Expression of Lmna-R225X nonsense mutation results in dilated cardiomyopathy and conduction disorders (DCM-CD) in mice: Impact of exercise training.

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Abstract

AIMS: To recapitulate progressive human dilated cardiomyopathy (DCM) and heart block in the Lmna R225X mutant mice model and investigate the molecular basis of LMNA mutation induced cardiac conduction disorders (CD); To investigate the potential interventional impact of exercise endurance.

METHODS AND RESULTS: A Lmna R225X knock-in mice model in either heterozygous or homozygous genotype was generated. Electrical remodeling was observed with higher occurrence of AV block from neonatal and aged mutant mice as measured by surface electrocardiogram and atrio-ventricular Wenckebach point detection. Histological and molecular profiles revealed an increase in apoptotic cells and activation of caspase-3 activities in heart tissue. Upon aging, extracellular cellular matrix (ECM) remodeling appeared with accumulation of collagen in Lmna R225X mutant hearts as visualized by Masson's trichrome stain. This could be explained by the upregulated ECM gene expression, such as Fibronectin: Fn1, collagen: Col12a1, intergrin: Itgb2 and 3, as detected by microarray gene chip. Also, endurance exercise for 3 month improved the ventricular ejection fraction, attenuated fibrosis and cardiomyocytes apoptosis in the aged mutant mice.
CONCLUSIONS: The mechanism of LMNA nonsense mutation induced cardiac conduction defects through AV node fibrosis is due to upregulated ECM gene expression upon activation of cardiac apoptosis. Lmna R225X mutant mice hold the potential for serving as in vivo models to explore the mechanism and therapeutic methods for AV block or myopathy associated with the aging process.

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