Korean Circ J. 2020 Mar;50(3):264-266
https://doi.org/10.4070/kcj.2019.0413
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Editorial

A New Member of Myocardial Ischemia-Reperfusion (MI/R) Associated miRNAs, miR-484: Its Potential Cardiac Protection Role

Heeyoung Seok, PhD

Division of Life Sciences, College of Life Sciences and Biotechnology, Korea University, Seoul, Korea

▸ See the article "MiR-484 Protects Rat Myocardial Cells from Ischemia-Reperfusion Injury by Inhibiting Caspase-3 and Caspase-9 during Apoptosis" in volume 50 on page 250.

Received: Dec 19, 2019
Accepted: Dec 27, 2019

Correspondence to
Heeyoung Seok, PhD
Division of Life Sciences, College of Life Sciences and Biotechnology, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 02841, Korea.
E-mail: hyseok1@korea.ac.kr

ORCID iDs
Heeyoung Seok
https://orcid.org/0000-0003-2699-9935

Funding
This work was supported by the grant from National Research Foundation of Korea funded by the Ministry of Education (NRF-2017R1D1A1B03030852) to H.S.

Conflict of Interest
The author has no financial conflicts of interest.

The contents of the report are the author's own views and do not necessarily reflect the views of the *Korean Circulation Journal*.

Heart diseases are the leading causes to death in the world. Myocardial ischemia is one of them, often occurred through blocking a coronary artery to restrict the oxygen supply to the myocardium resulting in acute myocardial damages, characterized by cardiomyocyte death, vascular leakage and interstitial edema.[1] Thanks to the recent therapeutic improvement to rescue a constricted artery by removing clogs, however, this nevertheless reintroduces oxygen to the ischemic region, resulting in the increased oxygen concentration to generate post-ischemic damage. This complex myocardial remodeling processes are mainly led by active inflammatory pathway, subsequently turning on reactive oxygen signaling to result in the expansion of the infarct size, fibrosis, ventricular dilation and eventually heart failure.[2] This is so-called "double-edged sword" and we always face unmet needs for further investigations of underlying mechanisms to overcome both acute and long-term complications, given on to the death in myocardial ischemia-reperfusion (MI/R).

During MI/R, transforming growth factor (TGF)-β signaling pathway has been considered as one of the master pathways to regulate MI/R. It governs remodeling events encompassing myocardial apoptosis, fibrosis, cardiac hypertrophy and inflammation. TGF-β pathway propagates their signals from activation of cell surface receptors to down-stream mediators via phosphorylation. As a downstream executor, Smad family has been identified and expanded as seven members-positive factors (alternatively known as canonical members; Smad2, Smad3, Smad1 and Smad5) and inhibitory factors (alternatively known as non-canonical members; Smad6 and Smad7) downstream factors in this pathway. While positive Smad members promote TGF-β mediated cellular apoptosis, fibrosis, and inflammation, inhibitory Smad repressed these responses, highlighted as attracting candidates for cardiac protection agents against MI/R.[3] Further reports regarding dual roles of Smad7 as either pro-inflammatory and anti-inflammatory factor,[4] together with emerging functions of microRNAs (miRNAs), small non-coding RNAs to regulate hundreds of target sets post-transcriptionally by minimum 6-mer seed mediated base-pairing,[3] initiated to expand TGF-β pathway further.

Interestingly, certain set of miRNAs, such as miR-1, miR-15, miR-133, miR-144, miR-21, miR-24, miR-29, miR-94a, miR-101, miR-126, miR-214, miR-451 and miR-494 have been

appreciated for their dysregulated expression level during MI/R.[5] These observations led researchers to define MI/R associated miRNAs for better understanding pathogenesis with translational applications such as developing diagnostic markers, supported by previous observation that miRNA's expressional signature can define certain cardiovascular diseases.[6] More miRNAs have been listed in MI/R model and miR-484 is one of them showing its dysregulation in human ischemic heart samples,[5] which suggests its potential function in MI/R model. Subsequently, there have been reports about those miRNAs such as miR-24 and miR-21 that post-transcriptionally regulate Smad members,[3] further expanding TGF-β mediated MI/R remodeling processes. Now, we are ready to add miR-484 in the TGF-β pathway as a regulator for Smad7 in MI/R.[7]

