

The Principles of RNA Structure Architecture

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Abstract

Being informational, enzymatic, as well as a nanoscale molecular machine, ribonucleic acid (RNA) permeates all areas of biology and has been exploited in biotechnology as drug and sensor. Here we describe the composition and fundamental properties of RNA and how the single-stranded RNA chains fold and shape certain motifs that are repeatedly observed in different structures. Small and large molecular mass RNA binders are being touched upon, as is the technology for selecting RNA molecules in vitro that bind almost any kind of natural or artificial target. Recognizing the versatility of RNA is expected to foster the development of tools which monitor RNA in the environment, including plants, animals, and patients. Many of the noncoding RNAs are yet to be identified in the rapidly emerging genomes and assigned to functions. It is hoped that these and similar worthwhile goals will be achieved by integrating the efforts of bench and computer scientists.

Key words Ribonucleic acid, Structure, RNA, RNA structure, Base pair, Genome, Motif, Antibiotics, Aptamer, Ribonucleoprotein

1 Introduction

Within the recent years a remarkable expansion has taken place in our understanding of the significance of the role of RNA in all aspects of biology. No longer are RNA molecules only transient intermediates which carry the DNA-encoded information from the nucleus into the cytosol, but as ribozymes they also catalyze biochemical reactions [3, 4]. The discovery of this twofold capacity of RNA to be informational and enzymatic made it possible to select in vitro a wide variety of artificial ribozymes with divergent substrate specificities. Furthermore, it fed the idea of an early “RNA world” where RNA perhaps represented the first primitive form of life [5]. A third attribute of RNA is linked to its ability to function as a nanoscale molecular machine, the ribosome being the prime example. Molecular nanodevices with RNA at their core include, among others, the signal recognition particle (SRP) which binds to ribosomes and directs nascent polypeptides to the

cell membrane [6], the transfer-messenger RNP (tmRNP) which rescues immobilized bacterial ribosomes [7], and the spliceosome which removes introns from other RNAs [8]. In the perception of some researchers who work in the areas of biology and biotechnology, there is no end in sight of what RNA might be capable to achieve.

Only about 1.5% of the human genome codes for proteins [9], while the remainder, long being ignored as “junk,” has the potential to be transcribed into a bewildering variety of noncoding (nc) RNAs. More than 80% of human disease-associated loci associate with non-protein-coding regions highlighting the physiological importance of the RNA [10]. Technological advances in the analysis of genomes continuously generate formidable amounts of data which require filtering and curation in order to become intelligible [11–13]. Computational tools for identifying ncRNA genes and their processed products are being actively developed and aim to bring order to the massive amount of sequence data. For example, the Rfam database (in its version 10) provides alignments for 1,446 RNA groups or “families” [14], and the catalog of functional RNAs at fRNAdb [15] distinguishes 116 RNAs by name. Nevertheless, with respect to structure and function, RNA molecules can be intrinsically more dynamic than what the databases confine themselves to, leaving much work to be done before we better understand the multifaceted roles of RNA.

This introductory chapter attempts to give a simple account of what RNA is made of. It introduces the names and nomenclature commonly used to describe RNA molecules and provides a small sample of the complexity of this fascinating biopolymer. It is hoped that this effort will encourage investigators to advance RNA research and develop urgently needed computational and biotechnological tools aimed to decipher RNA’s sophisticated and dynamic biochemistry as reflected in its structure.

2 RNA Fundamentals

RNA (ribonucleic acid) is a linear polymer of ribonucleosides arranged in sequence referred to as its primary structure. The average size transfer RNAs (tRNAs) contains 73–93 such residues [16], whereas the prototypical bacterial 16S ribosomal RNA (rRNA) of the *Escherichia coli* small ribosomal subunit is composed of 1,542 ribonucleotides [17]. At their size extremes are the 22-residues microRNAs [18] and, for example, the 17 kb Xist RNA [19].

