DNA Damage Response/TP53 Pathway Is Activated and Contributes to the Pathogenesis of Dilated Cardiomyopathy Associated with Lamin A/C Mutations.


Abstract

RATIONALE: Mutations in the LMNA gene, encoding lamin A/C (LMNA), are responsible for laminopathies. Dilated cardiomyopathy (DCM) is a major cause of mortality and morbidity in laminopathies.

OBJECTIVE: To gain insights into the molecular pathogenesis of DCM in laminopathies.

METHODS AND RESULTS: We generated a tet-off bigenic mice expressing either a wild type (WT) or a mutant LMNA (D300N) protein in cardiac myocytes. LMNA^{D300N} mutation is associated with DCM in progeroid syndromes. Expression of LMNA^{D300N} led to severe myocardial fibrosis, apoptosis, cardiac dysfunction, and premature death. Administration of doxycycline suppressed LMNA^{D300N} expression and prevented the phenotype. Whole heart RNA-sequencing in 2-week old WT and LMNA^{D300N} mice led to identification of ~6,000 differentially expressed genes (DEGs). Gene set enrichment and Hallmark pathway analyses predicted activation of E2F, DNA Damage Response (DDR), TP53, NFkB and TGFβ pathways, which were validated by western blotting, qPCR of selected targets, and/or immunofluorescence staining. DEGs involved cell death, cell cycle regulation, inflammation, and epithelial-mesenchymal differentiation. RNA-sequencing of human hearts with DCM associated with defined LMNA pathogenic variants corroborated activation of the DDR/TP53 pathway in the heart. Increased expression of CDKN2A, a downstream target of E2F pathway and an activator of TP53, provided a plausible mechanism for activation of the TP53 pathway. To determine pathogenic role of TP53 pathway in DCM, Tp53 gene was conditionally deleted in cardiac myocytes in mice expressing the LMNA^{D300N} protein. Deletion of Tp53 partially rescued myocardial fibrosis, apoptosis, proliferation of non-myocyte cells, left ventricular dilatation and dysfunction, and slightly improved survival.

CONCLUSIONS: Cardiac myocyte-specific expression of LMNA\textsuperscript{D300N}, associated with DCM, led to pathogenic activation of the E2F/DDR/TP53 pathway in the heart and induction of myocardial fibrosis, apoptosis, cardiac dysfunction, and premature death. The findings denote the E2F/DDR/TP53 axis as a responsible mechanism for DCM in laminopathies and as a potential intervention target.

KEYWORDS: DNA damage response; TP53 pathway; transcription factors

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