Elevated dual specificity protein phosphatase 4 in cardiomyopathy caused by lamin A/C gene mutation is primarily ERK1/2-dependent and its depletion improves cardiac function and survival.

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Abstract

Mutations in the lamin A/C gene (LMNA) encoding the nuclear intermediate filament proteins lamins A and C cause a group of tissue-selective diseases, the most common of which is dilated cardiomyopathy (herein referred to as LMNA cardiomyopathy) with variable skeletal muscle involvement. We previously showed that cardiomyocyte-specific overexpression of dual specificity protein phosphatase 4 (DUSP4) is involved in the pathogenesis of LMNA cardiomyopathy. However, how mutations in LMNA activate Dusp4 expression and whether it is necessary for the development of LMNA cardiomyopathy are currently unknown. We now show that female LmnaH222P/H222P mice, a model for LMNA cardiomyopathy, have increased Dusp4 expression and hyperactivation of extracellular signal-regulated kinase (ERK) 1/2 with delayed kinetics relative to male mice, consistent with the sex-dependent delay in the onset and progression of disease. Mechanistically, we show that the H222P amino acid substitution in lamin A enhances its binding to ERK1/2 and increases sequestration at the nuclear envelope. Finally, we show that genetic deletion of Dusp4 has beneficial effects on heart function and prolongs survival in LmnaH222P/H222P mice. These results further establish Dusp4 as a key contributor to the pathogenesis of LMNA cardiomyopathy and a potential target for drug therapy.

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