Unless modified, a ribonucleoside is a ribose sugar covalently bound to one of four different nitrogenous bases (Fig. 1). Adenine and guanine (abbreviated as A and G) are derived from a hete-

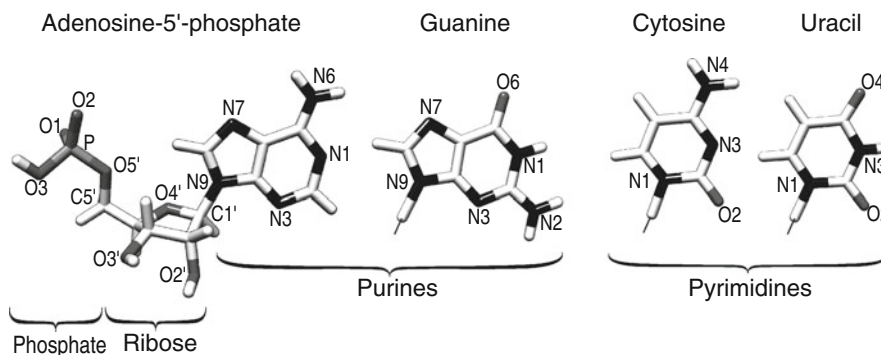


Fig. 1 The prominent building blocks of RNA

rocylic aromatic purine (abbreviated as R), whereas cytosine (C) and uridine (U) are pyrimidines (abbreviated as Y). The N9 of the purine or the N1 of the pyrimidine base connects via the stereochemically important glycosidic bond with the carbon (C1') of the ribose. A ribonucleotide forms by covalent attachment of one, two, or three phosphates to the ribose 5' carbon. 5'-nucleotide triphosphates (NTPs, where N stands for any of the four bases) are used within the cell to synthesize RNA in the 5'–3' direction. This process releases inorganic pyrophosphate with one phosphate left at each step to join the 3' and 5' positions of neighboring ribose rings. By convention, the sequence of an RNA molecule is written from 5' to 3', left to right starting with the numbering at the 5'-end, typically in groups of three or ten characters.

RNA can be modified after its transcription to include nucleoside methylations or less common bases such as inosine (abbreviated as I), dihydrouridine (D), or pseudouracil (ψ). When residues are removed or inserted by splicing, RNA editing, or other RNA processing steps, the primary structure of the functional RNA molecule is significantly different from the sequence of its gene.

Unlike in DNA, the 2' hydroxyl group of the ribose is capable of forming cyclic phosphate intermediates allowing RNA to be readily hydrolyzed and cleaved by intra- and extracellular RNases. Being able to turn over and reduce its active intracellular pool size allows RNA to regulate vital processes. The 2' hydroxyl group also contributes to the capacity of the RNA to interact in versatile ways with itself or a variety of ligands.

3 The Folded RNA

Although RNA is in general single stranded, the bases have a strong propensity to interact in two principal ways, either perpendicular to their planes (stacking) or hydrogen bonded within the base planes

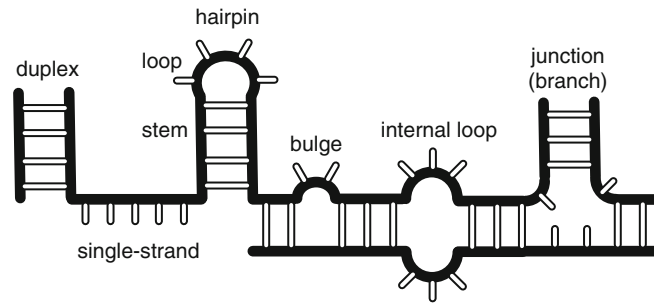


Fig. 2 RNA secondary structure features. Naming conventions for regions in the RNA secondary structure

(pairing). Paired residues are indicated by connecting lines in the RNA secondary structure diagrams composed of stems, bulges, and loops (Fig. 2) characteristic for a particular RNA molecule. Less consistently, stacking may be shown in the diagrams by placing letters closer to each other.

