

BET Bromodomain Inhibition Attenuates Cardiac Phenotype in Myocyte-Specific Lamin A/C-deficient Mice

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Abstract

Mutation in the LMNA gene, encoding Lamin A/C, cause a diverse group of diseases called laminopathies. Cardiac involvement is the major cause of death and manifests as dilated cardiomyopathy (DCM), heart failure, arrhythmias, and sudden death. There is no specific therapy for LMNA-associated cardiomyopathy. We report that deletion of Lmna in cardiac myocytes in mice leads to severe cardiac dysfunction, conduction defect, ventricular arrhythmias, fibrosis, apoptosis, and premature death within 4 weeks. The phenotype is similar to LMNA-associated cardiomyopathy in humans. RNA sequencing, performed prior to the onset of cardiac dysfunction, led to identification of 2,338 differentially expressed genes (DEGs) in Lmna-deleted cardiac myocytes. DEGs predicted activation of bromodomain-containing protein 4 (BRD4), a regulator of chromatin-associated proteins and transcription factors, which was confirmed by complementary approaches, including chromatin immunoprecipitation–sequencing. Daily injection of JQ1, a specific BET bromodomain inhibitor partially reversed the DEGs, including those encoding secretome, improved cardiac function, abrogated cardiac arrhythmias, fibrosis, and apoptosis, and prolonged the median survival time by 2-fold in the myocyte-specific Lmna-deleted mice. The findings highlight the important role of LMNA in cardiac myocyte and identify BET bromodomain inhibition as a potential therapeutic target in LMNA-associated cardiomyopathy, for which there is no specific effective therapy.

Keywords: Cardiology; Cardiovascular disease; Fibrosis; Heart failure.

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