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The mitogen-activated protein kinase (MAPK) pathway consists of the RAS family of small GTPases and a protein kinase cascade comprised of RAF, MEK, and ERK. A number of proteins mediate signaling from receptor tyrosine kinases (RTKs) to RAS, including adaptor proteins, phosphatase SHP2, and guanine nucleotide exchange factors (GEFs). The RTK-MAPK pathway is tightly regulated and feedback inhibition occurs at multiple levels of the pathway.

Mutations in RTKs, KRAS/NRAS/HRAS, and BRAF are frequently found in various cancers, resulting in aberrant activation of the MAPK pathway. Many inhibitors targeting this pathway have been developed but they only had limited efficacy in RAS mutant tumors. Feedback activation of the RTK-MAPK pathway following treatment with MAPK inhibitors is thought to contribute to the incomplete pathway inhibition. My lab is interested in the various feedback activation mechanisms of the RTK-MAPK pathway. This knowledge is critical to develop combination strategies for MAPK inhibitors to achieve durable pathway inhibition and better anti-tumor efficacy. Specific areas of interest include:

1. Characterizing feedback activation mechanisms following treatment with MAPK inhibitors in RAS mutant cells.
2. Performing CRISPR-based screens to identify modulators of sensitivity to MAPK inhibitors.
3. Studying clinically-relevant resistance mechanisms to RTK inhibitors and MAPK inhibitors.

Selected Publications

Inactivating mutations of RNF43 confer Wnt dependency in pancreatic ductal adenocarcinoma.
Jiang X, Hao HX, Growney JD, Woolfenden S, Bottiglio C, Ng N, Lu B, Hsieh MH, Bagdasarian L, Meyer R, Smith TR, Avello M, Charlat O, Xie Y, Porter JA, Pan S, Liu J, McLaughlin ME, Cong F.
Proc Natl Acad Sci U S A. 2013 Jul; 110(31):12649-54.

ZNRF3 promotes Wnt receptor turnover in an R-spondin-sensitive manner.
Hao HX, Xie Y, Zhang Y, Charlat O, Avello M, Lei H, Mickanin C, Liu D, Ruffner H, Mao X, Ma Q, Zamponi R, Bouwmeester T, Finan MP, Kirschner WM, Porter AJ, Serluca F, Cong F.
Nature. 2012 May; 485(7397):195-200.

SDH5, a gene required for flavination of succinate dehydrogenase, is mutated in paraganglioma.
Hao HX, Khalimonchuk O, Schraders M, Dephoure N, Bayley JP, Kunst H, Devilee P, Cremers CW, Schiffman JD, Bentz BG, Gygi SP, Winge DR, Kremer H, Rutter J.
Science. 2009 Aug; 325(5944):1139-42.

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