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EDITORIAL COMMENT

New Insights Into the Therapy for Lamin-Associated Dilated Cardiomyopathy*

Hao Zhang, MD,[a] Lu Ren, PhD,[a] Joseph C. Wu, MD, PhD[a,b,c]

In this issue of *JACC: Basic to Translational Science*, Cheedipudi et al[1] report a new approach to treat lamin-associated dilated cardiomyopathy (DCM) by genetic ablation of the DNA damage response (DDR) pathway. Lamin is a type V intermediate filament protein, which serves as a major structural component of the nucleus and a platform for binding proteins and chromatin. Two major types of lamins have been identified. A-type lamins (lamins A, C, AΔ10, and C2) are alternative splice variants from a single gene. B-type lamins (lamins B1, B2, and B3) are products of 2 separate genes (**Figure 1**). Type A lamins are widely expressed in all types of cells, and their various mutations lead to laminopathies. To date, approximately 400 mutations in LMNA are known to be associated with a wide spectrum of diseases in multiple systems, such as cardiovascular, neuromuscular, and metabolic systems, as well as the process of aging.[2] Specifically, associated muscular dystrophies include limb-girdle muscular dystrophy, Emery-Dreyfuss muscular dystrophy, and pediatric congenital muscular dystrophy. Associated metabolic disorders include insulin resistance, hypertriglyceridemia, partial lipodystrophy, and Malouf syndrome. LMNA mutations can also result in premature aging, including Hutchinson-Gilford progeria and atypical Werner's syndrome.

In the heart, LMNA has become one of the most commonly mutated genes in familial cardiomyopathy, accounting for 6% to 8% of idiopathic DCM.[3] Unlike most other forms of familial DCM, sudden cardiac death may be the first manifestation of LMNA cardiomyopathy, even in the absence of systolic dysfunction, because of malignant arrhythmias such as ventricular tachycardia and fibrillation. Current therapy for LMNA cardiomyopathy follows the standard heart failure regimen, including beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and aldosterone antagonists, but the specific efficacy in this population is undetermined. The implantable cardioverter-defibrillator is indicated to treat malignant arrhythmic events even without significant cardiac dysfunction. However, there is no specific target-oriented therapy approved by the U.S. Food and Drug Administration yet, largely because of a lack of understanding of the underlying disease mechanisms.

Cheedipudi et al[1] highlight the significant contributions of double-strand breaks to the pathogenesis of LMNA cardiomyopathy.[1] Double-strand breaks, released into the cytoplasm, are sensed by cyclic guanosine monophosphate-adenosine monophosphate synthase (CGAS), triggering the DDR pathways. This study indicates that targeting the CGAS/DDR pathway might be beneficial in treating LMNA cardiomyopathy. To test the hypothesis, the investigators leveraged a cardiomyocyte conditional LMNA knockout mouse model called Myh6-Cre:

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From the [a]Stanford Cardiovascular Institute, Stanford University School of Medicine, Stanford, California, USA; [b]Division of Cardiovascular Medicine, Department of Medicine, Stanford University School of Medicine, Stanford, California, USA; and the [c]Department of Radiology, Stanford University School of Medicine, Stanford, California, USA.

