JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 9, NO. 5, 2024

EDITORIAL COMMENT

Potential of Epigenetic Therapy in Alleviating Cardiac Death and Fibrotic Remodeling in Myocardial Infarction*

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Despite significant advancements in the management of ST-segment elevation myocardial infarction (STEMI), the development of effective cardioprotective strategies remains an ongoing challenge. Although prompt reperfusion therapy, primarily achieved through primary percutaneous coronary intervention, has transformed the acute management of STEMI by salvaging jeopardized myocardium and improving patient outcomes, patients often experience postreperfusion adverse cardiac events. These events, including myocardial stunning, reperfusion injury, and adverse ventricular remodeling, contribute to ongoing morbidity and mortality. Despite various pharmacological and nonpharmacological approaches targeting the renin-angiotensin-aldosterone system, sympathetic nervous system, inflammation, angiogenesis, mitochondrial function, cytochrome c release, and delivery of supersaturated oxygen, clinical trials have yielded limited success, emphasizing the need for novel strategies to enhance cardioprotection.[1,2]

Over the past decade, we have gathered significant insight into how epigenetic events contribute to the pathogenesis of cardiovascular disease.[3,4] Epigenetics involves regulatory networks governing gene expression and cellular behavior through reversible modifications of genomic DNA and histones.[5] An essential epigenetic change, known as N6-methyladenosine (m6A), occurs when the adenosine base is methylated at the N6 position. The m6A modification is a dynamic and reversible post-transcriptional modification process regulated by 3 distinct protein complexes: writers (enzymes that add chemical modifications), readers (effector proteins that bind to modified macromolecules), and erasers (enzymes that delete chemical modifications), which tune important biological processes by adding or removing the m6A sites. Among the proteins involved in m6A modification, methyltransferases play a crucial role in catalyzing the methylation of RNAs. Writers consist of large methyltransferase complexes in which the RNA-binding protein (RBM15) acts as a scaffold for methyltransferase-like proteins such as METTL3 and METTL4, facilitating their recruitment and the methylation of mRNA molecules. Significant functions performed by regulators of m6A include destruction, translocation, transportation, and RNA processing.[5,6]

In this issue of *JACC: Basic to Translational Science*, Cheng et al[7] provide pioneering data on the protective role of RBM15 in limiting cardiomyocyte apoptosis following myocardial infarction (MI).[7] Using mouse models of MI, the investigators highlighted the significance of m6A modification during the progression of myocardial ischemia, identifying 1,538 m6A peaks in MI tissues compared with control tissues. Additional analysis revealed the up-regulation of 167 genes and the down-regulation of 49 genes. Through Gene Ontology (GO) analysis, the investigators emphasized the enrichment of differentially expressed m6A-related transcripts in genes

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

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The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2024.03.005

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 9, NO. 5, 2024
MAY 2024:649–651

involved in extracellular matrix remodeling and apoptosis. Moreover, Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis highlighted the involvement of differentially expressed m6A-related transcripts in pathways such as histidine metabolism, the HIF-1 signaling pathway, complement and coagulation cascades, and extracellular matrix-receptor interactions.

To ascertain the relevance of this pathway in humans, RBM15 levels were quantified by enzyme-linked immunosorbent assay in 50 STEMI patients and 50 age-matched control patients with comparable cardiovascular risk factors, revealing a significant increase of RBM15 in STEMI patients. Overexpression of RBM15 attenuated cardiomyocyte apoptosis under hypoxic conditions ex vivo and adverse myocardial remodeling in mice, whereas silencing RBM15 (si-RBM15) provided the opposite effect. The importance of this pathway was underscored in mice through a functional approach using serial echocardiography and hemodynamic measurements coupled with histological analysis. To establish a model of cardiac overexpression of RBM15, adenovirus-RBM15 was injected into the mouse myocardial tissue at 3 to 5 points using an insulin needle. Western blot and quantitative polymerase chain reaction analyses were conducted to determine the peak expression of RBM15 3 weeks after injection. Subsequently, MI was induced using left coronary artery ligation, unveiling delayed improvement in heart function, reduced cardiac fibrosis at 4 weeks, and enhanced 60-day survival associated with RBM15 overexpression. Furthermore, analysis of downstream targets of RBM15 in neonatal rat left ventricle cardiomyocytes identified NEDD8 activating enzyme E1 subunit 1 (NAE1) as a crucial regulator of apoptosis. Elevated NAE1 mRNA expression within the infarct area tissue, coupled with ex vivo analysis illustrating enhancement of NAE1 via RBM15-mediated mRNA stabilization, provided additional insight into the mechanistic basis of RBM15-mediated cardioprotection. Finally, the inhibition of NAE1 demonstrated a noteworthy reduction in cardiomyocyte apoptosis, underscoring the significance of this pathway in post-MI remodeling.

