Preface

For almost 50 years, our understanding of molecular processes was very much influenced by a statement formulated by Francis Crick, which is known as the "central dogma of molecular biology." According to this dogma, DNA is converted to an mRNA and the mRNA to a protein. Another way of stating this dogma is that one gene is converted to one mRNA and the mRNA to one protein with one function. The present day molecular biology relies basically on genomic data for creating new hypotheses, which allow the replacement of the term "descriptive science" by the much more attractive "discovery science." The discovery science has revolutionized biology and gave new tools for hypothesis-driven research, which concerns primarily, but not exclusively, nucleic acids.

The interest to apply RNA structural and functional characteristics in molecular biology and medicine began in the late 1980s, when catalytic RNAs and in vitro selection approaches were an exciting new frontier. Now, thirty years after those discoveries, we begin to understand the novel aspects of RNA biology. Although the pathways and molecular components involved in RNA-mediated gene regulation are being elucidated very rapidly, the chemical and mechanistic basis still has to be worked out. The understanding of molecular mechanisms, and the possibilities for employing these processes for therapeutic purposes, falls surely into the realm of chemical biology.

The causal relationship between sequence, structure, and function significantly affects the interaction of RNA molecules with proteins, metabolites, and other nucleic acids, making RNA a malleable and attractive molecule to drive programmable function. RNA molecules, which derive sophisticated behavior from an ability to adopt complex structures, can be generated from potentially all possible sequence combinations, leading to diverse secondary structures and functions. These structures can exist in the form of modular domains, which confer specific and unique functionality. RNA molecules have evolved to regulate gene expression in a wide variety of ways in cells and viruses. Despite that, we are only beginning to appreciate how much of known phenotypic variation can be explained by these novel classes of RNA regulators.

The recognition of the biological roles of small molecular weight RNAs has been one of the most significant discoveries in molecular biology. These RNA molecules influence the translation of messenger RNAs (mRNAs) in posttranscriptional manner that makes the regulation of RNAs even more complex.

Recent advances in RNA biology and nucleic acid engineering are inspiring the use of RNA molecules for the construction of different RNA tools. RNA has become a focus of investigations into novel therapeutic schemes. Oligonucleotide-based approaches depend on the Watson–Crick base pairing of oligonucleotides to their corresponding mRNA target. This leads to posttranscriptional gene silencing by mRNA cleavage or translational inhibition. Oligonucleotide-based therapies have great potential for the treatment of RNA virus infections and various diseases. They include antisense oligonucleotides and their derivatives such as peptide nucleic acids, locked nucleic acids and morpholinos oligonucleotides (ONs), RNAi, microRNA ribozymes, aptamers, and Spiegelmers. Beyond sequence conservation, a very important point is the fact that the RNA target must be accessible for oligonucleotide interaction. Although the effects of antisense RNAs on the corresponding sense RNAs have not been clearly established, a number of examples indicate that they may exert control at various levels of gene expression, such as transcription, mRNA processing, splicing, stability, transport, and translation.

Multiple challenges, such as optimization of selectivity, stability, delivery, and long-term safety, have to be addressed in order for RNA drugs to become a successful therapeutic tool. Not all RNA classes (e.g., ribozymes or RNA decoys) were so far successfully developed as drugs. The use of RNA-mediated interference (RNAi) for gene silencing has provided a powerful tool for loss-of-function studies in a variety of metazoans. siRNA-mediated gene silencing by degradation of target messenger RNA has been widely used for the functional characterization of genes. The secondary structure of mRNA target sites has been reported to strongly influence RNAi activity. Compared with the laborious, time-consuming, and very costly gene knockout models, siRNA provides an efficient, specific, and economic solution for inhibiting the expression of target genes. Efficient siRNA delivery is essential for the success of specific gene silencing and is therefore understandable that a number of different laboratories are currently working on the problem of siRNA delivery in living organisms. Because high doses of siRNAs do provoke an altered expression of many other genes, selection of an optimal condition could be very helpful to minimize potential side effects. The advantage of the system lies in the application of short RNAs, which can be synthesized relatively cheap and can evolve quickly, to regulate a large and complex protein synthesis.

In this volume, 10 papers out of 19 are dealing with various aspects of RNA interference. They cover basic issues of the technique and its application in biology and medicine. There are also three contributions on antisense RNA approaches, which show a high therapeutic potential.

It is becoming clear that microRNAs are essential regulators of many of the key pathways implicated in tumor pathogenesis. While adding another layer of complexity, the discovery of the role of miRNAs in tumorigenesis has revealed a new

category of therapeutic targets. As miRNA studies continue to be developed, novel therapeutic targets for different types of tumors will continue to emerge.

The discovery of regulatory RNAs has revolutionized the traditional concept of RNA function and gene regulation. The fact that the protein coding RNA portion represents less than 1.5% of the total transcriptional output and the rest represent noncoding RNA (ncRNA) implies that apart from *cis* regulatory DNA sequences, ncRNA could also perform much of the regulatory tasks of complex organisms. ncRNAs have been shown to control every level of the multilevel-regulated gene expression pathway, including gene silencing. Small ncRNAs are highly conserved at the sequence level and regulate transcriptional and posttranscriptional gene silencing through specific pairing with their target genes, whereas long ncRNAs are poorly conserved and regulate transcriptional silencing ranging from a single gene to an entire chromosome through diverse mechanisms not involving any base pair interactions with the target genes. In the book, we have also included three chapters on ncRNAs and their functions and therapeutic potential.

We hope that the book will be of interest for biochemists and life scientists and that it will stimulate their future research.

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