Relief of feedback inhibition of HER3 transcription by RAF and MEK inhibitors attenuates their antitumor effects in BRAF-mutant thyroid carcinomas

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Abstract

The RAF inhibitor vemurafenib (PLX4032) increases survival in patients with BRAF-mutant metastatic melanoma, but has limited efficacy in patients with colorectal cancers. Thyroid cancer cells are also comparatively refractory to RAF inhibitors. In contrast to melanomas, inhibition of mitogen-activated protein kinase (MAPK) signaling by PLX4032 is transient in thyroid and colorectal cancer cells. The rebound in extracellular signal-regulated kinase (ERK) in thyroid cells is accompanied by increased HER3 signaling caused by induction of ERBB3 (HER3) transcription through decreased promoter occupancy by the transcriptional repressors C-terminal binding protein 1 and 2 and by autocrine secretion of neuregulin-1 (NRG1). The HER kinase inhibitor lapatinib prevents MAPK rebound and sensitizes BRAF-mutant thyroid cancer cells to RAF or MAP-ERK kinase inhibitors. This provides a rationale for combining ERK pathway antagonists with inhibitors of feedback-reactivated HER signaling in this disease. The determinants of primary resistance to MAPK inhibitors vary between cancer types, due to preferential upregulation of specific receptor tyrosine kinases, and the abundance of their respective ligands.Significance: Thyroid cancer cell lines with mutant BRAF are resistant to PLX4032. RAF inhibitors transiently inhibit the ERK pathway and de-repress HER3 transcription. In the context of constitutive NRG1 secretion, this results in an ERK and AKT rebound that diminishes the antitumor effects of RAF inhibitors, which is overcome by combination with lapatinib. Cancer Discov; 3(5); 520–33. ©2013 AACR.See related commentary by Girotti and Marais, p. 487This article is highlighted in the In This Issue feature, p. 471.