Foreword

Comprehending the functional diversity as well as the subtle organizational and biochemical roles of RNA molecules is becoming intellectually overwhelming. Thus, it is an almost impossible task to attempt to gather all the recent developments in molecular and structural biology of RNA in two issues of *Biochimie*. Besides, such an endeavor demands not only that choices be made but also requires receptive and available authors. I am therefore extremely grateful to the authors who accepted to contribute to these issues. The readers will appreciate the quality of the articles. Although the articles in these two volumes cover a wide range of functions of RNA molecules, several important biological functions are missing, especially mRNA splicing and the spliceosome (to which a whole issue could be devoted) [1], the newly discovered non-coding RNAs [2–4] and RNA interference [5,6].

The two present issues attempt to focus on the precise molecular descriptions of specific biological functions of various RNA molecules. They are arranged so that the first one is biologically oriented and the second one is more chemically oriented. Each of the issues starts with an article of recollections. I would like to convey my thanks and appreciation to both Sid Altman and Fritz Eckstein for having accepted this unusual task. We all read about the snake of Kékulé or about the train of Henri Poincaré ("Au moment où je mettais le pied sur le marchepied, l'idée me vint, sans que rien dans mes pensées antérieures parut m'y avoir préparé") and here we learn about the tortuous path that led to the discovery of the first natural ribozyme. The contributions of phosphorothioate chemistry to molecular biology are numerous, both for the characterization of enzymes and for the analysis of ribozymes. Fritz Eckstein, who pioneered the approach, describes some of the rich history of those compounds, useful in fundamental studies as well as in the applications of antisense or ribozyme strategies.

The first volume is centered on translation and the ribosome. Three articles deal with tRNAs. In a first article, Bill McClain and coworkers use knock out strains for selecting mutants of tRNA$^{\text{Ala}}$ with non-native acceptor stems. The results illustrate the limits of atomic reductionism since they show that the acceptor stem has to be considered as a whole to understand the observed mutants. Two articles follow on the first isolated natural ribozyme (but will it be the last one to be crystallized?), RNase P. Leif Kirsebom and collaborators analyze the determinants present in the pre-tRNA and close to the cleavage site selected, while Roland Hartmann and his group recount their search without success for the presence of RNase P activity in a hyperthermophile, *Aquifex aeolicus*, a puzzling result. The function of transfer-messenger RNA (tmRNA) is to rescue stalled eubacterial ribosomes. Bordeaux and Felden show that the ribosomal protein S1 alters the conformational state of tmRNA and helps in the switch from the tRNA mode to the mRNA mode. Markus Wahl and coworkers study the peculiar ribosomal protein L4 from the large subunit. It presents a stunning three-dimensional structure and regulates the transcription and translation of its own S10 operon encoding eleven ribosomal proteins. In the next article, Marina Rodnina and coworkers review the kinetic and structural parameters underlying the fascinating multi-step process of decoding by the ribosome. The molecular complexity of the ribosomal machinery inspires awe and perplexity. However, because this complexity is anchored in molecular interactions, several steps can be stalled or by-passed by other RNA or RNA-protein complexes. Encarnacion Martinez-Salas and her group present results on the internal ribosome entry site (IRES) of the foot-and-mouth disease virus that allows cap-independent translation and therefore bypasses several initiation steps. It is known to be functional and can be used as a model for other IRES, like the one of the hepatitis C virus. After the tmRNA and the IRES, Alain Krol describes another system altering the decoding of codons by ribosomes, the insertion into proteins of selenocysteine, the twenty-first amino acid. Translation elongation factors and the presence of defined mRNA hairpins are required for redirecting UGA stop codons into selenocysteine codons.

The atomic diversity of RNA molecules is very restricted and therefore RNA molecules are often chemically modified for protection against cleavages, stabilization of folds and maybe tagging of molecules which have undergone some biochemical process. In eukaryotes, 2′-O-methylation and pseudouridylation are directed by two large families of guide RNAs, the small nucleolar RNAs (snoRNAs). Jean-Pierre Bachellerie and associates present a striking overview of snoRNAs emphasizing the large range of function of those guides beyond their action on ribosomal RNAs. In a similar vein, RNA editing belongs certainly to the most disturbing case of post-transcriptional modifications.
Myriam Schaub and Walter Keller describe the various enzymes responsible for the A to I conversion, so central to the wobble hypothesis, but which occurs also in pre-mRNAs, viral RNAs, and double-stranded RNAs. In the next article, Michele Taylor Parker and Eugene Gerner discuss the influence of polyamines, small but abundant organic cations that are highly regulated metabolically, on RNA processing and gene expression. The first issue dedicated to RNA ends with two articles dealing with the behavior of mRNA molecules within eukaryotic cells. The first one describes the field, which I find particularly fascinating, of RNA mobility, its measurement and its visualization. In the cytoplasm, molecular motors closely associated with the cytoskeleton can carry mRNAs. Edouard Bertrand and collaborators show that in the absence of a clearly defined cytoskeleton equivalent, the organization of the nucleus is used to promote RNA transport. The second article by Jamal Tazi and coworkers describes all the control mechanisms and the intricacies of the factors involved in mRNA turnover and mRNA stability. The half-life of mRNAs can vary between a couple of minutes to more than a day. The new studies show that the sequence elements regulating mRNA stability are found throughout the message and are not localized solely at the cap structure or the poly(A) tail.

