MicroRNA-99a
A New Kid on the Block for Cardioprotection
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Recent evidence has suggested that reactive oxygen species (ROS) are continuously formed in myocardium as a byproduct of mitochondrial oxidative phosphorylation, and are also produced by several enzymes such as NADPH oxidases, xanthine oxidase, and uncoupled endothelial NO synthase. In normal cardiovascular physiology, ROS act as essential signaling molecules that modulate the activity of many bioactive molecules including protein kinases, phosphatases, transcription factors, and cytoskeletal proteins. However, excessive and aberrant production of ROS during pathological oxidative stress can cause cellular dysfunction and death by inducing irreversible damage of organelles and macromolecules such as lipids, proteins, and DNA. An increasing body of evidence has suggested that oxidative stress is crucially involved in the pathogenesis and progression of a wide range of cardiovascular diseases. For example, it was reported that the myocardial ROS levels were elevated in animal models of ischemia-reperfusion injury and heart failure, and that a number of antioxidant strategies using ROS scavengers provided cardioprotection in these animal models. However, clinical interventions by treatment with antioxidants have proven to be ineffective or even harmful for patients with cardiovascular diseases. Rather than simple antioxidant strategies, a strategy to reduce pathological oxidative stress without altering physiological ROS signaling will put forward the translation of ROS modulation into the clinic.

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Recently, micro RNAs (miRNAs) have attracted much attention due to their important roles in almost all biological processes, and have emerged as promising candidates as therapeutics for a wide variety of diseases. In this issue, Jing and colleagues have provided evidence that miR-99a targets for tumor suppression, and have emerged as promising candidates as therapeutics for a wide variety of diseases. Jing and colleagues demonstrated that transfecting H9c2 cells with miR-99a mimic prevented LPS-induced apoptotic cell death, which was associated with a decrease in ROS generation. Conversely, transfection with miR-99a inhibitor enhanced LPS-induced ROS generation and cell death. Mechanistically, activation of Notch signaling might participate in cardioprotection induced by miR-99a, because miR-99a mimic induced activation of Notch 1 and Notch 2 and increased JAG1 expression, while miR-99a inhibitor had the opposite effects. Notch proteins are transmembrane receptors that are highly conserved through evolution, and play a critical role in cardiovascular development and homeostasis. Several pathways are known to mediate the cytoprotective effect of the Notch signaling, such as the activation of Akt/PKB signaling, inhibition of p53 and JNK signaling, and up-regulation of Bcl-2, ubiquitination, and degradation of X-linked inhibitor of apoptosis protein (XIAP).

However, it remains unsolved whether Notch signaling works as a key pathway downstream of miR-99a, or just an innocent bystander. Although most reports supported the anti-apoptotic effect of Notch signaling, some provided the opposite results supporting the pro-apoptotic effect of Notch signaling. It might be context-dependent, and different according to the cell types and stimulations, whether Notch signaling contributes to anti-apoptosis or pro-apoptosis. Pharmacological or genetic inactivation of Notch signaling will provide insights into the role of Notch signaling in miR-99a-mediated cardioprotection. Furthermore, direct target genes of miR-99a for cardioprotection have not been identified, although the miR-99a targets for tumor suppression, DNA damage response, and wound healing have been reported. Searching for direct target genes of miR-99a in cardiomyocytes will advance our understanding of the mechanisms whereby miR-99a protects cardiomyocytes from oxidative injury. Recent studies demonstrated that overexpression of miR-99a in murine hearts using a lentiviral vector attenuated left ventricular remodeling after myocardial infarction, and cardiac hypertrophy induced by transverse aortic constriction. Further studies are necessary to determine whether overexpression of miR-99a also attenuates LPS-induced myocardial oxidative injury and dysfunction without altering physiological ROS signaling in a multiple mechanisms including enhanced oxidative stress.

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Received for publication March 29, 2017. Accepted March 31, 2017.
Released in advance online on J-STAGE May 23, 2017.
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Figure. MiR-99a-mediated cardioprotection against LPS-induced oxidative injury. Overexpression of miR-99a suppressed LPS-induced ROS production and apoptotic cell death in rat cardiomyocyte H9c2 cells, which was associated with activation of Notch signaling and up-regulation of anti-apoptotic protein Bcl-2. It remains unsolved whether activation of Notch signaling is critically involved in miR-99a-mediated cardioprotection, and which direct targets of miR-99a are responsible for inhibition of ROS generation, activation of Notch signaling, and up-regulation of Bcl-2.

A number of miRNAs have been identified that are expressed in cardiac tissue and thus likely to play a key role in cardiac physiology and pathophysiology. These include miR-1, miR-21, miR-23a, miR-25, miR-133, miR-145, miR-199a, miR-208, miR-214, miR-378, miR-494, and miR-574-3p. For example, miR-21 mediated anti-apoptotic effects of Akt by direct suppression of mRNA expression of Fas ligand (Fasl), and transgenic overexpression of miR-21 reduced infarct size in a murine model of ischemia/reperfusion.(32) In addition, miR-214 protected the murine hearts against ischemia/reperfusion injury by direct suppression of mRNA expression of sodium/calcium exchanger 1 (SlcBa1), a key regulator of Ca⁺⁺ influx.(33) Conversely, miR-25 suppressed mRNA expression of sarcoplasmic reticulum Ca⁺⁺ uptake pump (Ap2α2), and inhibition of miR-25 by injection of antisense oligonucleotide (antagomiR) improved cardiac function and survival in a murine model of heart failure induced by transverse aortic constriction.(34) The study of Jing and colleagues(35) provides promising, albeit not definitive, evidence that miR-99a joins the ranks of “cardioprotective miRNAs”. Further studies are required to explore the more precise mechanism and function of miR-99a-mediated cardioprotection, and ultimately, to develop miR-99a-based therapeutics against oxidative injury in cardiovascular diseases.

**Disclosure**

None.


