miRNAs in CVD and myocardial infarction

Over the last century, cardiovascular diseases (CVD) like myocardial infarction (MI) and stroke have overtaken infectious diseases as the leading cause of mortality worldwide. Researchers have put tremendous efforts into clinical and epidemiological studies, enabling us to unravel large parts of the etiology of the underlying risk factors leading to cardiovascular pathologies. These factors include ageing, arterial hypertension, diabetes, hyperlipidaemia, obesity and tobacco smoking, all of which result in atherosclerosis that becomes the main trigger for ischemic forms of CVD like MI. Despite some crucial revelations, CVD will likely remain the number one reason of death in the foreseeable future, while our current knowledge even predicts an exacerbation in the prevalence of CVD. Thus, in-depth investigations into key determining molecular and epigenetic mechanisms have been initiated, hopefully enabling us to discover novel and powerful markers of disease as well as potential therapies. Recent advances in the field have enabled us to unravel and functionally assess the role of non-coding RNAs (ncRNAs) in disease development and progression.

Insights into the transcriptomic regulation of different species were able to show that approximately 80% of our genome is getting transcribed. However, only 1–2% of this gets translated into protein, generating a large number of ncRNA transcripts. This ncRNA was long believed to be a sequencing artefact or simply non-functional 'junk DNA'. Over the past 10-15 years however, it has been indicated that ncRNA are key mediators and 'fine-tuners' in gene expression and epigenetic control, in particular in different stages of disease development and progression. We are still only scratching the surface of understanding the different forms and subclasses of ncRNAs, and the regulatory function they play in the homeostasis of an organism. These ncRNA subspecies include small nuclear and small nucleolar RNAs, microRNAs (miRNAs), Piwi-interacting RNAs, Y-RNAs and the extensive group of long-noncoding RNAs, which include long-intergenic-noncoding RNAs and natural antisense transcripts. Another interesting form of ncRNAs are circular RNA, which appear to be promising biomarkers due to their stable expression and extended protection from degradation within the circulation.

Currently, miRNAs appear as the most extensively studied and best characterized ncRNA subgroup. miRNAs are well-conserved and upon maturation in the cytoplasm 18-22 nucleotides short transcripts that can act as key post-transcriptional regulators of gene expression not only in humans, but also plants, nematodes, yeast, and other animals. By now, miRNAs have been identified to play major roles in almost every biological process via mediating the translation of target messenger RNAs (mRNAs) and thus their stability.

This present book entitled "*Key Leaders' Opinion on MicroRNA and Myocardial Infarction*" focuses mainly on the *in vivo* role of miRNAs in the pathogenesis of developing and existing myocardial disease. The therapeutic potential of targeting miRNAs and their contribution as biomarkers in CVD pathologies is thoroughly presented. Numerous preclinical experimental CVD models have indicated that either inhibition or induction/overexpression of a single miRNA can augment or diminish CVD development and/or progression.

miRNA modulation can be powerfully enforced by utilizing so called antimiRs or antagomiRs (synthetic antisense oligonucleotides) that bind and silence miRNA expression, or by using miRNA mimics or pre-miRNAs that act similarly to endogenous miRNAs. Human and animal efficacy data exists that implies the promising role antimiRs might play in disease management. Important features include the frequent conservation of target miRNAs across species and the small molecule size. Several candidate miRNA inhibitors have shown that they can silence their putative miRNA with convincing affinity and specificity. Intriguingly, until now no immunogenic or toxicity issues were reported in human Phase I and II clinical trials. One disadvantage of targeting miRNAs in CVD might be their ubiquitous expression throughout organs and different tissues of the human body. This favors local and cell type specific tools for miRNA modulator delivery, which would limit undesired off-target effects in organ systems in which anti-miRNAs can accumulate to a much higher extent than the targeted cardiovascular system. It will be interesting to see the results of the first miRNA-based therapy trials in CVD. Several candidates exist, with anti-miR-92a in patients with myocardial ischemia being the current frontrunner for a CVD-miRNA-therapy trial in humans. First-in-patient studies and subsequent data is here expected for 2019.

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