Mir-25 is a potential treatment target for myocardial ischemic-reperfusion injury

Shang-Feng Yang[a,d], Po-Hsun Huang[b,c,d,e,*]

[a]Division of Nephrology, Department of Medicine, Cheng Hsin General Hospital, Taipei, Taiwan, ROC; [b]Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [c]Department of Critical Care Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [d]Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan, ROC; [e]Cardiovascular Research Center, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Ischemic heart disease remains a leading cause of death worldwide. Because of a limited ability of cardiomyocytes to proliferate, the heart undergoes a pathologic remodeling after injury and contributes to heart failure and death in the long term.[1] In acute myocardial infarction, ischemic tissue releases danger-associated pattern molecules (DAMPs) and induces an intense inflammatory response via activation of toll-like receptor. Although early reperfusion is the mainstay therapy for acute myocardial infarction, it is well known that reperfusion also induces deleterious effects on viable tissues, including massive leukocytes recruitment, complement activation, generation of reactive oxygen species, and nitrosative stress.[2] Strategies to prevent degeneration of a heart from ischemic-reperfusion injury (IRI) are clinically relevant, and high mobility group box 1 (HMGB1) is one of the therapeutic targets that is under active research.

HMGB1 is an evolutionary conserved chromatin-binding factor that regulates transcription, DNA replication and repair, and nucleosome assembly.[3] In addition to its nuclear role, HMGB1 also acts as DAMPs that can elicit both harmful and beneficial responses after tissue injury.[4] HMGB1 can be passively released from damaged cells or actively secreted by immune cells. HMGB1 has three conserved cysteines that are susceptible to oxidation. The biologic activity of exogenous HMGB1 depends on the protein redox state and several receptors including the receptor for advanced glycation end products (RAGE), Toll-like receptor 2 and 4 (TLR2-4), and C-X-C-chemokine receptor 4 (CXCR4).[5] Thus, the redox status of the environment decides the activity and function of HMGB1.

Increased circulating and myocardial HMGB1 levels have been demonstrated in experimental models of IRI.[6] Circulating HMGB1 is released from necrotic cardiomyocytes and secreted by infiltrating inflammatory cell.[6] Besides, upregulation of HMGB1 has also been shown in neonatal murine cardiomyocytes exposed to hypoxia and reoxygenation.[6] Increased myocardial HMGB1 occurs early in the IRI and results in the activation of proinflammatory pathways and enhanced myocardial injury.[7] Therefore, manipulation of HMGB1 may be a novel therapeutic strategy in myocardial IRI.

In this article, Liu et al[8] have demonstrated a protective role of miR-25 in myocardial IRI–induced damage by targeting HMGB1. The authors used a rat myocardial IRI model by conducting a temporary ligation of the left anterior descending coronary artery for 45 minutes. The hearts were then harvested after a different reperfusion period of 2, 4, or 6 hours. The authors demonstrated a time-dependent downregulation of miR-25 and upregulation of HMGB1 in the myocardium following different reperfusion durations.

To evaluate the role of miR-25 during myocardial IRI, miR-25 agomir or negative control was injected intravenously 48 hours before IRI was induced in the experimental rats. After a 2-hour reperfusion, the miR-25 agomir treatment group had attenuated myocardial injury and inflammation compared with the control group, as indicated by reduced serum myocardial enzymes (creatine kinase-MB [CK-MB], lactic dehydrogenase [LDH]) and inflammatory cytokines (tumor necrosis factor-α [TNF-α], interleukin-1β [IL-1β]) levels. The percentage of infarct areas and the number of apoptotic cells in the heart were also significantly decreased in the miR-25 agomir treatment group. Moreover, IRI-induced increase in myocardial HMGB1 expression was reduced by miR-25 agomir administration, indicating that miR-25 agomir–mediated alleviation of myocardial IRI may be associated with HMGB1 downregulation.

To determine the role of HMGB1 in the process of mir-25–mediated cardioprotective effect, Lentivirus-mediated short hairpin RNA (LV-shRNA) interference targeting HMGB1 or negative control was injected 48 hours before IRI event. Compared with the negative control, serum markers of myocardial injury and inflammation and the number of apoptotic cells were reduced in the LV-sh HMGB1 treatment group. Therefore, the myocardial protective effects, including decreased myocardial apoptosis and inflammation, of miR-25 may, in part, be mediated by downregulation of HMGB1 expression in the myocardium.

MicroRNAs (miRNA) are a class of small noncoding RNAs that function in RNA silencing and posttranscriptional regulation of gene expression. MiR-25 is one of the members in the miR-106b-25 cluster that is highly conserved in vertebrates.[9] Under physiological conditions, miR-25 participates in the regulation of developmental events and the target mRNAs are involved in the cellular response to DNA damage, cell cycle regulation, cell proliferation, migration, and differentiation.[10] Under pathophysiological conditions, miR-25 is a well-known

*Address correspondence. Dr. Po-Hsun Huang, Department of Critical Care Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: huangbsvgh@gmail.com (P.-H. Huang).

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oncogenic miRNA and has been shown to involve in various cardiovascular disease conditions.[11]

In a previous study, Lin et al demonstrate a direct interaction between miR-25 and HMGB1 in H9c2 cells subjected to hypoxia/reoxygenation (H/R).[12] They also provide evidence that miR-25 protects H9c2 cells from H/R-induced fibrosis and apoptosis, at least partly by suppressing HMGB1 expression and by downregulation of the TGF-β1/Smad3 signaling pathway.[12] In the current study, the authors took a step further and proved that miR-25 administration before myocardial ischemia may be a strategy to ameliorate myocardial IRI. This result was consistent with previous reports, although the Bcl-2-like protein 11 gene was considered as the target of miR-25.[13]

Some other studies showed similar effects of cardiac protection when HMGB1 was blocked before IRI.[6] Conversely, blocking HMBG1 in the postischemic phase and before reperfusion caused an enlargement of the infarct size and increased inflammation.[14] Transforming growth factor-β (TGF-β) exerts anti-inflammatory actions and promotes fibroblast conversion to myofibroblast during postinfarction cardiac remodeling.[15] Whether targeting the miR-25/HMGB1/TGF-β/Smad3 signaling pathway in the later stage of myocardial IRI will prevent pathological cardiac remodeling also worth further investigation.

In conclusion, this study by Liu et al[8] demonstrated the protective effect of miR-25 on myocardial IRI, partly explained by lowering HMGB1 expression. Besides, pretreatment with miR-25 agomir significantly decreases myocardial inflammation, infarction size, and cardiomyocyte apoptosis after IRI. Treatment targeting the miR-25/HMGB1/TGF-β/Smad3 signaling pathway may be a future direction of preventing myocardial IRI or managing postinfarction remodeling. More studies are needed to confirm the findings. Besides, further studies focusing on the off-target effects and potential toxicities with the treatment of miR-25 agomir are also required before any proof-of-concept clinical trial can be conducted.

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