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MeRNA: a database of metal ion binding sites in RNA structures

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ABSTRACT

Metal ions are essential for the folding of RNA into stable tertiary structures and for the catalytic activity of some RNA enzymes. To aid in the study of the roles of metal ions in RNA structural biology, we have created MeRNA (Metals in RNA), a comprehensive compilation of all metal binding sites identified in RNA 3D structures available from the PDB and Nucleic Acid Database. Currently, our database contains information relating to binding of 9764 metal ions corresponding to 23 distinct elements, in 256 RNA structures. The metal ion locations were confirmed and ligands characterized using original literature references. MeRNA includes eight manually identified metal-ion binding motifs, which are described in the literature. MeRNA is searchable by PDB identifier, metal ion, method of structure determination, resolution and *R*-values for X-ray structure and distance from metal to any RNA atom or to water. New structures with their respective binding motifs will be added to the database as they become available. The MeRNA database will further our understanding of the roles of metal ions in RNA folding and catalysis and have applications in structural and functional analysis, RNA design and engineering. The MeRNA database is accessible at http://merna.lbl.gov.

INTRODUCTION

The significance of metal ion interaction with RNA structures became apparent in the mid-1960s when Fresco *et al*. (1) discovered that cations are essential for the stabilization of the native structure of transfer RNA. Over a decade later, the first crystal structures of $tRNA^{Phe}$ revealed at least four specific magnesium ion binding sites that are important in maintaining the fold of the tRNA molecule (2–4). Since then, numerous studies have shown that metal ions play a crucial role in RNA 3D folding, structure stabilization and catalytic activity [reviewed in (5–11)].

In order to analyze the binding of metal ions to RNA and the role metal ions play in overall RNA structure and function, we have created a comprehensive database, MeRNA (Metals in RNA), of all metal binding sites identified in RNA 3D structures available from the PDB (12) and Nucleic Acid Database (NDB) (13). The MeRNA database is an adjunct to the Structural Classification of RNA database (SCOR) (14), which focuses on RNA structural and functional motifs.

MeRNA catalogs 9764 metal ions corresponding to 23 elements that interact with RNA in 256 PDB entries solved by X-ray diffraction, NMR and fiber diffraction, with coordinates released before July 1, 2005 and containing one or more metal cations bound to RNA. An analysis of our data identifies the characteristic coordination geometries and role of specific RNA functional groups in binding particular metal ions, as well as the presence of specific RNA metal binding motifs.

DATABASE CONTENT AND INTERFACE

Content

For each PDB or NDB entry we have extracted the experimental method, resolution, quality of the model, and primary and secondary references. Distances from the metals in each structure to the nearest RNA atoms, as well as protein atoms and water molecules, are calculated from atomic coordinates. Only RNA and protein atoms which can serve as ligands for metal ions (e.g. N, O, S) are included in MeRNA analysis. These data are stored in a MySQL database. The binding motifs and types of binding were manually determined by analyzing each RNA structure and comparing to certain binding motifs previously described in the literature. In particular, eight well-characterized metal ion binding motifs were identified and included in the database. These eight include (i) the major groove of a G•U wobble base pair, followed by a

