Preface

The heart may respond to chronic and acute injury by hypertrophic growth and pathological remodeling. Cardiomyocyte hypertrophy is a dominant cellular response to all kinds of hemodynamic overload, inherited mutations in many structural and contractile proteins, and other factors and may be compensatory or maladaptive. In the latter case pathological remodeling may result from diverse molecular pathomechanisms which are still incompletely understood.

Small deviations in a mechanism controlling cardiac morphology and function may lead to enormous negative effects including loss of function and, in severe cases, even death. Despite great progress in understanding various aspects of heart development, cardiovascular diseases remain a major problem for medicine. Therefore, there is a need for new diagnostic and therapeutic strategies to detect, classify and cure heart diseases.

Ribonucleic acid (RNA) in its many facets of structure and function is more and more understood, and therefore it is possible to design and use RNAs as valuable tools in molecular biology and medicine. An understanding of the role of RNAs within the cell has changed dramatically in recent years (Fig. 1). Its status expanded with reports on catalytic RNAs (ribozymes) 25 years ago, of endogenous RNA interference 15 years later, and other noncoding RNA very recently. Today, it is obvious that RNAs are not merely the intermediary molecules between DNA and proteins, but that they can also be functional end products. Large stretches of genomic DNA do not contain protein-coding sequences and have, therefore, been considered as ‘junk’. However, a significant fraction of this noncoding DNA have actually been found to hold the information for some of these functional noncoding RNAs. Diverse eukaryotic organisms harbor a class of noncoding small RNAs which are thought to function as regulators of gene expression. Thus, RNAs can be the transmitters (mRNAs) of genetic information to the ribosome for proteins to be synthesized, and also the regulators in protein synthesis. The conclusion to be drawn is that RNA is much more than solely a messenger RNA, and therefore this class of molecules are truly renaissance molecules. Most of the noncoding DNA is occupied by various units of repeats, satellite sequences and transposons. These sequences have been sought to be epigenetic elements that control stability of gene expression programs, and organize heterochromatic domains at centromers and telomers. Their role appears to be mainly regulatory. 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.

RNA has become a focus of investigations into novel therapeutic schemes. Ribozymes, antisense RNAs, RNA decoys, aptamers, micro RNAs and small interfering (siRNAs) have been used to down regulate undesired gene expression (Fig. 2). Multiple challenges, such as optimization of selectivity, stability, delivery and long term safety, have to be addressed in order for RNA drugs to become successful therapeutic agents. Not all RNA classes (e.g., ribozymes or RNA decoys) have been so far successfully developed as drugs. The recognition of the biological roles of small molecular weight RNAs have been one of the most significant discoveries in molecular biology. These RNA molecules influence the translation of messenger RNAs (mRNAs) in post-transcriptional manner that makes the regulation of RNAs even more complex.

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 RNAs have been widely used in gene function characterizations. Compared with the laborious, time-consuming, and very costly gene knockout models, siRNA provides an efficient, specific and cheap solution for inhibiting expression of target genes. Efficient siRNA delivery is essential for the success of specific gene silencing. As the popularity of RNAi technology grows, so does the frustration it still causes for many researchers. Direct measurement at the mRNA level is always needed for direct verification that RNA interference is decreasing the amount of mRNA. Because high doses of siRNAs may provoke an altered expression of many other genes, selections of optimal conditions are essential to minimize potential side effects. The most informative experiments in understanding the specificity of a siRNA would consider acquiring global gene expression of relevant genes, which unfortunately is lacking in many siRNA studies. These small RNAs of about 15–49 nucleotides in length guide the RNA-induced silencing complex (RISC). The beauty of the system lies in the application of short RNAs, which can be synthesized at reasonable cost and can evolve quickly, to regulate a large and complex protein synthesis.
In several recent studies, microarray analyses were performed to determine whether miRNAs are deregulated in hyperthrophic and failing hearts. The results implicate that miRNAs function as negative regulators of cell growth or as regulators of prosurvival pathways such that their downregulation predisposes the heart to pathological remodeling. A major challenge for the future will be to identify the mRNA targets of RNAs that participate in cardiac remodeling and to understand the functions of their target mRNAs.

Finally, the recent application of advanced vector technologies developed initially in the gene therapy field has had an enormous impact on the efficacy by which RNAi and microRNAs can be employed for therapeutic purposes in vivo. These most recent developments have brought clinical translation of certain RNA-based therapies within reach.
RNA Technologies in Cardiovascular Medicine and Research
Erdmann (Deceased), V.A.; Poller, W.; Barciszewski, J. (Eds.)
2008, XIV, 358 p. 55 illus., Hardcover
ISBN: 978-3-540-78708-2