Editorial

miR-126: a potential new key player in hypoxia and reperfusion?

Sabina P. W. Guenther[1,2,3,4,5], Sonja Schrepfer[1,2,3,4]

[1]Transplant and Stem Cell Immunobiology Laboratory, Department of Surgery, University of California, San Francisco, CA, USA; [2]Transplant and Stem Cell Immunobiology Laboratory, University Heart Centre Hamburg, University of Hamburg, Cardiovascular Research, Hamburg, Germany; [3]Cardiovascular Research Center (CVRC), University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [4]German Centre for Cardiovascular Research (DZHK) e.V., University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [5]Department of Cardiac Surgery, University Hospital Munich, Ludwig-Maximilian-University, Munich, Germany

Correspondence to: Sonja Schrepfer, MD, PhD. Transplant and Stem Cell Immunobiology Laboratory, Department of Surgery, University of California San Francisco (UCSF), Medical Sciences S1207, 513 Parnassus Avenue, San Francisco, CA 94143-2205, USA. Email: sonja.schrepfer@ucsf.edu.

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It is well known that microRNAs (miRNAs) have recently emerged as multifaceted regulators of biological processes and thus of various diseases. miRNAs are small single-stranded non-coding RNAs that bind to their cognate messenger RNAs (mRNAs) via recognition of seed sequences, i.e., the 2nd–8th nucleotide of the miRNA. This binding can trigger mRNA degradation and translational repression leading to a decrease in the protein products encoded by the corresponding mRNA. In contrast to profound effects of conventional transcription factors, individual miRNAs are rather considered as nuancing regulators of particular mRNA expression. However, since a single miRNA may act on different mRNAs and vice versa single mRNAs can be regulated by various miRNAs and additionally since miRNAs may have multiple target sites within one mRNA, cumulating effects result and complex regulatory networks are created (1).

Besides regulating translational control, circulating miRNAs act as endocrine signalling molecules and may furthermore serve as diagnostic disease markers (2). Conversely, targeting miRNA pathways offers novel therapeutic options (1).

Cardiovascular diseases remain to be among the leading causes of morbidity and mortality worldwide and impose a relevant economic burden on the health care systems. Multiple recent studies suggested a relevant role of miRNAs in cardiovascular processes and diseases.

Initially, miR-126 was demonstrated to have significant impact on tumor development and metastasis. Amongst others, it can influence inflammation, proliferation and plays a role in tumor-angiogenesis (3,4). Specifically, it seems to serve as a tumor and metastasis suppressor (3,4). In colon cancer, its expression is significantly lower especially in highly metastatic colon cancer cells. It reduces cancer cell viability and migration as well as invasion via downregulation of CXCR4 expression (3). Comparable findings have also been reported for other malignant cell lines, for example in non-small cell lung cancer via Crk (5).

More recently, a growing body of scientific findings points out the role of miR-126 in cardiovascular diseases, paralleling the earlier findings in cancer research. Endothelial cells are essential for maintaining vascular integrity, play a major role in angiogenesis and in the response to ischemia or injury (6). Vascular remodelling can be both, beneficial with repair and adaption after injury and ischemia or deleterious as for example in atherogenesis. In this context, a single miRNA can regulate multiple processes and thus affect both, positive and negative vascular remodelling (7). Due to overlappings, therapeutic targeting of miRNAs may thus influence several mechanisms in remodelling and result in unexpected and unwanted additional effects (7).

The miR-126 gene is located within an intron on the epidermal growth factor-like-domain 7 (*EGFL7*) gene on chromosome 9 and gives rise to two mature miRNAs: miR-126-3p and miR-126-5p (6,7). miR-126 is highly expressed in the vascular endothelium and exerts distinct yet dichotomous effects in the embryonic, healthy adult and diseased adult vascular system (8). Opposing to the induction of angiogenetic signalling and promotion of endothelial cell