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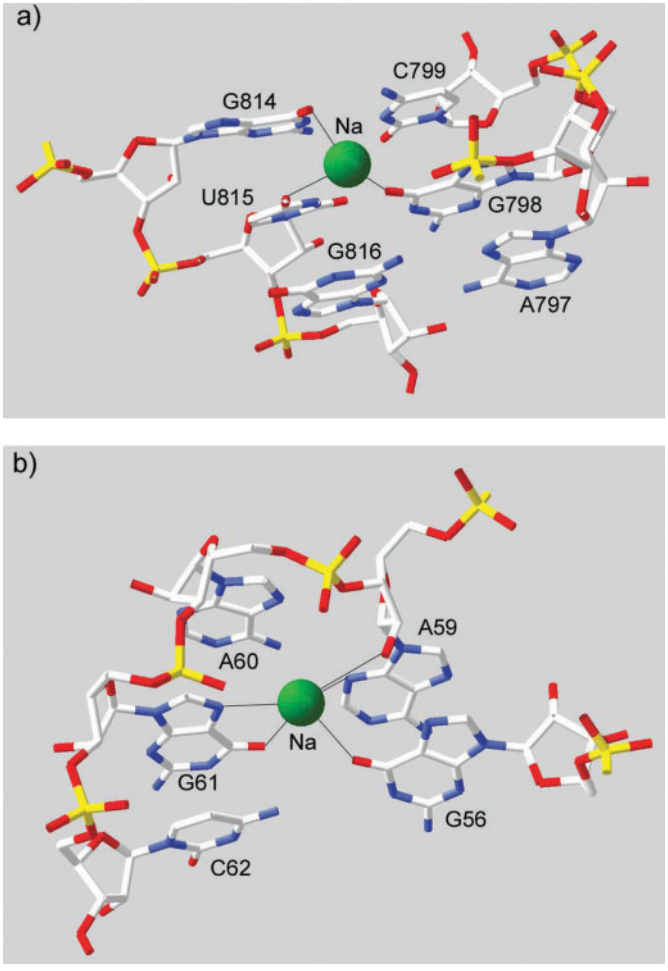

Figure 1. (**a**) Major groove of G-U wobble pair binds a sodium ion (pdb code 1s72); (**b**) AA-platform motif from 23S RNA binds a sodium ion (pdb code 1s72). Thin black lines indicate direct bonding between the sodium ion and RNA atoms. Figures generated with Swiss-PdbViewer, version 7.5 (45).

Y•G pair (see Figure 1a) (15–21), (ii) sheared G•A pairs (22–25), (iii) magnesium clamp (26), (iv) metal ion zipper (25), (v) loop E motif (25,27–29), (vi) AA platform (see Figure 1b) (30–32), (vii) tetrads (33–36) and (viii) the G-phosphate Mg ion binding motif (37). The content of the database with respect to the cations included in the PDB entries and their preference for certain binding motifs is illustrated in Table 1.

As expected, magnesium ions occur in the most structures and are most numerous in the database, followed by sodium ions. This is due to the abundance of structures containing these ions and the particularly important role they play in the structure and function of nucleic acids. For instance, magnesium ions play an essential role in the tertiary folding of tRNA (2–4) as well as in the structure and catalytic function of ribozymes (23,24,31,32,38–44). The large number of occurrences of tungsten is due to the use of the octadecatungstenyl diphosphate complex with the formula $O_{62}P_2W_{18}$ for crystallographic phasing in large RNA structures.

Interface

The home page contains a simple search by either PDB ID or metal ion type. The advanced search page (shown below)

Table 1. Metal ions bound to RNA structures

Metal	Charge	Ionic radius (Å) (46)	No. of PDB files	No. of cations	Binding motif(s)
Magnesium	+2	0.72	162	5530	i, ii, iii, iv, v, vi, viii
Sodium	+1	1.02	47	2281	i, vi, vii
Potassium	+1	1.38	45	116	vii
Zinc	+2	0.74	44	151	
Cadmium	+2	0.95	30	162	
Calcium	+2	1.00	17	173	i
Cobalt	+2	0.65 (LS) 0.745 (HS)	4	25	i
	+3*	0.545 (LS) 0.61 (HS)	13	32	
Manganese	+2	0.67 (LS) 0.83 (HS)	12	43	ii
Strontium	+2	1.18	7	133	
Tungsten	+5, +6	0.62, 0.60	6	997	
Barium	+2	1.35	6	41	vii
Rhodium	+3*	0.665	4	10	
Mercury	+1	0.97	3	10	
Lead	+2	1.19	3	29	
Osmium	+3*	0.63	2	8	
Iridium	+3*	0.68	1	2	
	+4	0.625	1	4	

Charges, ionic radii and binding motifs (if any) are tabulated. Asterisks indicate ions as metal hexamine coordination complexes. LS and HS stand for low and high spin states.

