

Editorial



LOXL1-AS1/miR-761/PTEN as a Novel Signaling Pathway in Myocardial Ischemia and Reperfusion Injury (MIRI): Epigenetic Regulation by Long Non-Coding RNA (LncRNA) in MIRI

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OPEN ACCESS

► See the article “LOXL1-AS1 Aggravates Myocardial Ischemia/Reperfusion Injury Through the miR-761/PTEN Axis” in volume 53 on page 387.

Received: Mar 6, 2023

Accepted: Mar 21, 2023

Published online: May 4, 2023

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Funding

The author received no financial support for
the research, authorship, and/or publication
of this article.

Conflict of Interest

The author has no financial conflicts of
interest.

Myocardial infarction is one of the leading causes of death in patients with coronary heart disease worldwide. In acute myocardial infarction, treatment to restore blood supply to the ischemic heart muscle reduces the risk of death.¹⁾ However when myocardial infarction is improved through cardiac surgery and blood supply to the myocardium is restored, the original ischemic myocardium is more seriously damaged, which is myocardial ischemia and reperfusion injury (MIRI).¹⁾

One of the pathophysiological mechanisms that cause such MIRI is pyroptosis.²⁾ Pyroptosis is an inflammatory cell death induced by microbial infection, accompanied by inflammasome activation and secretion of pro-inflammatory cytokines interleukin (IL)-1 β and IL-18.³⁾ Pyroptosis induces an anti-tumor immune response and is applied to the treatment of suppressing cancer.³⁾ It is known that pyroptosis is induced by activating NLRP3 inflammasomes even after myocardial infarction.²⁾ Therefore, understanding the regulation of cardiac pyroptosis is critical for elucidating the molecular mechanisms of MIRI.

Phosphatase and tensin homolog (PTEN) was identified as tumor suppressor and inhibited the progression of various cancers.⁴⁾ PTEN also acts as a regulator of gene expression in pyroptosis. For example, PTEN is negatively regulated by miR-25-3p, and overexpression of METTL3 targets the miR-25-3p/PTEN axis to increase the level of phosphorylated Akt (p-Akt), thereby attenuating pyroptosis.⁵⁾

LncRNA, transcripts longer than 200 nucleotides, acts as an essential epigenetic regulator in various biological processes, including chromatin remodeling, and transcription.⁶⁾ LOXL1-AS1 is also a lncRNA that plays crucial roles in various cancers. For example, LOXL1-AS1 contributes to the proliferation and migration through miR-589-5p/TRAF6 axis in laryngocarcinoma.⁷⁾ Epigenetic regulation by non-coding RNA, including lncRNA, is important in myocardial infarction. The circular RNA CircZNF609 exacerbates MIRI through the mediation of the miR-214-3p/PTGS2 axis.⁸⁾ In addition, lncRNA AC005332.7 inhibits ferroptosis to alleviate acute myocardial infarction through the regulation of the miR-331-3p/CCND2 Axis.⁹⁾

Data Sharing Statement

The data generated in this study are available from the corresponding author upon reasonable request.

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

In this issue of the *Korean Circulation Journal*, He et al.¹⁰⁾ investigated the LOXL1-AS1 play a key epigenetic regulator in cardiomyocyte pyroptosis in MIRI. The authors proposed LOXL1-AS1/miR-761/PTEN as a novel signaling pathway affecting pyroptosis in MIRI. First, the authors confirmed that LOXL1-AS1 was highly expressed under hypoxia/reoxygenation conditions.¹⁰⁾ This increased LOXL1-AS1 negatively regulated miR-761 level the as a molecular sponge. In addition, the authors also confirmed that miR-761 downregulates the mRNA level of PTEN. Finally, the authors found that the LOXL1-AS1/miR-761/PTEN signaling axis was also applied in an in vivo ischemia/reperfusion (I/R) mouse model.¹⁰⁾

The results of this study are significant in that they suggest a molecular mechanism in which the lncRNA LOXL1-AS1 and miR-761 directly regulate the expression of PTEN, a key regulator of cardiac pyroptosis in MIRI. Through this regulation of PTEN expression, the authors identified a new signaling pathway that regulates the expression of pyroptosis target genes in MIRI. In addition, LOXL1-AS1 and miR-761 were proposed as new targets for future MIRI therapeutics by linking in vitro results using human cardiomyocyte with in vivo experimental results using I/R model mice.¹⁰⁾

Since this study confirmed the epigenetic regulation by LOXL1-AS1 and miR-761 in pyroptosis, it will be interesting to investigate the possibility of epigenetic regulation such as histone modification other than non-coding RNA. In addition, studies that confirm global changes in various pyroptosis-related genes using RNA sequencing are expected to be critical for understanding the epigenetic regulation of MIRI.

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