Interference with ERK-dimerization at the nucleocytosolic interface targets pathological ERK1/2 signaling without cardiotoxic side-effects.

Tomasovic A, Brand T, Schanbacher C, Kramer S, Hümmert MW, Godoy P, Schmidt-Heck W, Nordbeck P, Ludwig J, Homann S, Wiegering A, Shaykhutdinov T, Kratz C, Knüchel R, Müller-Hermelink HK, Rosenwald A, Frey N, Eichler J, Dobrev D, El-Armouche A, Hengstler JG, Müller OJ, Hinrichs K, Cuello F, Zernecke A, Lorenz K (2020) Interference with ERK-dimerization at the nucleocytosolic interface targets pathological ERK1/2 signaling without cardiotoxic side-effects. *Nat Commun* 11(1), 1733.

Abstract

Dysregulation of extracellular signal-regulated kinases (ERK1/2) is linked to several diseases including heart failure, genetic syndromes and cancer. Inhibition of ERK1/2, however, can cause severe cardiac side-effects, precluding its wide therapeutic application. ERKT188-autophosphorylation was identified to cause pathological cardiac hypertrophy. Here we report that interference with ERK-dimerization, a prerequisite for ERKT188-phosphorylation, minimizes cardiac hypertrophy without inducing cardiac adverse effects: an ERK-dimerization

inhibitory peptide (EDI) prevents ERKT188-phosphorylation, nuclear ERK1/2-signaling and cardiomyocyte hypertrophy, protecting from pressure-overload-induced heart failure in mice whilst preserving ERK1/2-activity and cytosolic survival signaling. We also examine this alternative ERK1/2-targeting strategy in cancer: indeed, ERKT188-phosphorylation is strongly upregulated in cancer and EDI efficiently suppresses cancer cell proliferation without causing cardiotoxicity. This powerful cardio-safe strategy of interfering with ERK-dimerization thus combats pathological ERK1/2-signaling in heart and cancer, and may potentially expand therapeutic options for ERK1/2-related diseases, such as heart failure and genetic syndromes.

Beteiligte Forschungseinheiten

Microbiome Dynamics Gianni Panagiotou Mehr erfahren

Leibniz-HKI-Autor*innen

Wolfgang Schmidt-Heck

Details

Themenfelder

Systembiologie von Erkrankungen

Identifier

doi: 10.1038/s41467-020-15505-4

PMID: 32265441