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GUEST EDITORIAL
New Dimensions of RNA in Molecular Recognition and Catalysis

RNA molecules are now moving to the forefront of biology and emerging as important drug targets. Long thought to be mere messengers or scaffolds, RNAs fold into complex three-dimensional structures for selective molecular recognition, catalysis, and information transfer. Ribosomal RNAs are often the target of natural antibiotics but mRNA noncoding structures are emerging as even more important drug targets both in bacteria and especially organisms with differentiated cells; here the mRNA population of each cell type is distinct and there are a smaller number of mRNA molecules than of the "translated" protein molecules. We now know that a genome is not simply a string of genes that are transcribed into mRNAs before being translated by ribosomes. We fully appreciate that the coding segments in eukaryotes are only a fraction of the total amount of DNA (less than 2% in humans). Although the precise amount is still controversial, it is also realized that most, if not all, of the DNA of a genome is transcribed into RNA transcripts, the noncoding RNAs. Some of those are short (less than 25−30 nucleotides), and others are very long (several kilobases). Noncoding RNAs with dedicated biological functions are being discovered every month. The range of biological function spanned is huge: for example, they are involved in the virulence of bacteria, in the maintenance of chromosome ends, and in the inactivation of the female (X) chromosome of humans. Genetic expression is not simply a matter of DNA promoters and transcription factors but depends on whole networks of molecular interactions between coding segments and noncoding transcripts as well as between noncoding RNAs. The new technologies in sequencing, which provide massive amounts of data that demand new bioinformatics tools for comparative genomics, are only glimpsed in this issue of *Accounts of Chemical Research* dedicated to RNA. Rather, we have chosen topics that stress the central role of chemistry in the biological function of RNA. Every single physicochemical property of the four bases, A, G, C, U, and of the ribose sugar−phosphate backbone of RNA molecules, within the constraints of molecular evolution, is exploited by biological evolution.

How the chemistry of the sugar−phosphate backbone and bases influences RNA structure and catalysis is described in the first two Accounts in the RNA *Accounts of Chemical Research* and reflects the tremendous research activity stimulated by the discovery of RNA catalysis. Piccirilli and colleagues review oxygen-to-sulfur substitution in the phosphodiester backbone, with emphasis on synthesis oligonucleotides with a phosphorothiolate linkage. Phosphorothioate nucleotides and oligonucleotides, pioneered by Fritz Eckstein, play key roles in mechanistic studies of protein enzymes the catalytic action of nucleolytic ribozymes; recent discoveries of ribozymes in several bacteria suggest they may be widespread in nature. Then, Bevilacqua and colleagues describe the contributions of the states of the nucleobases to mechanisms of ribozyme action. A striking fact that emerges is the important roles of charged nucleobases during catalysis. Mg(II), which are required for RNA folding of many RNAs and generally, for ribozyme activity, act as Lewis acids during ribozyme catalysis exemplified by group I or group II self-splicing introns. However, recently, in ribozymes such as VS and hairpin ribozymes, the mechanism depends on general acid−base catalysis supported by adenine and guanine.[1] Not only is base protonation involving A or C important in catalysis but also deprotonation and ionization of a base such as G.

The largest subject in the RNA *Accounts of Chemical Research* focuses on ramifications of the three-dimensional RNA structure. Often erroneously depicted as "strings", RNAs assume multiple, complex, three-dimensional structures driven by self-organizational properties that are beginning to be understood. The first four Accounts in the section discuss general features of RNA structure, and the second set discusses functional features of natural riboregulators and targeted, synthetic oligoribonucleotides (aptamers).

