Korean Circ J. 2024 May;54(5):253-255
https://doi.org/10.4070/kcj.2024.0114
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Editorial

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Cardiomyocyte Autophagy: A Novel Therapeutic Target by LncRNA PART1

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▸ See the article "LncRNA PART1 Attenuates Myocardial Ischemia-Reperfusion Injury by Regulating TFAP2C/DUSP5 Axis via miR-302a-3p" in volume 54 on page 233.

OPEN ACCESS

Received: Apr 10, 2024
Accepted: May 7, 2024
Published online: May 8, 2024

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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.

Data Sharing Statement
The data generated in this study is available from the corresponding author upon reasonable request.

Ischemic heart disease remains the leading cause of death worldwide, despite rapid advances in therapeutic development including small molecules, immune cells, exosomes, and monoclonal antibodies. The increase in incidences of cardiovascular disease over the past decades has highlighted the importance of identifying critical mediator for developing improved therapeutic approaches.

In this issue of the *Korean Circulation Journal*, Zeng et al.[1] demonstrated that long non-coding RNA (lncRNA) prostate androgen regulated transcript 1 (PART1) was responsible for inducing cardiomyocyte autophagy in the myocardial ischemia-reperfusion injury model. LncRNA PART1 was downregulated by ischemic stress in cardiomyocytes, resulting in significant autophagy and apoptosis. The direct target of lncRNA PART1 was microRNA (miR)-302-3p, which in turn regulated transcription factor AP-2 gamma (TFAP2C) and dual-specificity phosphatase 5 (DUSP5), inhibiting mediators of autophagy. Introducing lncRNA PART1 into cardiomyocytes successfully restored the DUSP5 by inhibiting miR-302-30 to attenuate autophagy and apoptosis. They also presented multiple experimental data, such as overexpression or knockdown of lncRNA PART1, miR-302a-3p, TFAP2C, and DUSP5 in cardiomyocytes to show their functional relevance in terms of autophagy regulation. This study showed cardiomyocyte autophagy could be a successful target of lncRNA PART1 for therapeutic intervention of myocardial ischemia-reperfusion injury.

LncRNAs are transcripts >200 nucleotides in length, which have no capacity to code proteins. The molecular functions of lncRNA encompass numerous and diverse functions, such as transcriptional regulation and chromatin remodelling, dependently on their localization in cellular compartments. LncRNAs may act as decoys, scaffolds, guides and enhancers to regulate DNA, RNA, and proteins, and competitive endogenous RNAs against miRNAs.[2]

Intensive studies are underway to explore the significance of lncRNA regulation in cardiomyocyte death such as apoptosis, ferroptosis, and autophagy, aiming to develop biomarkers and therapeutics candidates. Circular RNAs (circRNAs), a class of non-coding RNA with a circular structure, can interact with miRNA binding site to act as a sponge of miRNA. In a myocardial ischemia-reperfusion mouse model, CircZNF609 was significantly increased along with cardiomyocyte death and reactive oxygen species generation.

Importantly, apoptosis of cardiomyocyte and infarct size were remarkably inhibited by CircZNF609 knockdown.[3] Ferroptosis, a form of programmed cell death caused by iron-dependent lipid peroxidation, is also involved in cardiac ischemia-reperfusion injury. Recently, lncRNA AC005332.7 was found to impede cardiomyocyte ferroptosis via inhibiting lipid peroxidation in both in vitro and in vivo models.[4]

Autophagy is a stress-activated catabolic process that digests and recycles cellular components to maintain cellular homeostasis in response to environmental stimuli. Therefore, autophagy is crucial in various pathological and physiological processes such as immunity, cancer, cardiovascular diseases and neurodegenerative diseases.[5] In heart disease, for instance, activation of autophagy improves cardiac remodeling in a myocardial infarction mouse model. However, excessive autophagy contributes to functional decline through overconsumption of cellular components and autophagic cell death. Inefficient autophagy and homeostatic imbalance may lead to overwhelmed autophagy, which may result to heart failure. So, the abnormal autophagy is critical contributor to the development of heart failure, and targeting autophagy could be a significant therapeutic strategy.

A number of studies have demonstrated that lncRNAs are related to the initiation and termination of the autophagy process. Exogenous overexpression of lncRNA H19 was reported to induce autophagic cell death in cerebral ischemia and reperfusion injury.[6] LncRNA MEG3 is involved in cardiomyocyte autophagy and cardiac fibrosis, and silencing of lncRNA MEG3 ameliorated cardiac hypertrophy via the miRNA-129-5p/ATG14/Akt pathway in a mouse model.[7] A transcription factor ETS2 modulated the lncRNA TUG1/miR-1205p/ATG7 axis to promote heart failure progression by inducing cell apoptosis and autophagy.[8]

On the other hand, lncRNA CAIF modulated autophagy and inhibited cardiac injury by blocking p53-mediated myocardin transcription,[9] and lncRNA Mhrt was correlated with cardiac hypertrophy and heart failure by protection by improving autophgy.[10]

Despite substantial improvements in the filed of molecular therapy over the years, critical barriers to the clinical implementation of findings from small RNA studies still remain. Extensive validation and assessment of the lncRNAs would lead to druggable target identification, and it would be possible to develop lncRNA-based approaches to modulate autophagy flux that may serve as biomarkers and therapeutic modalities.

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