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Identification of Genes and Pathways Regulated by Lamin A in Heart

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Abstract

Background Mutations in the *LMNA* gene, encoding LMNA (lamin A/C), causes distinct disorders, including dilated cardiomyopathies, collectively referred to as laminopathies. The genes (coding and noncoding) and regulatory pathways controlled by LMNA in the heart are not completely defined. Methods and Results We analyzed cardiac transcriptome from wild-type, loss-of-function (*Lmna*$^{-/-}$), and gain-of-function (*Lmna*$^{-/-}$ injected with adeno-associated virus serotype 9 expressing LMNA) mice with normal cardiac function. Deletion of *Lmna* (*Lmna*$^{-/-}$) led to differential expression of 2193 coding and 629 long noncoding RNA genes in the heart ($q<0.05$). Re-expression of LMNA in the *Lmna*$^{-/-}$ mouse heart, completely rescued 501 coding and 208 non-coding and partially rescued 1862 coding and 607 lncRNA genes. Pathway analysis of differentially expressed genes predicted activation of transcriptional regulators lysine-specific demethylase 5A, lysine-specific demethylase 5B, tumor protein 53, and suppression of retinoblastoma 1, paired-like homeodomain 2, and melanocyte-inducing transcription factor, which were completely or partially rescued upon reexpression of LMNA. Furthermore, lysine-specific demethylase 5A and 5B protein levels were increased in the *Lmna*$^{-/-}$ hearts and were partially rescued upon LMNA reexpression. Analysis of biological function for rescued genes identified activation of tumor necrosis factor-α, epithelial to mesenchymal transition, and suppression of the oxidative phosphorylation pathway upon *Lmna* deletion and their restoration upon LMNA reintroduction in the heart. Restoration of the gene expression and transcriptional regulators in the heart was associated with improved cardiac function and increased survival of the *Lmna*$^{-/-}$ mice. Conclusions The findings identify LMNA-regulated cardiac genes and their upstream transcriptional regulators in the heart and implicate lysine-specific demethylase 5A and B as epigenetic regulators of a subset of the dysregulated genes in laminopathies.

Keywords: KDM5; LMNA; cardiomyopathies; laminopathies.

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