ERK1/2 Phosphorylation of FHOD Connects Signaling and Nuclear Positioning Alternations in Cardiac Laminopathy.

Antoku S¹, Wu W², Joseph LC³, Morrow JP³, Worman HJ², Gundersen GG⁴.

Author information
1 Department of Pathology and Cell Biology, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA.
2 Department of Pathology and Cell Biology, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA; Department of Medicine, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA.
3 Department of Medicine, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA.
4 Department of Pathology and Cell Biology, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA. Electronic address: ggg1@cumc.columbia.edu.

Abstract
Mutations in the lamin A/C gene (LMNA) cause cardiomyopathy and also disrupt nuclear positioning in fibroblasts. LMNA mutations causing cardiomyopathy elevate ERK1/2 activity in the heart, and inhibition of the ERK1/2 kinase activity ameliorates pathology, but the downstream effectors remain largely unknown. We now show that cardiomyocytes from mice with an Lmna mutation and elevated cardiac ERK1/2 activity have altered nuclear positioning. In fibroblasts, ERK1/2 activation negatively regulated nuclear movement by phosphorylating S498 of FHOD1. Expression of an unphosphorylatable FHOD1 variant rescued the nuclear movement defect in fibroblasts expressing a cardiomyopathy-causing lamin A mutant. In hearts of mice with LMNA mutation-induced cardiomyopathy, ERK1/2 mediated phosphorylation of FHOD3, an isoform highly expressed in cardiac tissue. Phosphorylation of FHOD1 and FHOD3 inhibited their actin bundling activity. These results show that phosphorylation of FHOD proteins by ERK1/2 is a critical switch for nuclear positioning and may play a role in the pathogenesis of cardiomyopathy caused by LMNA mutations.

Copyright © 2019 Elsevier Inc. All rights reserved.
KEYWORDS: ERK1/2; FHOD; LINC complex; actin bundling; cardiomyopathy; formins; lamin; nuclear positioning; phosphorylation

PMID: 31794718    DOI: 10.1016/j.devcel.2019.10.023