Although a translational approach was undertaken, the study faced challenges in obtaining extensive human data regarding RBM15 expression throughout the progression of MI. The study lacked information on RBM15's expression in human ischemic myocardial tissue, and this could be a valuable addition to future studies. The characterization of STEMI patients would have benefited from further elaboration, particularly in assessing coronary reperfusion (TIMI flow grade, blush), infarct size, left ventricular ejection fraction. A key point, likely to drive future study design, is the relationship between RBM15 levels and key prognostic biomarkers of MI, such as natriuretic peptides, cardiac troponin I, C-reactive protein, or interleukin 6. Although not reported here, this warrants further discussion and exploration. Despite these limitations, this study elucidated a novel and important pathway involved in mitigating cardiac death and fibrotic myocardial remodeling. It aligns with previous research demonstrating the significance of METTL3 up-regulation in heart failure and m6A modifications in various experimental models and human tissues, emphasizing the potential clinical relevance of targeting these pathways in the context of MI.[3,6] Whereas the Cheng et al[7] study focused on the primary role of writers in regulating m6A modification and lacked evidence for any modification of erasers proteins within myocardial tissue, another recent study provided convincing data showing a key role for the eraser fat mass and obesity-associated protein (FTO), an m6A demethylase.[8] FTO expression was found to be down-regulated in heart failure, leading to an aberrant increase in global cardiac m6A levels, as well as m6A levels in selective contractile transcripts, resulting in decreased protein expression. Loss of FTO resulted in abnormal calcium handling and sarcomere dynamics, leading to impaired contractile function. By contrast, overexpression of FTO in failing murine myocardium attenuated ischemia-induced cardiac remodeling and loss of cardiac contractile function, demonstrating the therapeutic potential of FTO.[8]

Beyond apoptosis regulation and calcium handling, recent evidence highlighted the importance of epigenetically regulated networks in governing the functional phenotype shift of cardiac macrophages.[9] The transition of cardiac macrophages to a reparative phenotype plays a crucial role in resolving inflammatory responses and facilitating efficient tissue repair following MI. Notably, nucleophosmin 1 (NPM1) has been implicated in promoting atherosclerosis through the induction of vascular inflammation via the nuclear factor-κB signaling pathway.[10] Conversely, NPM1 plays a critical role in controlling the inflammatory phenotype of cardiac macrophages, thereby antagonizing cardiac repair. Macrophage-specific deletion of NPM1 emerges as a promising strategy for promoting cardiac repair and alleviating post-MI cardiac dysfunction and adverse remodeling. The epigenetic machinery, mediated by the NPM1-KDM5b interaction, governs cardiac macrophages transition and post-MI tissue repair via metabolic reprogramming. NPM1 acts as an epigenetic factor

targeting the *Tsc1* gene, then recruiting histone demethylase KDM5b, to form an inhibitory epigenetic complex that ultimately suppresses reparative transition via the mTOR pathway. Antisense oligonucleotides and NPM1 inhibitors demonstrated therapeutic efficacy in promoting cardiac repair in wild-type mice after MI.[9]

Collectively, these innovative studies offer novel and pertinent insights into how epigenetic therapy could mitigate adverse cardiac remodeling in MI and alleviate inflammation-related damage. Historically, many therapies that showed promise in experimental models failed to translate successfully from bench to bedside and have consequently been consigned to the graveyard of therapies. Let us remain hopeful that the fate of epigenetic therapies will diverge from this trend.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The author has reported that he has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS apoptosis, m6A, MI therapy, RBM15