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EDITORIAL

Review focus on the role of microRNA in cardiovascular biology and disease

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See Reviews in this series by Dangwal *et al.*,[8] Zampetaki *et al.*,[9] Da Costa Martins and De Windt,[11] Tijsen *et al.*,[13] Shantikumar *et al.*,[14] McDonald *et al.*,[15] Schroen and Heymans,[16] and Jakob and Landmesser.[17] Original articles in this series are by Diehl *et al.*,[10] Han *et al.*,[12] Ruan *et al.*,[19] and van Mil *et al.*[20]

MicroRNAs (miRNAs; miR) are emerging therapeutic targets in a broad range of diseases, including cardiovascular disease. There are many programmes at the international level currently investigating the suitability of miRNA therapeutics for clinical purposes, and these new developments may potentially result in a novel armada of more powerful and mechanism-oriented therapeutics. It is now well accepted that miRNAs represent critical regulators of cardiovascular function.[1,2] Initial reports about the role of miRNAs in cardiovascular development[3] and disease[4] have stimulated tremendous interest, resulting in a substantial gain of knowledge about miRNAs in the cardiovascular system. This almost unprecedented speed of development can probably be explained by the direct translational impact of miRNA research: the suitability of miRNAs to serve as potential prognostic biomarkers[1,5] and as therapeutic targets[6,7] for cardiovascular disease is intriguing and justifies our initial excitement about non-coding RNAs. This review focus issue of *Cardiovascular Research* summarizes novel and exciting aspects of miRNA-based mechanisms, diagnostics, and therapeutic developments for cardiovascular diseases.

To start with, it is important to note that the fast pace of miRNA research has required the development of many new techniques and methods. Thus, the review article by Dangwal *et al.*[8] mainly focuses on techniques and methods in cardiovascular miRNA research. In essence, the authors describe new methods to screen for miRNA expression and to identify and validate miRNA targets. They also address advances in the manipulation of miRNA expression both *in vitro* and *in vivo*, a prerequisite for studies using miRNA-based therapeutics. Surprisingly, miRNAs also exist extracellularly, where they may serve as biomarkers for disease in the circulation and other bodily fluids. This aspect is introduced by Dangwal *et al.*[8] and in more detail by Zampetaki *et al.*[9] The latter group points out that most circulating miRNAs are probably derived from blood cells, and miRNA patterns in the circulation are therefore often highly correlated. Thus, miRNAs should not be studied in isolation but rather within the context of the overall miRNA networks, and the assessment of their biomarker potential requires high analytical standards. Another important aspect is the 'packaging' of circulating miRNAs, and thus, the original article of Diehl *et al.*[10] about microparticles as miRNA carriers provides new insights in this field.

In addition to technological advances and the utility of miRNAs as biomarkers, there are exciting new developments in the understanding of the molecular mechanisms of how miRNAs are involved in cardiovascular disease processes. The review of Da Costa Martins and De Windt[11] gives an update on the role of miRNAs and their respective targets in cardiac growth and outlines the delicate balance of protagonist and antagonist miRNAs within the context of cardiac hypertrophy. The original paper by Han *et al.*[12] shows novel data concerning miRNA-mediated regulation of the cardiomyocyte-relevant transcription factor GATA4 and pressure-induced cardiac hypertrophy. It is apparent that the non-cardiomyocyte fraction also plays an important role in cardiac function as well as disease; Tijsen *et al.*[13] review the role of miRNAs in non-cardiomyocytes, especially cardiac fibroblasts, endothelial cells, and immune cells in response to myocardial stress.

It is also of great interest how cardiovascular risk factors might affect miRNA signalling. Indeed, diabetes is one of the most important risk factors for the development of cardiovascular diseases, and miRNAs involved in diabetic-related cardiovascular disorders have received a great deal of attention, especially within the last 2 years. The review article of Shantikumar *et al.*[14] summarizes our current understanding on how miRNAs regulate insulin secretion and β-cell function and highlights differentially regulated miRNAs in diabetes during endothelial dysfunction, diabetic heart disease, and diabetic retinopathy. Another important aspect of miRNA function is the regulation of smooth muscle cells (SMCs). SMCs in the vessel wall contribute to vascular remodelling and activation of inflammatory cells. McDonald *et al.*[15] describe miRNAs involved in acute vascular injury and pulmonary vascular remodelling. The identification of key miRNAs in vascular SMCs may result in novel therapeutic strategies,

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i.e. for the treatment of pulmonary arterial hypertension. The review by Schroen and Heymans[16] highlights miRNAs involved in inflammatory processes during heart failure, atherosclerosis, obesity, and diabetes and emphasizes their pathophysiological role in the elderly.

Regenerative medicine is at the forefront of scientific interest in many organ systems. Many studies have shown that miRNAs are involved in such processes. For instance, miRNAs may also help to differentiate stem/progenitor cells into cardiovascular-specific cell types. Regenerative medicine holds great promise for future development of improved therapeutic strategies. Various stem and/or progenitor cells are currently being tested for their potential to repair damaged tissue in the cardiovascular system. This is addressed by the review of Jakob and Landmesser,[17] which focuses on miRNAs important for cardiomyogenesis, endogenous cardiovascular repair responses, and stem/progenitor differentiation. Among the most promising stem cells are induced pluripotency stem cells (iPSC). Nowadays, it is possible to reprogramme patient-derived differentiated cells (e.g. fibroblasts) to iPSC that gain the potential to differentiate to other cell types. Using a robotics-assisted functional miRNA screening system, a recent study identified miRNAs involved in iPSC formation.[18] The original article by Ruan *et al.*[19] reports that an miRNA from the miR-23/27/24 cluster, miR-23a, is down-regulated in endothelial cells upon tumour necrosis factor-α treatment and is involved in the regulation of endothelial cell apoptosis. In addition, van Mil *et al.*[20] show a new role of miR-214 in regulating angiogenesis and identify miR-214 as a potential important target for pro- or anti-angiogenic therapies.

In summary, this special review series covers broad aspects of cardiovascular miRNA research such as technological advances, new insight into molecular mechanisms, the utility of circulating miRNAs as disease biomarkers, and finally, the development of new miRNA-based therapeutic strategies. These articles highlight the current promising and exciting advances in the field of miRNAs that will hopefully stimulate further research into this important area.

Conflict of interest: T.T. has filed and licensed patents concerning the use of miRNAs as cardiovascular diagnostics and therapeutics.

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