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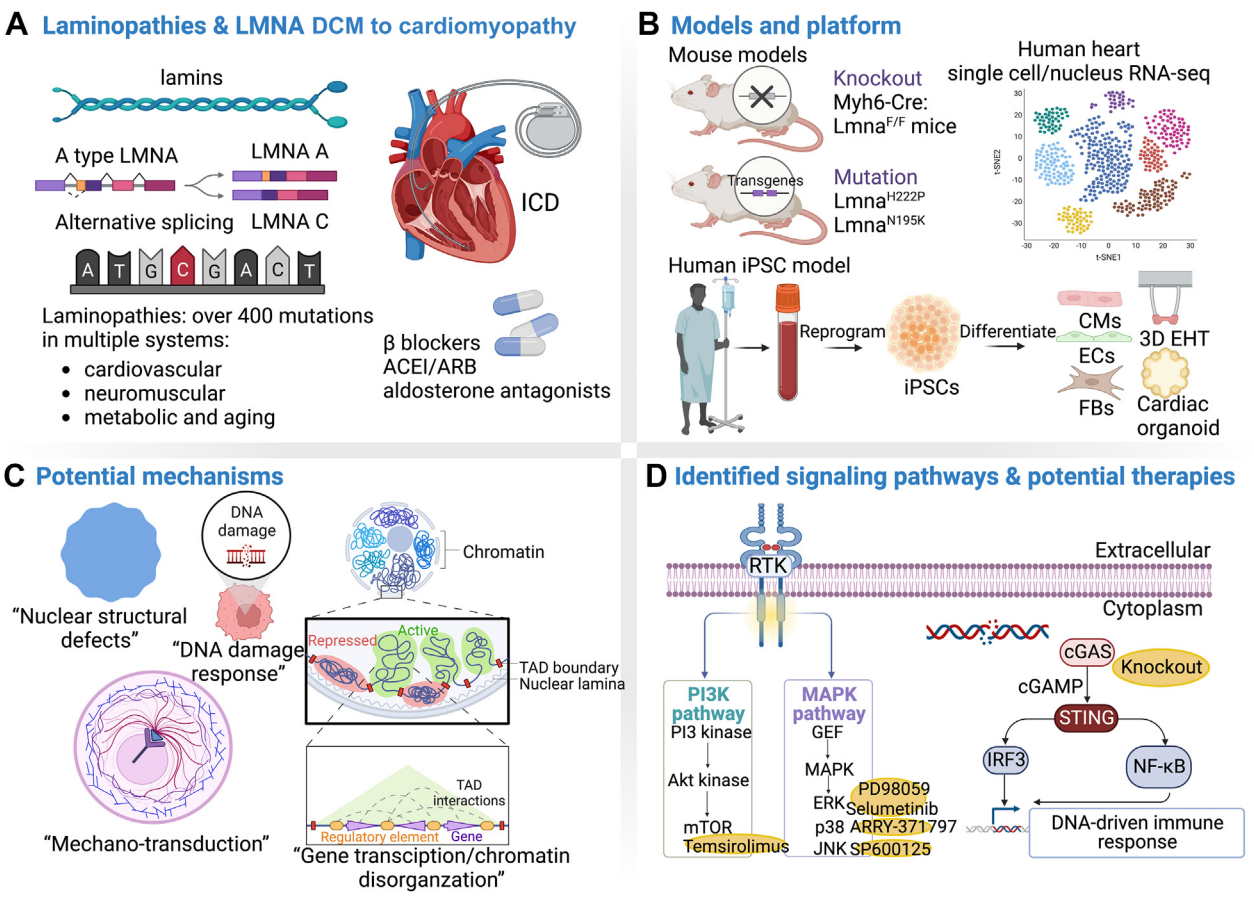
FIGURE 1 Summary of Current Understanding of LMNA Cardiomyopathy



(A) Lamin structure, mutation, and clinical treatments of LMNA cardiomyopathy. **(B)** The models and platform to study LMNA cardiomyopathy. **(C)** Potential mechanisms of LMNA cardiomyopathy. **(D)** Identified signaling pathways and potential mechanism-based therapies of LMNA cardiomyopathy. CM = cardiomyocyte; EC = endothelial cell; EHT = engineered heart tissue; FB = cardiac fibroblast; ICD = implantable cardioverter-defibrillator; iPSC = induced pluripotent stem cell; RTK = receptor tyrosine kinase; TAD = topological associated domains.