Probing conformation in RNA, using access of the ribose-specific hydroxyl groups to acylation (Selective 2′-Hydroxyl Acylation analyzed by Primer Extension, SHAPE), discussed by Weeks and Mauger leads to information on how RNA structures fold into regulatory motifs and regulate rates of RNA splicing and assembly of ribonucleoproteins. NMR spectroscopy to study landscapes of RNA dynamics, which may be even more tightly linked to function than for DNA or

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protein, is reviewed by Schwalbe and colleagues. Patterns of stabilizing forces in RNA tertiary structures, such as stacking and backbone bonds, interhelix "ribose zippers", and sequence specific interactions, now known from combining physiochemical, small molecule chemical genetics and informatics are described in the Account by Butcher and Pyle. RNA folding and self-assembly of the largest known RNA catalyst, rRNA that makes the peptide bonds in proteins, is the subject of the final Account in the RNA conformation section, by Woodson, describing staged assembly, as in ribozymes, and the potential of specific proteins, to enhance correct RNA folding.

Messenger RNA structures, usually noncoding, self-regulate rates of protein synthesis, which is the most bioenergetically expensive process in living cells. Even triplet nucleotide coding can be changed by noncoding, folded RNA structures exemplified by selenocysteine insertion during the synthesis of selenoproteins.[2] In the first RNA *Accounts of Chemical Research* Account on mRNA regulatory structures, Goss and Theil discuss a small noncoding riboregulator structure in animal mRNAs, the IRE, which recognizes two proteins that block or facilitate ribosome binding depending on whether or the feedback metabolite, ferrous ion, is bound to the riboregulator. Riboswitches, multidomain noncoding RNA regulatory structures discovered in the early 21st century in bacteria, recognize small organic molecules that are cellular metabolites, such as cofactors (cobalamin or FMN) amino acids, purines called aptamers; riboswitch RNA/aptamer recognition and binding induce massive RNA conformational changes that alter function.[3,4] Deigan and Ferré-D'Amaré introduce riboswitches and describe the impact of riboswitches on the development of new antibacterial agents, while Micura and colleagues consider the contributions of riboswitch kinetics in the control of aptamer-induced RNA folding. Famulok and Mayer conclude the section on 3D RNA structure by discussing the chemical biology of synthetic RNA aptamer oligonucleotides to capture different types of cellular analytes for sensitive biosensors in clinical diagnostics and basic biology.

A fascinating example of the power of Darwinian molecular evolution, in the test tube, is described by Suga and co-workers in their Account on Flexixymes. Nowadays, tRNAs are aminoacylated with their cognate amino acids by aminoacyl tRNA synthetases. In a past RNA only world, one can envision some catalytic RNAs that would selectively bind a particular amino acid and aminoacylate its own terminus or that of another RNA. Suga proved that such reactions occur with in vitro evolution techniques and, with Ferré-d'Amaré, managed to crystallize the active elements of the selected RNA. The ways used by RNA to recognize and catalyze the aminoacyl transfer are unexpected. With the Account, by Kiga and co-workers on RTRACS (Reverse-transcription-and-TRanscription-based Autonomous Computing System), we enter the field of RNA synthetic biology. The authors assemble various combinations of RNA, DNA, and nucleic acid enzymes into specific modules. These modules when fed with a given RNA input produce a specific RNA output through the internally programmed sequence of events. Synthetic biology based on RNA systems is still in its infancy, and more complex biomolecular modules with defined biological monitoring properties are expected in the near future. In the final Account, Yi and Pan present new understanding of nucleic acid modifications. Epigenetics describe heritable phenomena caused by changes unrelated to the genomic DNA sequence (for example, methylation of DNA or of histone). Noncoding RNAs play key roles in the maintenance and changes of those methylation patterns (see above). Yi and Pan coin the term of RNA epigenetics and describe how RNA modifications are dynamic and vary with cell type, stress or nutrition. Most importantly, they describe how new methods especially in high throughput sequencing and mass spectrometry techniques are necessary to advance RNA epigenetics.

The goal of the special *Accounts of Chemical Research* issue of RNA is to introduce to a wider fraction of the Chemistry community the third dimension of RNA structure and function accessible through the complex folding of the single-stranded polyribonucleotide, modulated by inorganic metal ions and small organic molecules. We hope this introduction to the extra dimension of RNA, richer than the base "code", and eclipsing the midcentury "central dogma" that relegated RNA to carrying information between genes and proteins, will tempt many readers of *Accounts of Chemical Research* to experiment and find the new RNA features that await discovery.

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