In their elucidation of the structure of the DNA double helix, Watson and Crick proposed two planar purine–pyrimidine base pairs, A–T and G–C, where the bases of each pair are held together by two or three specifically arranged hydrogen bonds [20]. The corresponding pairs in RNA are A–U and G–C, but the non-Watson–Crick G–U wobble pair has approximately the same stability as an A–U [21] and is commonly observed in all the medium-size and larger RNA molecules. The two ribose groups attach to the same side of a base pair and define two types of indentations: a major groove, delineated by N7 of the purine and the C6 of the pyrimidine, and a minor groove with purine N3 and pyrimidine O2 (Fig. 3). The three most frequently used RNA base pairs (A–U, G–C, and G–U) share almost identical overall dimensions and, when placed next to each other, stack continuously to form a rigid A-type helix with 11 bp/turn, a deep narrow major groove, and a relatively shallow minor groove (Fig. 4a, b).

Computational calculations which determine the secondary structure (the base-paired helical regions) of an RNA molecule using energy calculations are readily available but can be unreliable [22, 23]. Considering that biologically active RNAs often bind proteins and other factors that are excluded from the calculation, it is unclear why the structure with the overall low free energy should exist preferentially. A more accurate method observes covariances and compensating base changes (e.g., changes from a G–C to a C–G or A–U pair) in a group of phylogenetically related aligned sequences [24]. A sufficiently large number of compensations strongly support the existence of a base pair because, during evolution, random mutations would not have been corrected to

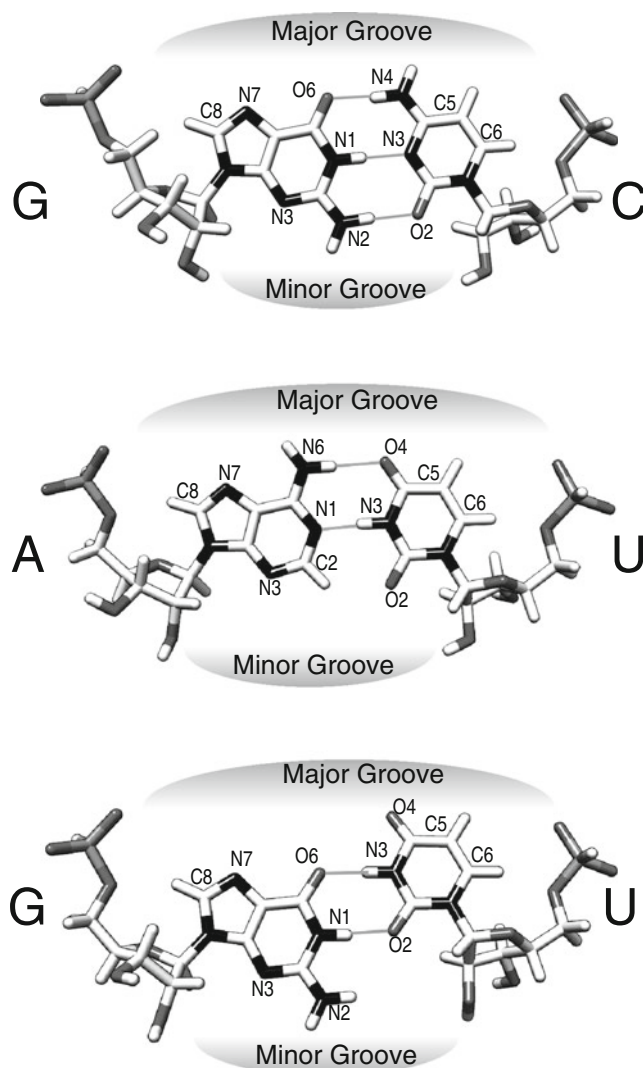


Fig. 3 Watson–Crick and G–U wobble pair geometries

maintain the base pair unless it was required [25]. Semiautomated procedures and tools have been developed to help identify the compensatory base changes and calculate the level of support for each base pair [26].

Canonical A–U and G–C pairs and the G–U wobble pair engage the Watson–Crick edges of the bases to form two or three hydrogen bonds. Planar base interactions can however also occur through the Hoogsteen edge (defined by the purine positions 6, 7, and 8 or the pyrimidine positions 4 and 5) or the sugar edge formed by the 2' hydroxyl group of the ribose with purine positions 2 and 3 or with the pyrimidine oxygen atom at position 2 (Fig. 3). Given that the glycosidic bonds can be oriented either in *cis* or

