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The RhoGEF GEF-H1 is required for RAS oncogene-driven Pancreatic cancer

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Activating mutations in RAS are a nearly uniform genetic feature of pancreatic adenocarcinomas. Cellular transformation by oncogenic RAS engages the MAPK pathway under strict spatiotemporal regulation by the scaffold protein KSR-1. In order to gain insight into the signaling elements required for RAS transformation we performed a high content shRNA based genetic screen on human cancer cell lines harboring RAS mutations. We describe the identification of GEF-H1, a RHO guanine nucleotide exchange factor known to be associated with the microtubule-array required for RAS transformation. We show that GEF-H1 is essential for the growth and survival of RAS^{V12}-transformed cancer cells and for tumor growth in *in vivo* pancreatic xenograft models. GEF-H1 expression is induced by oncogenic RAS and is correlated with pancreatic neoplastic progression in patient tumor samples. We provide mechanistic insight into a novel function for GEF-H1 as an activator of the MAPK pathway: GEF-H1 is required to recruit PP2A B' subunits to its substrate KSR-1 which when dephosphorylated on S392 potentiates flux through the MAPK pathway. Our results therefore identify GEF-H1 as an amplifier of MAPK signaling and provide mechanistic insight to the progression of RAS-mutated cancers.

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