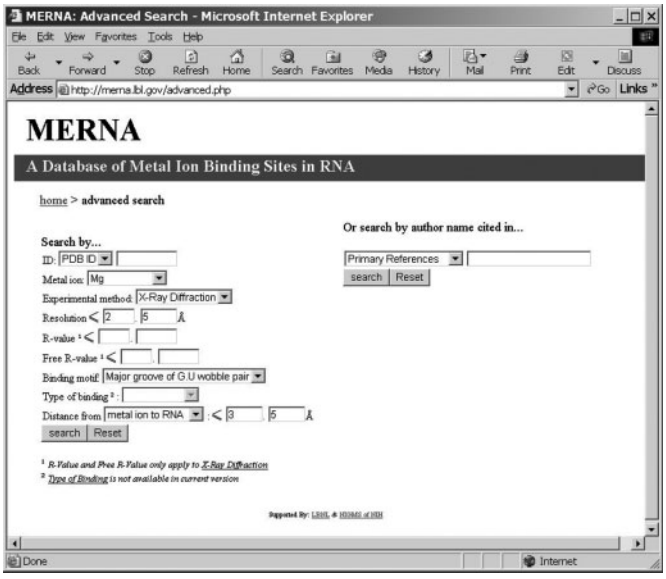

Figure 2. A snapshot of MeRNA interface showing the advanced search page.

contains a form allowing searches by any of the following: PDB or NDB IDs, metal ion, experimental method, resolution, *R* and free *R*-values, binding motif, distance to any RNA or protein atom or water molecule and any combination of the above. It is also possible to search by author name either in the primary or in additional references, or both. An example of the advanced search page and its result page is given in Figures 2 and 3.

Applications

Using the information contained in our database, one can explore approaches to predict metal ion binding sites in RNA

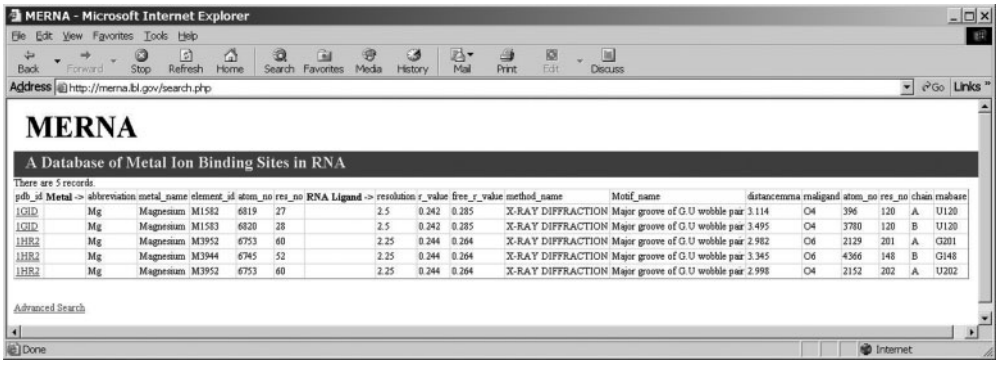

Figure 3. A snapshot of MeRNA interface showing the results of previous search query.

sequence and structure and to identify new RNA metal ion binding motifs.

MeRNA can also be used with the SCOR database to understand RNA 3D structures in a comprehensive way, on the basis of their structure and function. This can be achieved relating RNA structural and tertiary interaction motifs classified in the SCOR database to the metal ion binding motifs included in MeRNA.

As it develops, MeRNA will become an invaluable resource for understanding the role of metal ions in forming and maintaining RNA structure and RNA function. Such insight will ultimately aid in the design of RNA structures with specific properties.

According to the published descriptions, many RNA structures have been determined, for which the bound (localized) metal ion coordinates have not been deposited to the PDB or NDB. This is often the case for heavy atom derivatives of the native RNA prepared for crystallographic phasing. The availability of these additional metal ion coordinates in RNA structures should provide a better overall description and understanding of the roles of metal ion binding in RNA.

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Conflict of interest statement. None declared.

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