Cofilin-1 phosphorylation catalyzed by ERK1/2 alters cardiac actin dynamics in dilated cardiomyopathy caused by lamin A/C gene mutation.

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Abstract

Hyper-activation of extracellular signal-regulated kinase (ERK) 1/2 contributes to heart dysfunction in cardiomyopathy caused by mutations in the lamin A/C gene (LMNA cardiomyopathy). The mechanism of how this affects cardiac function is unknown. We show that active phosphorylated ERK1/2 directly binds to and catalyzes the phosphorylation of the actin depolymerizing factor cofilin-1 on Thr25. Cofilin-1 becomes active and disassembles actin filaments in a large array of cellular and animal models of LMNA cardiomyopathy. In vivo expression of cofilin-1, phosphorylated on Thr25 by endogenous ERK1/2 signaling, leads to alterations in left ventricular function and cardiac actin. These results demonstrate a novel role for cofilin-1 on actin dynamics in cardiac muscle and provide a rationale on how increased ERK1/2 signaling leads to LMNA cardiomyopathy.

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