The second volume has a stronger chemical and structural bent. After the story of the phosphorothioates by Fritz Eckstein, Martin Egli describes the use of selenium, an atom closely related to sulfur, for solving the crystallographer’s nightmarish problem, the phasing of the diffracted intensities. The relationships between positively charged metal ions and the negatively charged RNA molecules possess some Freudian complexities: RNA molecules require metal ions for folding and often for function but several metal ions cleave and degrade RNA molecules. Christine Chow and her colleagues describe the cleavage specifically photoinduced by rhodium complexes at GoU wobble pairs or exposed guanines. It is now accepted that RNA architectures can be sufficiently intricate for moulding pockets and cavities specific enough to act as drug targets. Thomas Herrmann discusses the respective roles of the static and dynamic structures of the RNA target for the binding to the decoding site of aminoglycosides, a rich family of antibiotics for which there exists a great variety of chemical mimics. After the discovery of catalytic RNA molecules by Tom Cech [7] and Sidney Altman [8], RNA has been intimately connected with the origins of life or at least with early biological metabolism [9]. Vasant Jadhav and Michael Yarus present an overview of the coenzyme-RNA aptamers and coenzyme ribozymes which have been produced by the techniques of selection-amplification in vitro Darwinian evolution in the last couple of years. Around RNA aptamers a new emerging field is developing fast around their use as therapeutic and diagnostic tools [10–12]. Three articles follow on ribozymes. The first one, by David Lilley and coworkers describe the present knowledge of the so-called VS ribozyme found in the mitochondria of Neurospora crassa, the last small ribozyme waiting to be crystallized. Although the hammerhead ribozyme was first crystallized several years ago, its mechanism of action especially in the trans-cleaving form is far from being fully understood [13]. Robert Hornes and Georg Szcakiel show that the lengths of the helices formed between the ribozyme and its substrate play a decisive role in the cleavage kinetics. The last article on ribozymes discusses the very unique and fascinating twintrons which comprise a group I intron within another group I intron. Steinar Johansen and his colleagues describe two of them, one from the myxomycete Didymium iridis and the other one from the amoeboflagellate Naegleria. The next two articles approach, each in their own way, a related complexity of RNA molecules. The architecture of RNA molecules is dominated by helices maintained by the two complementary Watson-Crick pairs and, therefore, it is difficult to escape from alternative pairings. Jord Nagel and Cornelis Pleij describe what they call ‘self-induced switches’ where metastable structures switch to stable conformations with gain or loss of function following the presence of an additional structural element. In the following article, Chantal Ehresmann and her colleagues present a rather unique review of the role of loop-loop interactions, a very versatile dynamic functional motif, in RNA dimerization and oligomerization.

The second volume ends with three articles in the field of RNA bioinformatics. In the first one Nancy Bourassa and François Major present a specific example of the previous review, the assembly of the prohead of bacteriophage φ29 of Bacillus subtilis where RNA-RNA associations via loop-loop interactions play a crucial role. The next paper by Daniel Gautheret and coworkers describe a new method for searching in genomic sequences for novel selenoproteins by detecting conserved elements characteristic of selenocysteine inserting motifs in the 3’UTR of mRNAs. Finally, Neocles Leontis and associates evaluate the efficiency in the prediction of RNA motifs on the basis of sequence alignment performed with consideration of isostericity of non-Watson-Crick pairs. Examples are given which show how RNA motifs, like Russian dolls, present an inherent self-similarity property with smaller motifs embedded within larger ones, emphasizing the importance of geometric isostericity in local interactions. RNA architecture is now understood on the basis of two central design principles, modularity and hierarchy between organizational levels. Unifying principles are, thus, emerging since the notion of hierarchical organization of modularity has been uncovered recently in metabolic networks [14, 15]. Such design principles, characteristic of robust and error-tolerant scale-free networks [16], were first described in non-biological systems like the World Wide Web network [17]. The integration of sequences, structures, biochemical functions, regulatory roles, and metabolism of RNAs in cellular organization should lead in the near future to further unifying and explanatory principles of biological systems.
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References


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