Decreased WNT/β-catenin signalling contributes to the pathogenesis of dilated cardiomyopathy caused by mutations in the lamin a/C gene.


Abstract
Cardiomyopathy caused by lamin A/C gene (LMNA) mutations (hereafter referred as LMNA cardiomyopathy) is characterized by cardiac conduction abnormalities and left ventricular systolic dysfunction predisposing to heart failure. Previous cardiac transcriptional profiling of LmnaH222P/H222P mouse, a small animal model of LMNA cardiomyopathy, suggested decreased WNT/β-catenin signalling. We confirmed decreased WNT/β-catenin signalling in the hearts of these mice by demonstrating decreased β-catenin and WNT proteins. This was correlated with increased expression of soluble Frizzled-related proteins that modulate the WNT/β-catenin signalling pathway. Hearts of LmnaH222P/H222P mice also demonstrated lowered expression of the gap junction connexin 43. Activation of WNT/β-catenin activity with 6-bromoindirubin-3'-oxime improved cardiac contractility and ameliorated intraventricular conduction defects in LmnaH222P/H222P mice, which was associated with increased expression of myocardial connexin 43. These results indicate that decreased WNT/β-catenin contributes to the pathophysiology of LMNA cardiomyopathy and that drugs activating β-catenin may be beneficial in affected individuals.

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