

EDITORIAL COMMENT

Targeting Mitochondria Dysfunction in LMNA Cardiomyopathy



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Pathologic variants in the *Lmna* gene encoding the nuclear envelope protein lamin A/C are highly penetrant and can lead to a spectrum of diseases known as laminopathies, with dilated cardiomyopathy (DCM) being among the common clinical manifestations in adult patients.¹ LMNA-associated DCM is characterized by left ventricular enlargement and progressive restrictive phenotype, often accompanied by conduction abnormalities and arrhythmias. Cardiac dysfunction resulting from these mutations often leads to progressive heart failure, necessitating heart transplants or resulting in premature death. This progressive and highly malignant clinical course and the lack of effective therapies that can alter the natural history highlight the need for targeted therapies beyond standard medical therapy.

Mitochondria are indispensable for cardiac metabolism, as they generate the adenosine triphosphate necessary for continuous cardiac contractions. The efficiency and functionality of mitochondria directly correlate with their ability to perform their contractile functions. Therefore, maintaining mitochondrial integrity and function is paramount for sustaining heart health. Studies have demonstrated that mitochondrial pathways are down-regulated in the hearts of *Lmna*^{-/-} mice early in the disease progress, indicating a direct impact on mitochondrial function due to the absence of lamin A/C.² Specifically, these pathways involve critical processes such as

mitochondrial biogenesis, energy production, and oxidative stress response, all of which are crucial for maintaining cardiac function.² This down-regulation decreases mitochondrial efficiency, leading to impaired adenosine triphosphate production and increased oxidative damage. Meanwhile, the presence of pathogenic *LMNA* variant demonstrated enhanced heterochromatic gene suppression and disrupted mitochondria functions, which is associated with progression of DCM in both humans and mouse models.³ Understanding these mitochondrial perturbations is pivotal in exploring therapeutic targets aimed at restoring mitochondrial health and improving cardiac function, highlighting the opportunity to target aberrant mitochondrial pathways for therapeutic interventions in LMNA-associated DCM.

Silent information regulator 1 (SIRT1) is a nicotinamide adenine dinucleotide (NAD⁺)-dependent class III deacetylase that plays crucial roles in the pathogenesis of numerous diseases.⁴ SIRT1 regulates various cellular processes, including metabolism, inflammation, and aging, through its deacetylation of both histone and nonhistone proteins. It is known to enhance mitochondrial function, reduce oxidative stress, and improve cellular metabolism, making it a promising target for therapeutic interventions in cardiac diseases. SIRT1 has been studied extensively in the context of metabolic and age-related diseases, with emerging evidence suggesting its potential in cardiovascular diseases, including DCM. Clinical trials investigating SIRT1 activators or mimetics have shown promising results in improving metabolic profiles and reducing inflammation, but their application specifically for LMNA-associated DCM is still in the early stages. Understanding the precise role of SIRT1 in this context could open new therapeutic avenues and improve patient outcomes.

The present study by Du et al⁵ in this issue of *JACC: Basic to Translational Science* connects the role of

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mitochondrial dysfunction in LMNA-associated DCM with the potential for SIRT1-associated pathway as a potential therapeutic target. Du et al⁵ conducted extensive mitochondrial analysis including numerous mitochondrial biogenesis markers and related pathways in a mouse model of LMNA generated by CRISPR/Cas9 technique that knocked out exons 8-11 that resulted in a DCM phenotype with increased fibrosis at 1 month old. Du et al⁵ demonstrated that down-regulation of mitochondrial pathways manifested in decreased cristae density with early mitochondrial injury exacerbated cardiac dysfunction in their mouse model. They further identified this early injury of mitochondria to reduced expression of the epigenetic regulator, SIRT1, in 2-week *Lmna*^{-/-} hearts in proteomic analyses. By overexpressing SIRT1 in *Lmna* knockdown neonatal rat ventricular myocytes, Du et al⁵ observed an improvement in mitochondrial oxidative respiration capacity.

Furthermore, adeno-associated virus (AAV)-mediated SIRT1 overexpression in *Lmna*^{-/-} mice significantly improved mitochondrial injury, enhanced cardiac systolic function, reduced ventricular dilation and fibrosis, and ultimately prolonged the lifespan of these mice.⁵ These findings highlight the key role of SIRT1 in maintaining mitochondrial bioenergetics and its potential as a therapeutic target in LMNA-associated DCM. Another mechanistic insight from the study is the identification of the SIRT1/PARKIN axis in maintaining mitochondrial function. PARKIN, an E3 ubiquitin ligase, is essential for mitophagy, the process of removing damaged mitochondria to preserve cellular health. SIRT1 can act upstream of the PINK1/Parkin pathway to activate mitophagy. The study suggests that SIRT1 positively regulates PARKIN, thereby facilitating efficient mitophagy and ensuring mitochondrial quality control.⁵ Taken together, this study demonstrated that early intervention targeting the SIRT1/PARKIN pathway could favorably influence the progression of the LMNA-associated DCM.

The concepts regarding mitochondrial dysfunction in LMNA-associated DCM as well as the contributions of SIRT1/PARKIN in heart and mitochondrial diseases are not new. Nevertheless, Du et al⁵ successfully connected the 2 concepts and demonstrated abnormal mitochondrial structure and function, which was confirmed by in vitro experiments with small, interfering RNA knockdown of rat *Lmna* in neonatal rat ventricular myocytes. As Du et al⁵

pointed out, the exact mechanisms in which LMNA deletion leads to SIRT1 down-regulation remains unclear. Furthermore, it remains unclear whether the timing of SIRT1 overexpression is important—meaning, whether SIRT1 overexpression is required prior to phenotype manifestations occur to yield the benefits.

While the study presents compelling evidence for the therapeutic potential of targeting SIRT1/PARKIN pathway in attenuating disease progression of LMNA-associated DCM, several questions and challenges remain. The current homozygous *Lmna*^{-/-} mouse model has a highly malignant clinical course that resembles more the progeria phenotype than the adult-onset LMNA-associated DCM phenotype in humans that invariably involves heterozygous *Lmna* gene variants. Further studies are needed to ascertain whether the SIRT1 activation effects can be seen in other *Lmna* mouse models or in humans with the broad spectrum of disease phenotypes.⁶ Assessing the long-term effects of SIRT1 overexpression on cardiac function and overall health is essential to ensure that the benefits observed in the study are sustainable and do not lead to unforeseen adverse effects. Whereas overexpression of SIRT1 using the AAV approach can be promising, other pharmacologic strategies such as small molecular traditional SIRT1 activators such as resveratrol or SRT2104⁷ may avoid potential pitfalls of administering viral vectors. Also, despite improvement in cardiac contractility and function with AAV-mediated SIRT1 activation, there appears to be a limited extension of lifespan, suggesting that restoration of cardiac function only mitigates some pathologic features of the defect despite early administration (ie, prior to disease manifestation). Studies have shown that targeting other epigenetic regulators, such as lysine-specific histone demethylase 1A, may yield promising results.⁸ Therefore, combining SIRT1-targeted therapies with interventions that modulate other epigenetic regulators may be necessary to enhance therapeutic outcomes and provide a more comprehensive approach to managing LMNA-associated DCM. Nevertheless, insights gained from this study will undoubtedly catalyze innovations in therapeutic strategies that focus on preserving mitochondrial function, bringing us closer to overcoming the challenges posed by LMNA-associated DCM and improving the lives of countless individuals affected by this relentless disease.

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