LmnaF/F mice. In this model, the DDR pathway is activated in the heart, provoking inflammatory responses and contributing to cell death, cardiac dysfunction, and fibrosis. Genetic blockade of the CGAS component of the DDR pathway by deletion of the Mb21d1 gene, which encodes the CGAS protein, improved survival and cardiac function, and attenuated myocardial fibrosis and apoptosis.

In the past 2 decades, several hypotheses have been proposed to delineate the mechanism of laminopathies.[2] First, the softer nuclear structure associated with LMNA mutations and the resulting morphologic abnormalities may form the basis of lamin-related cardiac phenotypes, referred to as the "structural hypothesis," which attributes lamin-associated phenotypes to structural defects. Second, A-type lamins may be involved in the regulation of the structural architecture of the contractile tissue, conferring resistance and protection against mechanical stress, which is known as the "mechano-transduction hypothesis". Third, the "gene expression hypothesis" proposes that mutation-induced defects attributable to abnormal chromatin organization may lead to the abnormal control of gene expression and signaling pathways.

The strengths of the study are 3-fold. First, the research demonstrates the beneficial effects of genetic ablation of the CGAS/DDR pathway in the LMNA knockout mice model of cardiomyopathy. Second, this finding, along with the investigators' previous study, advances our current understanding of the disease mechanism by raising a new hypothesis that

"DNA damage" contributes to the pathogenesis of LMNA cardiomyopathy. As CGAS inhibitors are available, such as G108, G140, and G150, this study has a high translational value by providing drugs to inhibit CGAS to use small-molecule drugs for patients with LMNA cardiomyopathy. Third, given that CGAS and the DDR pathways are implicated in other forms of cardiomyopathy, this research may have broader clinical implications. One of the limitations of this study is that Mb21d1 was knocked out before the deterioration of cardiac dysfunction in the Myh6-Cre: LmnaF/F mice model in a preventive setting. Whether inhibition of CGAS expression by inducible knockout or small-molecule drugs exerts therapeutic effects after cardiac dysfunction is established needs further validation.

The discovery of new mechanisms and signaling pathways of LMNA cardiomyopathy relies heavily on the model and platform. Besides the knockout mouse model used in this study, the generation of LmnaH222P and LmnaN195K transgenic mice also recapitulated DCM, with no phenotype at the neonatal stage and displaying disease traits in adult stage similar to patients. The pathogenesis of LmnaH222P mice was associated to elevated MAPK and AKT/mTOR signaling pathways. Several MAPK inhibitors have shown beneficial effects in mouse models, such as PD98059, selumetinib, and SP600125. Notably, ARRY-371797, a small-molecule inhibitor of p38α used in LmnaH222P mice, has now completed a phase 2 clinical trial and is currently being tested in phase 3 clinical trials.[3]

The development of patient-derived human-induced pluripotent stem cells (iPSCs) has proved to be an invaluable platform for studying genetic cardiomyopathy. For example, the detrimental role of the chromatin conformation and abnormal gene expression profile was identified by recruiting a large family cohort whose members carry a frame-shift mutation in their LMNA iPSC-derived cardiomyocytes.[4] Moreover, the recently published human single-nucleus RNA-Sequencing dataset of LMNA cardiomyopathy demonstrated distinct right and left ventricular responses, highlighting genotype-associated pathways, intercellular interactions, and differential gene expression at single-cell resolution.[5]

In conclusion, treatment of LMNA cardiomyopathy is an emerging field with tremendous potential and formidable challenges. A few targets have been identified, and several drugs have entered preclinical and clinical stages. By combining the human iPSC platform, mice models, and bioinformatics of single-cell/nucleus RNA-Sequencing datasets from human tissue, additional new promising therapeutic strategies will be developed in the future.

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ADDRESS FOR CORRESPONDENCE: Dr Joseph C. Wu, Stanford Cardiovascular Institute, Stanford University School of Medicine, 265 Campus Drive, Room G1120B, Stanford, California 94305-5454, USA. E-mail: joewu@stanford.edu.

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