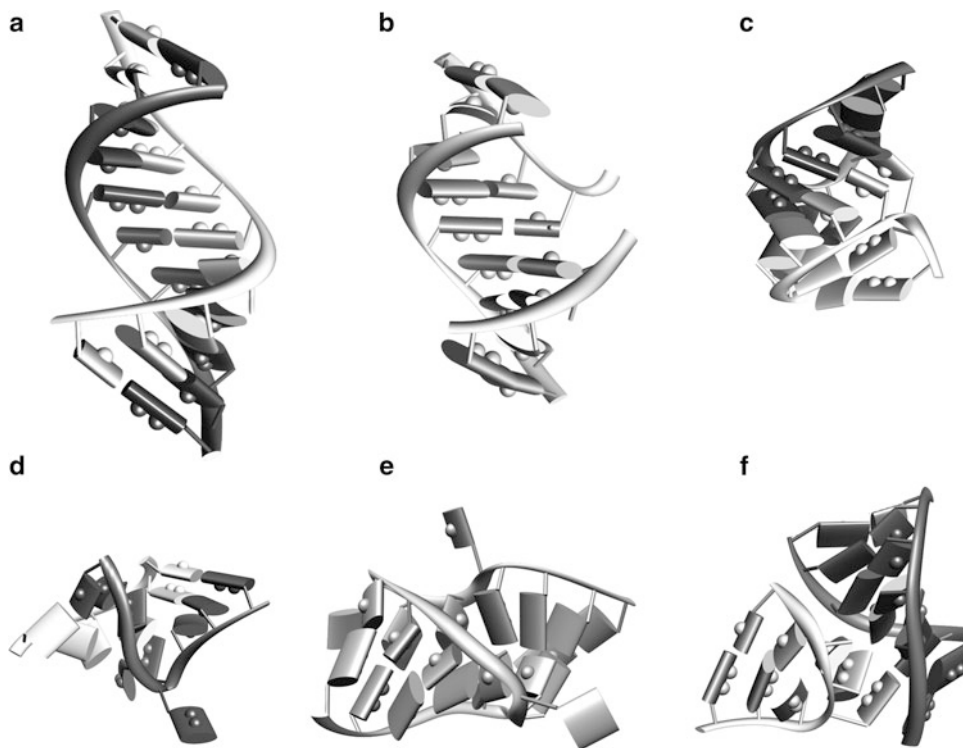


Fig. 4 RNA interactions and motifs. Helix (a), helix stacking (b), kissing hairpin loops (c), kink-turn (d), pseudoknot (e), and tetraloop–tetraloop receptor complex (f). Coordinates were chosen from RCSB PDB files 1KF0, 1EVV, 2JLT, 1FFK, 2RP0, and 2JYJ [54] and displayed with UCSF Chimera [55]

trans, 12 principal geometric types are possible with at least two hydrogen bonds connecting the bases [27]. This ability of the RNA bases to form hydrogen bonds in a multitude of combinations, sometimes involving more than two bases, is largely responsible for a formidable structural and functional variability.

Verification of a predicted RNA secondary structure by carrying out chemical and enzymatic modification experiments is often useful but provides clues only for surface-exposed sites. Watson–Crick and wobble base pairs, even when hidden inside the folded RNA, can be verified by testing the biological activities of molecules with compensatory double mutations which regenerate these pairs. Experimentally derived data guide in the building of three-dimensional models to gain insight into the structure and function of an RNA, an exercise that is often the only option when the high-resolution structure is unavailable [28, 29].

Tertiary interactions in RNA are generally considered to be those which occur between separate regions of the secondary structure. The various ways by which bases stack and form hydrogen bonds provide ample opportunities for secondary structure elements to come together. The first RNA structure determined at

atomic resolution was that of yeast tRNA^{Phe} and key to understand some of the architectural principles of an RNA molecule [30, 31]. One such fundamental rule is the ability to preserve its overall three-dimensional shape despite differences in sequence. More recent examples of how unrelated sequences fold unexpectedly the same way are the GUUA and UNCG tetranucleotide (tetra) loops [32]. Another principle is the capacity of RNA strands to adopt a compact and relatively RNase-resistant conformation (*see, e.g.,* 1EHZ.pdb [33]).

