Editorial

Association of miR-223 expression with myocardial ischemia/reperfusion injury: new insight for the role of miR-223 in inflammatory response

Lijun Wang, Junjie Xiao

Cardiac Regeneration and Ageing Lab, Institute of Cardiovascular Sciences, School of Life Science, Shanghai University, Shanghai 200444, China

Correspondence to: Prof. Junjie Xiao. Cardiac Regeneration and Ageing Lab, Institute of Cardiovascular Sciences, School of Life Science, Shanghai University, 333 Nan Chen Road, Shanghai 200444, China. Email: junjiexiao@shu.edu.cn.

Comment on: Oerlemans MI, van Mil A, Liu J, *et al.* Inhibition of miR-223 reduces inflammation but not adverse cardiac remodelling after myocardial ischemia-reperfusion *in vivo*. Non-coding RNA Investig 2018;2:15.

Received: 02 April 2018; Accepted: 12 April 2018; Published: 20 April 2018.

doi: 10.21037/ncri.2018.04.07

View this article at: http://dx.doi.org/10.21037/ncri.2018.04.07

Early reperfusion strategy is the most effective therapy to improve survival rates in patients suffering acute myocardial infarction (1). However, reperfusion therapy always results in myocardial ischemia reperfusion injury (I/RI) and patients are at risk of developing heart failure (2). Cardiac remodeling is a progression which is linked to heart failure and is associated with poor prognosis clinically. The initial infarction size and sufficiency of cardiac repair play critical roles in determining the extent of post infarction remodeling (3). Cardiac repair is initiated by the inflammatory phase, consisting of intense sterile inflammation and recruitment of immune cells. And then shifted into the reparative and proliferation phase resulting in wound healing (4). Extensive research evidences have suggested that prolonged or aggravated the inflammation phase could lead to worse remodeling and cardiac dysfunction (5). Therefore, several clinical trials aim at inhibition of early inflammatory response to protect ischemia myocardium have processed (6,7). Unfortunately, due to the complexity of the clinical context and the close link between inflammation and repair, targeting the inflammation phase has not yet achieved effective therapy (8). Understanding of inhibitory factors involved in the infarcted heart is needed to develop novel therapeutic strategies.

In a recent paper published in *Non-coding RNA investigation*, Martinus and colleagues have reported the role microRNA (miRNA, miR)-223 in the inflammatory phase after cardiac ischemia and demonstrated the effect of miR-223 inhibition on inflammation and cardiac remodeling in a mouse model of myocardial I/RI (9). MiRNAs are a class of highly conserved small non-coding RNAs that regulate gene expression by base pairing to target mRNAs (10). In the progress of cardiovascular diseases, chronic immune activation and aberrant microRNA expression are often present (11). MiR-223 was first identified in myeloid cells in the bone marrow (12). MiR-223 is highly conserved and preferentially expressed in the hematopoietic system. In progenitor cells, miR-223 triggers myeloid differentiation to maintain granulocyte function (13). MiR-223 has been reported to have a prominent role in monocyte/macrophage differentiation and granulocytic differentiation as well as different types of cancers (14,15). In type II diabetes and from patients with left ventricular dysfunction, overexpression of miR-223 in cardiomyocytes increases basal glucose uptake through positively regulating total cellular Glu4 protein levels (16). During the development of pathological cardiac hypertrophy and heart failure in mice, miR-223 acts as a positive regulator by targeting ARC (17). As to ischemia injury, a previous study suggests that miR-223 is increased in hepatic ischemia/reperfusion injury in mice (18).

To study the role of miRNAs in cardiac repair after myocardial infarction, Martinus *et al.* performed a microarray on miRNAs after cardiac I/RI and discovered the expression level of miR-223 was elevated during the early inflammatory phase. RNA *in situ* hybridization demonstrates that miR-223 highly expressed in cardiomyocytes after I/RI. This is also in accordance with previous investigation

that miR-223 is associated with the development of cardiac disease (17). The authors also show that inhibition of miR-223 suppressed the early immune cell infiltration. However, further detection about the left ventricular function by magnetic resonance imaging demonstrates that inhibition of miR-223 does not influence adverse remodeling after myocardial I/RI *in vivo*. Taken together, these results have promising implications for the field of the function of miRNAs in immune cell and inflammation. The concept of targeting the inflammatory response in patients with myocardial infarction has been raised for decades. Unfortunately, in clinical and preclinical studies, several trails have produced disappointing results. Martinus and colleagues show the important role of miR-223 in the early inflammatory phase after myocardial I/RI, although long-term benefits are not detected.

During the early inflammatory reaction, cardiomyocytes, immune cells, vascular cells and fibroblasts have been implicated as cellular effectors. Once ischemia impairs happened, necrotic cardiomyocytes is the main stimulus of post infarction inflammatory response (7,19,20). It has been reported that overexpression circular RNA HRCR, the endogenous sponge of miR-223, inhibited cardiomyocytes hypertrophy induced by isoproterenol (ISO) treatment and attenuated cardiac hypertrophy in mice (17). The opposite effects of inhibition miR-223 on cardiomyocytes and immune cells would lead to the modulation much more complicated. Thus, targeting miR-223 may action on different cell types and therefore modulate several cellular responses.

