miR-21: a central regulator of fibrosis not only in the broken heart

EXPERT’S PERSPECTIVE

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This editorial refers to an article by S. Roy et al. published in Cardiovascular Research in 2009. It is accompanied by a retrospective editorial by two of the authors of that original article, C.K. Sen and S. Roy, pp. 230–233, this issue, as part of this Spotlight on Landmark Papers in Cardiovascular Research.

Adverse remodelling of the heart associated with hypertension, valve disease, or myocardial infarction includes diverse functional, structural, and metabolic abnormalities, such as sarcomere disorganization, cardiomyocyte loss, and interstitial and perivascular fibrosis, ultimately leading to left ventricular hypertrophy, dilatation, and failure.1,2

MicroRNAs, endogenous single-stranded molecules consisting of ~22 non-coding nucleotides, are important regulators of cardiovascular (patho)physiology.2–4 The work by the group of C.K. Sen appearing in Cardiovascular Research early in 20095 was among the first (i) to recognize the importance of microRNAs for ischaemic injury of the heart, (ii) to characterize the expression of a specific microRNA, miR-21, in a time-dependent and cell-specific manner, and (iii) to define a specific target gene and pathophysiological response.

Reactive myocardial fibrosis is associated with reduced microvascular network and disruption of normal myocardial structures, and results from an excessive deposition of extracellular matrix by fibroblasts. While reactive fibrosis accompanying hypertrophy in response to pressure overload or late remodelling of the surviving myocardium after myocardial infarction is viewed as clearly maladaptive, early reparative fibrosis of the infarct area seems to be a necessary healing event, also preventing left ventricular rupture early after myocardial infarction. So-called myofibroblasts expressing features of smooth muscle differentiation play a key role in reparative fibrosis of the infarct area. In contrast with the detrimental effects of miR-21 up-regulation in fibroblasts in response to pressure overload, there is evidence that early after myocardial infarction, up-regulation of miR-21 may be protective. Overexpression of miR-21 via adenovirus that expresses miR-21 reduced myocardial infarct size and left ventricular dimensions.6 The lack of any obvious phenotype induced by overexpression of miR-21 in cardiomyocytes in vivo and in vitro supports the dominant role of fibroblasts for miR-21 effects and the minor importance of cardiomyocyte expression of miR-21.8

Sen et al. using an array system, screened for changes in microRNA expression after myocardial ischaemia-reperfusion injury and validated miR-21 as a consistently up-regulated microRNA. Expression of miR-21 was mainly confined to fibroblasts in the infarct area. In isolated cardiac fibroblasts, the phosphatase and tensin homologue (PTEN) was identified as a direct target of miR-21 regulating the expression of matrix metalloprotease-2 (MMP-2). A putatively miR-21-mediated decrease in PTEN expression in the infarct zone was associated with increased MMP-2 expression in the infarct area.5

In striking similarity to the work of Sen’s group, we showed that the up-regulation of miR-21 in the heart in response to pressure overload was mainly confined to enhanced expression in cardiac fibroblasts (published some months earlier, in 2008).8 While in this model PTEN did not appear to be modulated by miR-21, Sprouty1 was identified as a direct target of miR-21 regulating apoptosis of cardiac fibroblasts via ERK-MAP kinase signalling. IV injection of chemically modified antisense oligonucleotides directed against miR-21 (so-called antagomiR-21) in mice with left ventricular hypertrophy, induced by either transverse aortic constriction or isoproterenol-infusion, normalized changes in Sprouty1 expression and MAP kinase activation and reduced fibrosis.6 The role of miR-21 in organ fibrosis is not confined to the heart: miR-21 was highly up-regulated in bleomycin-induced lung fibrosis.

The opinions expressed in this article are not necessarily those of the Editors of Cardiovascular Research or of the European Society of Cardiology.

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as well as in the lungs of patients with idiopathic pulmonary fibrosis. miR-21 was primarily enriched in myofibroblasts in the fibrotic lungs, and miR-21 inhibition was able to prevent lung fibrosis in vivo. Likewise, increased miR-21 expression in colorectal cancer tissue was mainly found in fibroblasts surrounding the cancer cells. miR-21 was up-regulated by TGF-β, which in turn inhibited Smad7 (inhibitory Smad) and led to amplification of TGF-β signalling, finally resulting in a fibrotic response in human primary fibroblasts. Thus, miR-21 may play an important role in TGF-β-induced pro-fibrotic effects, possibly via promoting epithelial mesenchymal transition (for review see Kumarswamy et al.). Recently, miR-21 was also shown to be involved in TGF-β-induced endothelial-to-mesenchymal transition via a PTEN/Akt-dependent pathway.

During the last few years, a plethora of work has been published characterizing cell-specific effects of miR-21, not only in fibroblasts but also in myocytes, endothelial cells, and inflammatory cells (Figure 1, for review see refs12,14,15). We identified a novel miR-21-dependent mechanism related to the dysfunction of angiogenic progenitor cells in patients with coronary artery disease. Angiogenic progenitor cell dysfunction was rescued by miR-21 blockade, suggesting that interference with angiogenic processes may also contribute to the modulation of cardiac hypertrophy and fibrosis by miR-21.

In summary, the merit of Sen’s work was to open an early window to the cell-specific role of miR-21 in the heart. Nevertheless, further research is still needed to decipher in detail the regulation of miR-21 expression in cardiovascular (patho)physiology, the impact of miR-21 modulation on the complex pathophysiological processes, and the optimal time point for miR-21 modulation in various cardiovascular diseases (e.g. coronary artery disease and acute myocardial infarction vs. cardiac hypertrophy vs. heart failure).

References

Figure 1 Selected cell-specific actions of miR-21 in the heart and potential target genes. Spry1, sprouty homologue 1; Spry2, sprouty homologue 2; PTEN, phosphatase and tensin homologue; MMP2, matrix metalloproteinase 2; FasL, fas ligand; PDCD4, programmed cell death 4; RhoB, ras homologue gene family member B.