What we have been known about miR-484 are quite interesting. It has been initially profiled in the human ischemic heart failure patient samples.[5] Later, miR-484 was reported to regulate mitochondrial fission protein, Fis1, as its direct target and Foxo3a was observed as its trans-activator in MI/R.[8] Furthermore, Liu et al.[7] investigated how miR-484 ameliorated MI/R induced cellular death and inflammatory signaling. Particularly, Liu et al.[7] claimed that miR-484 expression is attenuated under MI/R, mirroring human ischemic patients' profiling pattern[5] and defined Smad7 as its direct target, to expand its experimentally validated target repertoire. Simultaneously, their study also provided an additional evidence to support dual functions of Smad7 in the TGF-β signaling pathway in MI/R.[4]

MicroRNAs are very promising candidates for the therapeutic application in cardiovascular diseases.[9,10] Indeed, miRNAs have been shown their tight controls for pathophysiology of cardiovascular diseases, including myocardial infarction. Specific expression patterns of miRNAs in MI/R model have been continuously reported and their mechanisms underlying MI/R have been kept updated.[1)2)8)11)] These could be valuable resources for diagnosis and prevention/intervention for myocardial infarction. For example, human miR-199a-3p has been shown its uncontrolled cardiac repair activity against MI/R in the pig model, more human relevant large animal model[11] and it is a rationalized study-candidate based on its dysregulated expression in MI/R.[5] Likely, list of certain miRNAs associated with MI/R together with dissecting their mechanisms are increasing and Liu et al.'s investigation[7] participates on this. In the future, miRNA mediated therapeutics in MI/R could be more reliable based on further accumulations of our knowledge, such as a complete-list of MI/R associated miRNAs to identify the most effective candidates, together with technical improvements for their delivery and dosage-control.

REFERENCES

1. Fiedler J, Thum T. MicroRNAs in myocardial infarction. *Arterioscler Thromb Vasc Biol* 2013;33:201-5.
PUBMED | CROSSREF
2. Boon RA, Dimmeler S. MicroRNAs in myocardial infarction. *Nat Rev Cardiol* 2015;12:135-42.
PUBMED | CROSSREF
3. Euler G. Good and bad sides of TGFβ-signaling in myocardial infarction. *Front Physiol* 2015;6:66.
PUBMED | CROSSREF
4. Zhu L, Chen S, Chen Y. Unraveling the biological functions of Smad7 with mouse models. *Cell Biosci* 2011;1:44.
PUBMED | CROSSREF
5. Sucharov C, Bristow MR, Port JD. miRNA expression in the failing human heart: functional correlates. *J Mol Cell Cardiol* 2008;45:185-92.
PUBMED | CROSSREF

6. van Rooij E, Sutherland LB, Liu N, et al. A signature pattern of stress-responsive microRNAs that can evoke cardiac hypertrophy and heart failure. *Proc Natl Acad Sci U S A* 2006;103:18255-60.
PUBMED | CROSSREF

7. Liu H, Li S, Jiang W, Li Y. MiR-484 protects rat myocardial cells from ischemia-reperfusion injury by inhibiting caspase-3 and caspase-9 during apoptosis. *Korean Circ J*. 2020;50:250-63.
PUBMED | CROSSREF

8. Wang K, Long B, Jiao JQ, et al. miR-484 regulates mitochondrial network through targeting Fis1. *Nat Commun* 2012;3:781.
PUBMED | CROSSREF

9. Olson EN. MicroRNAs as therapeutic targets and biomarkers of cardiovascular disease. *Sci Transl Med* 2014;6:239ps3.
PUBMED | CROSSREF

10. Zhou SS, Jin JP, Wang JQ, et al. miRNAS in cardiovascular diseases: potential biomarkers, therapeutic targets and challenges. *Acta Pharmacol Sin* 2018;39:1073-84.
PUBMED | CROSSREF

11. Gabisonia K, Prosdocimo G, Aquaro GD, et al. MicroRNA therapy stimulates uncontrolled cardiac repair after myocardial infarction in pigs. *Nature* 2019;569:418-22.
PUBMED | CROSSREF