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NUCLEAR YAP INDUCES AGGRESSIVE THYROID TUMORS AND CONFERS PRIMARY RESISTANCE TO VEMURAFENIB

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OBJECTIVES

YAP overexpression or activation promotes tumorigenesis in many human cancers. However, mutations in the YAP-Hippo pathway are rare. Despite this, nuclear YAP correlates with poor prognosis in various cancers and its aberrant activation induces EMT, proliferation, a pro-tumoral microenvironment and metastasis. YAP is implicated in resistance to targeted therapies; the mechanisms are unknown. We investigated YAP localization, pathway dependency, and its role in response to BRAF-inhibitors in thyroid cancer.

METHODOLOGY

We screened 52 thyroid cancer cell lines and 62 tumor samples for illegitimate nuclear YAP. We engineered doxycycline-inducible thyroid-specific mouse model expressing YAPS127A, alone or in combination with endogenous expression of BRAFv600E. We generated cell lines expressing dox-inducible shmiR-E-YAP and/or YAPS127A and used cell viability, invasion assays, immunofluorescence, western-blotting, qRT-PCRS, flow cytometry, RNA-seq and in vivo tumorigenesis.

RESULTS

We found that 27/52 thyroid cancer cell lines had constitutively aberrant nuclear YAP, which rendered them dependent on YAP for viability, invasiveness and sensitivity to a YAP inhibitor. Nuclear YAP was found frequently in human thyroid cancers, especially in those harboring BRAF/RAS-driver mutations. Constitutively nuclear YAP was sufficient to induce thyroid tumor formation in vivo and in cooperation with BRAFv600E induced a more aggressive phenotype. Presence of nuclear YAP in BRAF-mutant thyroid cells conferred resistance to vemurafenib through transcriptional activation of nrg1/her2/her3; which was abrogated by silencing YAP and relieved by pan-HER kinase inhibitors.

CONCLUSIONS

YAP activation generates a dependency on this transcription factor. Nuclear YAP governs intrinsic resistance to RAF kinase inhibitors and induces a gene expression program in BRAFv600E-mutant cells encompassing effectors in the NRG1 pathway.