Subsequent milestones included the deciphering of the molecular structures of the hammerhead ribozyme [34, 35], the P4–P6 domain of the group I intron RNA [36], and the hepatitis delta ribozyme [37]. Solving the structures of ribosomes and its subunits, composed predominantly of RNA, was an astonishing accomplishment [38–40]. Like proteins, RNAs were shown to be able to adopt complicated and yet precise structures. Examples of base triples, adenosine platforms, and ribose zippers were discovered, as were interactions between GNAR tetraloops and their receptors. Drawn in the secondary structures as nondescriptive internal loops, these features were shown to form distinct kinks and helix distortions some suited to bind proteins.

4 RNA Motifs

As more and more structural information became available, the same folding principles were frequently observed in the known RNA structures. It is now clear that, like lego blocks, these structurally strictly defined entities or motifs are reused in combination to generate a rich variety of molecular shapes. As motif examples, the kissing hairpin loops, a kink- or K-turn, a pseudoknot, and the complex between a tetraloop and its receptor are depicted in Fig. 4.

The naming conventions for the different RNA motifs are vague, but classifications according to their structure, functions, and tertiary interaction have been initiated [41, 42] and provide a useful selection of building blocks for constructing “from scratch” biologically meaningful three-dimensional models [28]. Locating RNA motifs in the genomic sequences is possible using computationally intensive pattern matching programs [43]. Progress in this area is desirable in order to identify RNA genes and annotate the genomes.

5 RNA Ligands

Small Molecules. Water and metal or other ions contribute significantly to the folding and conformation of the predominantly negatively charged RNA. Magnesium ions, together with

spermidine, have been known to bind in the major groove of tRNA^{Phe} [44]. The relative contributions of these site-bound versus the delocalized ions to RNA folding and stability remain to be explored [45].

RNA-Targeting Drugs. Aminoglycosides, paromomycin, and spectinomycin are among the antibiotics which impede translation by binding to ribosomal RNA [46]. Given the essential role of RNA in biology and the continuing emergence of new RNA families, there appears to be a fertile ground for the discovery of new compounds that inhibit the functions of certain vital RNA molecules. The non-ribosomal ribonucleoproteins (RNPs), such as signal recognition particles and the tmRNPs, are now sufficiently characterized to explore them as promising targets for the development of new antibiotic compounds.

Proteins. We now live in an RNA plus protein world where DNA is being tasked mainly with storing information within the genome. Considering the induced fit-type structural changes commonly observed upon the formation of protein–RNA complexes, proteins and RNA must have experienced a long coevolutionary history. Indeed, the majority of RNAs function with full capacity only when assembled into RNPs. A protein may bind to an RNA molecule or an RNP only temporarily to regulate a biological activity. Being aware of the close structural and functional partnership between RNA and protein is expected to contribute significantly to the genome annotation efforts and an understanding of RNP phylogeny [47].

RNA Aptamers. SELEX (systematic evolution of ligands by exponential enrichment) has been widely used to select in vitro RNA molecules which bind a wide variety of targets, including proteins and antibiotics, with high affinity and specificity [48]. Compared to antibodies, the aptamer approach has the advantage of circumventing the costly use of animals or cultured cells. RNase-resistant aptamers with 2' modification can be chemically synthesized on a large scale and applied as drugs. Several such aptamers for use as therapeutic molecules are currently in development [49].

6 Prospects

The field of RNA research is rapidly expanding into areas beyond biotechnology, RNA-based therapeutics, or the development of new antibiotics. Crop yields, and ultimately our capacity to respond to challenges in the face of climate change and increasing global populations, are determined by plant noncoding RNAs that control growth, development, and breeding capability [50]. The ribosomal RNAs are now being joined by a host of other non-coding RNA sequences in efforts to better understand phylogeny

and the changing diversity and ecology of life. The identification of microRNAs (miRNAs) and Piwi-interacting RNAs (piRNA) [51] in the genomes presents itself as a formidable experimental and computational challenge. The CRISPR RNAs protect bacteria and archaea from phage infections, thereby influencing population dynamics with important ecological consequences [52, 53]. It is almost certain that additional RNAs with unimagined properties and functions will be discovered in the near future. We will be ready to explore.

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