Preface

Nucleic Acids Meet Human Genetic Medicine

With this volume of the series RNA Technologies, we aim to cover current and important developments in RNA chemistry, RNA biology, and the application of RNA molecules in molecular medicine.

Cellular gene expression is based on several levels of information. First the sequence of the canonical adenine, cytosine, guanosine, and thymine bases in DNA encodes for the primary structures of proteins through their specific base triplet arrangements. The "Central Dogma of Molecular Biology" taught us that the DNA is transcribed into RNAs and the protein-coding messenger RNA genes are then translated into proteins by ribosomes. For its function the ribosomes are directly dependent upon noncoding RNAs such as ribosomal RNAs, tRNAs, and small nuclear RNA. It is now evident that RNA, in gene expression, functions far beyond the established roles of these RNAs, for example, in RNA splicing and editing, telomere maintenance, protein secretion, small-molecule sensing, and reaction catalysis. Thus, RNA molecules play a key role in several fundamental cellular processes, serving as a carrier of genetic information and, very importantly, also as its regulator.

In human eukaryotic cells only ca. 1.8% of the genomic DNA is transcribed into mRNAs, while the remaining 98.2% represents the so-called noncoding DNA sequences. As discovered over the last 20 years, a large amount of this noncoding DNA represents actually noncoding RNA. The important role of noncoding RNAs in cellular processes has recently become more and more apparent. How RNA achieves its large number of different functions with a limited assortment of four different building blocks is still a question of great interest, and the answer lies in deciphering the RNA structures at its different levels of complexity. More detailed knowledge about the structural and functional properties of ribonucleic acids, and how they are functioning in the cells, is still required before methods can be developed to use these regulators in solving the problems in molecular medicine. In this book, up-to-date studies are presented, which follow exactly this goal: to

understand the structures and functions of RNA molecules and to use this information for applications in cellular biology and molecular medicine.

Over 25 years ago, the central dogma of molecular biology was expanded with the discovery that in addition to proteins, ribonucleic acids can also exhibit enzymatic activities. These RNA enzymes (ribozymes) spurred intense studies into the structural basis of RNA catalysis. All naturally occurring ribozymes catalyze phosphodiester transfer or hydrolysis with exquisite substrate specificity.

Thus, RNA has received increasing interest as a target of chemotherapy and as chemotherapeutic agents to be applied in molecular medicine. The demonstration that synthetic oligonucleotides could be used to interfere with biological information transfer in the 1970s of the last century induced a great interest to a novel type of therapy. Oligomeric nucleic acid-based therapeutics can be subdivided into groups according to their target molecule: antisense oligonucleotides (ODN), ribozymes, microRNAs inhibitors, and short interfering RNAs. These oligonucleotides interact by Watson–Crick base pairing with cellular transcripts leading to their degradation or functional inhibition. First antisense therapies have reached the patients. However, a requirement for the effective application of antisense therapy is based on three fundamental issues, and they are stability, site-specific delivery, and no off-target effects. This is, of course, also true for the employment of the other RNA molecules, such as siRNAs, microRNAs, or different ribozymes. To overcome the stability problems of RNA molecules in the human serum and in the cells, efforts have been directed to chemically modify these ribonucleic acids in such a way that they would become resistant to cellular ribonucleases. But with these modifications one may also increase the unwanted side effects, so that the problems of stability have so far not been optimally solved. Very promising approaches with these goals in mind are also presented in this book.

In the cells oligonucleotides are known to modulate gene expression by binding to proteins as aptamers, and not only that, in addition, the physiological binding to transcription factors to reduce their capacity to mediate gene transcription has also been observed. Very interesting and promising are also antisense molecules that recruit RNase H or RISC factors to mediate RNA hydrolysis. RNA interference, for example, is best known for its various roles in posttranscriptional gene silencing in the cytoplasm.

In this volume the reviewers discuss the general aspects of structure and function of ribonucleic acids as indicated above. Very interesting are the results reported, because they show how new and very promising RNA regulators can be developed for the next generation of therapeutic agents directed at various types of diseases.

In the book, we collected chapters on general aspects of RNA, its stability, and chemical modification. Several reviews highlight recent progress in development and application of antisense technologies for RNA silencing. The therapeutic potential of ribozymes and DNAzymes is also extensively discussed. A current knowledge on microRNA pathways in human diseases is covered in several chapters and will help to round up the current knowledge of RNA technologies and as these technologies may be applied in the field of future molecular medicine.

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