Importantly, it should be noted that the distinct pathological process among the infarct, border and remote region of myocardium making the spatial location of the therapeutic intervention essential (7). In addition, the reparative phase is highly dynamic and dependent on the infarct size, cellular environment as well as individual differences (19). Consequently, the temporal and spatial roles of miR-223 are critical determinants of the effectiveness of the treatment. To illustrate this issue, several important questions relevance to miR-223 should be addressed in the future studies. It would be critical to take further investigation on the detailed mechanism of miR-223 underlying the time course and topographical characteristics of cardiac repair responses. In conclusion, the studies on miR-223 not only helps to understanding how miR-223 are associated with myocardial I/RI, but also offers an additional opportunity for myocardial infarction therapy.

Acknowledgments

Funding: This work was supported by the grants from National Natural Science Foundation of China (No. 81722008, 91639101 and 81570362 to J Xiao), Innovation Program of Shanghai Municipal Education Commission (2017-01-07-00-09-E00042 to J Xiao), the grant from Science and Technology Commission of Shanghai Municipality (17010500100 to J Xiao), the development fund for Shanghai talents (T. 39-0112-17-201 to J Xiao).

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Non-coding RNA Investigation*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ncri.2018.04.07). JX serves as Editor-in-Chief of *Non-coding RNA Investigation*. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Parikh NI, Gona P, Larson MG, et al. Long-term trends in myocardial infarction incidence and case fatality in the National Heart, Lung, and Blood Institute's Framingham Heart study. Circulation 2009;119:1203-10.
2. Oerlemans MI, Koudstaal S, Chamuleau SA, et al. Targeting cell death in the reperfused heart: pharmacological approaches for cardioprotection. Int J Cardiol 2013;165:410-22.

3. Frangogiannis NG. The immune system and cardiac repair. Pharmacol Res 2008;58:88-111.
4. Nahrendorf M, Pittet MJ, Swirski FK. Monocytes: protagonists of infarct inflammation and repair after myocardial infarction. Circulation 2010;121:2437-45.
5. Kain V, Prabhu SD, Halade GV. Inflammation revisited: inflammation versus resolution of inflammation following myocardial infarction. Basic Res Cardiol 2014;109:444.
6. Seropian IM, Toldo S, Van Tassell BW, et al. Anti-inflammatory strategies for ventricular remodeling following ST-segment elevation acute myocardial infarction. J Am Coll Cardiol 2014;63:1593-603.
7. Saxena A, Russo I, Frangogiannis NG. Inflammation as a therapeutic target in myocardial infarction: learning from past failures to meet future challenges. Transl Res 2016;167:152-66.
8. Frangogiannis NG. Targeting the inflammatory response in healing myocardial infarcts. Curr Med Chem 2006;13:1877-93.
9. Oerlemans MI, van Mil A, Liu J, et al. Inhibition of miR-223 reduces inflammation but not adverse cardiac remodelling after myocardial ischemia-reperfusion in vivo. Non-coding RNA Investig 2018;2:15.
10. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 2004;116:281-97.
11. Self-Fordham JB, Naqvi AR, Uttamani JR, et al. MicroRNA: Dynamic Regulators of Macrophage Polarization and Plasticity. Front Immunol 2017;8:1062.
12. Chen CZ, Li L, Lodish HF, et al. MicroRNAs modulate hematopoietic lineage differentiation. Science 2004;303:83-6.
13. O'Connell RM, Zhao JL, Rao DS. MicroRNA function in myeloid biology. Blood 2011;118:2960-9.
14. Gao Y, Lin L, Li T, et al. The role of miRNA-223 in cancer: Function, diagnosis and therapy. Gene 2017;616:1-7.
15. Johnnidis JB, Harris MH, Wheeler RT, et al. Regulation of progenitor cell proliferation and granulocyte function by microRNA-223. Nature 2008;451:1125-9.
16. 16. Lu H, Buchan RJ, Cook SA. MicroRNA-223 regulates Glut4 expression and cardiomyocyte glucose metabolism. Cardiovasc Res 2010;86:410-20.
17. Wang K, Long B, Liu F, et al. A circular RNA protects the heart from pathological hypertrophy and heart failure by targeting miR-223. Eur Heart J 2016;37:2602-11.
18. Yu CH, Xu CF, Li YM. Association of MicroRNA-223 expression with hepatic ischemia/reperfusion injury in mice. Dig Dis Sci 2009;54:2362-6.
19. Frangogiannis NG. Regulation of the inflammatory response in cardiac repair. Circ Res 2012;110:159-73.
20. Prabhu SD, Frangogiannis NG. The Biological Basis for Cardiac Repair After Myocardial Infarction: From Inflammation to Fibrosis. Circ Res 2016;119:91-112.

doi: 10.21037/ncri.2018.04.07
Cite this article as: Wang L, Xiao J. Association of miR-223 expression with myocardial ischemia/reperfusion injury: new insight for the role of miR-223 in inflammatory response. Non-coding RNA Investig 2018;2:18.

