosome, discussed in Chapter 8, is a massive complex of 5 RNAs and many proteins that associate to catalyze precursor mRNA splicing, which is an essential step in eukaryotic gene expression. A wealth of data indicates that the core of the spliceosome is comprised of RNA, suggesting that the spliceosome is a ribozyme. There is also growing evidence for a magnesium-dependence with at least two metal ions in the active site. "Metal ions are the salt in the soup of essentially every biological system", as the authors of Chapter 9 point out. Also in the ribosome, the largest natural ribozyme that produces all proteins in every living cell, metal ions have been found to contribute significantly to the highly dynamic and accurate process of translation. Indeed, the catalytic center and surrounding domains are densely packed with divalent metal ions and direct roles in mRNA decoding and reading frame maintenance are likely.

The means of *in vitro* selection has yielded a number of artificial ribozymes with functions that have not been discovered yet in modern biological systems. The metal ion requirements of two such artificial ribozymes, which catalyze aminoacylations and redox reactions, are discussed in Chapter 10. In Chapter 11 the fundamental structure and metal ion-binding properties of four naturally occurring RNA enzymes, i.e., the hammerhead, hairpin, hepatitis delta virus, and *glms*-metabolite sensing ribozyme, are described. In addition, the fold and metal ion coordination of three artificial ribozymes are discussed, namely of the leadzyme, the flexizyme, and the Diels-Alder ribozyme. An emergent theme is that natural and artificial ribozymes that catalyze single-step reactions often possess a pre-formed active site and that multivalent ions facilitate RNA-active site formation.

In the terminating Chapter 12 several aspects of the kinetically inert platinum(II) are highlighted, focusing on Pt(II)-RNA adducts and the possibility that they influence RNA-based processes in cells. Nucleic acids are targets of metal-based therapeutic agents, the most extensively studied being the Pt(II) anticancer compounds, especially *cis*-diamminedichloro-Pt(II) (*Cisplatin*). Indeed, the formation of Pt(II)-RNA adducts provides a rationale for the observation that the treatment with Pt(II) compounds disrupts RNA-based processes including enzymatic processing, splicing, and translation.

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