differentiation and maturation in embryonic vasculogenesis, it preserves vascular homeostasis and integrity via inhibition of angiogenesis and endothelial cell proliferation maintaining a quiescent phenotype in the mature state (6,8-10). Besides, it is a key regulator of inflammation, which is a major contributor to vascular pathology including endothelial dysfunction, remodelling and atherosclerosis, and has effects on cells of the hematopoietic system (9,11,12). Confirmed targets include VCAM1, SPRED1 and DLK1 (7). Interestingly, the blood flow pattern and thus intravascular shear stress seem to contribute to the different effects exerted by miR-126 on endothelial cells and the vascular system (12). In the context of vessel injury and also in hypoxia, miR-126 does have differential effects. Van Solingen *et al*. showed that antagomir silencing of miR-126 did not have any effect on the proliferation and migration of HUVECs *in vitro*. Likewise, in a hindlimb ischemia model in mice induced by electrocoagulation of the femoral artery 24 h after injection of antagomir-126, no differences in blood flow recovery were seen (6). However, quantitative analysis of capillaries in the calf muscle showed a significantly lower density of capillaries in mice treated with high-dose antagomir-126. Even though miR-126 is supposed to target VCAM1 and downregulation of miR-126 might result in increased leukocyte adherence, the latter findings suggest that while not directly or at least not rate-limitingly affecting arteriogenesis, miR-126 exhibits a distinct effect on the ischemia-induced angiogenic response. In line with these findings, silencing of miR-126 impaired endothelial cell outgrowth in aortic explant cultures. A suggested mechanism for promoting angiogenesis in this setting includes a reduced expression of repressors of VEGF signalling by overexpressed miR-126 (6).

In humans, miR-126-3p was significantly downregulated in patients with acute myocardial infarction and it was suggested that administration of miR-126 could rescue endothelial cell function whereas the authors did not state the exact time of blood analysis, i.e., before or after revascularization (2).

In another analysis, an altered expression of miRNAs in patients with chronic total coronary artery occlusion and insufficient collateral arteries was recently demonstrated, with a significantly elevated level of miR-126, miR-423-5p, miR-30d and miR-10b. Even though probably suitable as biomarkers, it remains to be elucidated, however, whether these miRNAs are upregulated due to direct effects on collateral artery development or whether they are part of other pathways that affect collateral vessel growth (13). Schober *et al*. demonstrated that miR-126-5p promotes endothelial proliferation and limits atherosclerosis by suppressing Dlk1 (12).

The recent *Genet Mol Res* article by Li *et al*. adds to the growing body of scientific findings the role of miR-126 in myocardial ischemia reperfusion injury. Revascularization is the gold standard for the treatment of myocardial infarction. Reviewing the current literature, Li *et al*. explain that while the exact underlying pathophysiology still needs to be elucidated injury resulting from reperfusion is a significant cause of cardiac cell death after ischemia and accounts for a relevant portion of the necrosis. Thus not only ischemia itself but also sudden blood flow restoration has a harmful effect on cell survival and apoptosis (14,15). In order to assess the role of miR-126 in reperfusion injury *in vitro*, miR-126 inhibitor and mimic were transfected into rat myocardial H9c2 cells and the cells were subjected to simulated ischemia-reperfusion injury afterwards. miR-126 as assessed by real-time PCR was significantly downregulated after ischemia-reperfusion. The miR-126 inhibitor reduced injury-induced myocardial cell apoptosis and caspase 3 protein expression. For the mimic contrary effects were observed. For *in vivo* analysis, female Wistar rats underwent lentivirus miR-126 mimic or inhibitor injection and 7 days later 30 min of myocardial ischemia induced by ligation of the left anterior descending coronary artery followed by 2 h of reperfusion. Infarction area size was significantly smaller in miR-126 inhibitor-injected animals and larger in mimic-injected animals in comparison to the control group, respectively (14). Obviously, miR-126 affects regulation of myocardial cell apoptosis in ischemia-reperfusion injury.

Contrastingly, in other investigations hypoxia itself resulted in a profound up-regulation of endothelial miR-126 (8). Furthermore, miR-126 upregulation was shown to have the capability of re-inducing angiogenesis, promoting re-endothelialization and of re-activating endothelial (progenitor) cells whilst inhibiting apoptosis and thus to contribute to healing mechanisms and to exhibit vasculoprotective effects (8). Thus, there obviously are substantial differences in the regulatory effects during hypoxia and reperfusion as well as varying effects on the vascular system and cardiomyocytes including the involved downstream targets and mediating components. A major contributing factor in this setting might be actual blood flow and thus shear stress within the vessel. Additionally, a key role of heat shock protein 70 in influencing myocardial cell apoptosis has been suggested (14,16).

As explained earlier, miRNAs have been considered as sensitive diagnostic and prognostic biomarkers. Considering its pathophysiological implications, miR-126 may have a potential value in diagnosing not only myocardial ischemia, acute myocardial infarction, but also in stroke and other acute or chronic ischemic diseases (2,8). Additionally, the abovementioned findings underline the powerful therapeutic implications of targeting miRNAs in cardiovascular diseases. Further elucidating both conditions, hypoxia and reperfusion, could thus substantially contribute to the development of novel therapeutic agents.

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Footnote

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