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Précis: Clinically observed in-frame tandem duplication of the EGFR kinase domain is a recurrent oncogenic driver alteration in NSCLC and confers sensitivity to EGFR inhibitors.

Genomic Characterization of Brain Metastases Reveals Branched Evolution and Potential Therapeutic Targets ... 1164
Précis: Sequencing of matched primary tumors and brain metastases reveals branched evolution and frequent oncogenic alterations in potentially targetable pathways.
See commentary, p. 1124

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**NF2 Loss Promotes Oncogenic RAS-Induced Thyroid Cancers via YAP-Dependent Transactivation of RAS Proteins and Sensitizes Them to MEK Inhibition** .......................... 1178


**Précis:** Loss of NF2 promotes thyroid tumorigenesis by increasing expression of both wild-type and mutant RAS in a YAP-dependent manner, resulting in enhanced dependency on MAPK signaling.

PtDNA(3,4,5)P3-Dependent Activation of the mTORC2 Kinase Complex ........ 1194


**Précis:** Association of the SIN1 PH domain with the mTOR kinase domain suppresses mTORC2 kinase activity, which is relieved by PtDNA(3,4,5)P3 binding to SIN1 or by cancer patient-derived SIN1 PH domain mutations that prohibit mTOR binding.

See commentary, p. 1177

**ON THE COVER**

García-Rendueles, Ricarte-Filho, and colleagues found that chr22q LOH is a common event in poorly differentiated thyroid cancer (PDTC) and is preferentially associated with RAS mutations. In mice, neither thyroid-specific activation of Hras nor NF2 deletion was sufficient for transformation, but their combined disruption led to highly penetrant PDTC characterized by increased MAPK signaling. Inactivation of the Hippo pathway in NF2-deficient cells increased YAP-mediated transcription of wild-type and mutant RAS isoforms, whereas disruption of YAP–TEAD binding blocked RAS transcription and inhibited cancer cell growth. Additionally, NF2 loss sensitized RAS-mutant thyroid cancer cells to MEK inhibitors. These results identify YAP as a critical effector of RAS-induced tumorigenesis and suggest that inhibition of YAP or MEK may be effective in RAS-driven thyroid cancer. For details, please see the article by García-Rendueles, Ricarte-Filho, and colleagues on page 1178.

**Harnessing Connectivity in a Large-Scale Small-Molecule Sensitivity Dataset** .......................... 1210


**Précis:** Integration of small-molecule cancer cell line sensitivity profiles with known drug targets and genomic features reveals context-driven vulnerabilities and small-molecule mechanisms of action.

See commentary, p. 1130