Targeting p130Cas- and microtubule-dependent MYC regulation sensitizes KRAS mutant pancreatic cancer to ERK MAPK inhibition

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Abstract

To identify therapeutic targets for KRAS-mutant pancreatic cancer, we conducted a druggable genome siRNA screen and determined that suppression of BCAR1 sensitizes pancreatic cancer cells to ERK inhibition. Integrative analysis of genome-scale CRISPRCas9 screens also identified BCAR1 as a top synthetic lethal interactor with mutant KRAS. BCAR1 encodes the SRC homology subunit of p130Cas. We determined that SRC inhibitor-mediated suppression of p130Cas phosphorylation impairs MYC transcription through a DOCK1-RAC1-β-catenin dependent mechanism. Additionally, genetic suppression of TUBB3, encoding the α III-tubulin subunit of microtubules, or pharmacological inhibition of microtubule function, decreased levels of MYC protein and potently sensitized pancreatic cancer cells to ERK inhibition. Accordingly, the combination of a dual SRC/tubulin inhibitor with an ERK inhibitor cooperated to reduce MYC protein and to synergistically suppress the growth of KRAS-mutant pancreatic cancer. Thus, we demonstrate that mechanistically diverse combinations with ERK inhibition suppress MYC to impair pancreatic cancer proliferation.

siRNA screen identifies BCAR1 and TUBB3 as sensitizers to ERKi with SCH772984

BCAR1 transcriptionally regulates MYC levels through a SRC-p130Cas-DOCK1-RAC1-β-catenin pathway

Combination KX2-391 and ERKi treatment causes synergistic MYC suppression and apoptosis

Model

Combination KX2-391 and ERKi treatment synergistically reduces PDAC tumorigenic growth

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