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Targeted Therapy

Major finding: MEK inhibition suppresses *HRAS*-mutant skin tumors in BRAF inhibitor–treated mice.

Concept: Secondary tumors with *RAS* mutations arise due to paradoxical MAPK activation.

Impact: BRAF inhibitors do not initiate cancer but potentiate preexisting oncogenic *RAS* mutations.

COMBINED MEK AND BRAF INHIBITION MAY BLOCK SECONDARY SKIN CANCERS

Approximately 15% to 30% of melanoma patients treated with BRAF inhibitors such as vemurafenib develop cutaneous squamous-cell carcinomas and keratoacanthomas within the first few weeks of therapy, but the mechanisms underlying the rapid formation of these secondary malignancies remain incompletely characterized. Previous studies have indicated that BRAF inhibitors drive paradoxical activation of the mitogen-activated protein kinase (MAPK) pathway in *BRAF* wild-type tumor cell lines harboring *RAS* mutations. Furthermore, a recent analysis of squamous-cell carcinomas and keratoacanthomas in BRAF inhibitor–treated patients identified several mutations in *RAS* genes. Su and colleagues identified frequent *RAS* mutations in the vemurafenib–treated tumors they tested, with the most prevalent mutation being HRAS Q61L. The vast majority of the tumors arose in patients with chronically sun-damaged skin, suggesting that these mutations may have existed prior to treatment. To further characterize the interaction between BRAF inhibitors and mutant HRAS, the authors exposed cells harboring *HRAS* mutations to vemurafenib and observed that treatment induced anchorage-independent growth in soft agar that corresponded with increased extracellular signal-regulated kinase (ERK) phosphorylation and expression of MAPK pathway genes. Because these observations were consistent with a mechanism whereby paradoxical activation of the MAPK pathway by vemurafenib drives proliferation of *HRAS*-mutant cells, the authors tested the effects of BRAF inhibition in a mouse skin carcinogenesis model. The vemurafenib analogue PLX4720 dramatically accelerated tumor growth in mice treated with carcinogens and tumor promoters but did not induce tumors in mice treated with carcinogens alone. Thus, PLX4720 accelerated tumor growth in susceptible individuals but is not a tumor promoter. Further, the MAP–ERK kinase (MEK) inhibitor PD184352 almost completely blocked the growth of the tumors, providing preclinical evidence that MEK inhibitors may prevent secondary tumor development driven by BRAF-drug mediated paradoxical activation of the MAPK pathway in cells with oncogenic *RAS* mutations. ■

Su F, Viros A, Milagre C, Trunzer K, Bollag G, Spleiss O, et al. RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. N Engl J Med 2012;366:207–15.

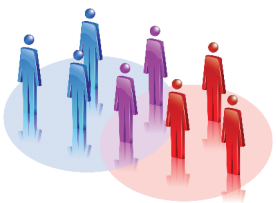
Hepatocellular Carcinoma

Major finding: ER recruitment by FOXA1/2 protects against HCC, and AR recruitment promotes HCC.

Mechanism: EREs and AREs are found near the same FOXA1/2 binding sites in the liver.

Impact: Mutations in FOXA1/2 binding sites that impair ER binding may increase HCC risk in women.

FOXA1 AND FOXA2 ARE REQUIRED FOR HCC SEXUAL DIMORPHISM



Hepatocellular carcinoma (HCC) is sexually dimorphic in mammals, with males being much more likely to develop HCC than females. Because of the common roles of the forkhead box A (FOXA) transcription factors FOXA1 and FOXA2 in liver function and recruitment of estrogen receptor α (ER) and androgen receptor (AR) to *cis*-regulatory elements, Li and colleagues hypothesized that these proteins mediate the differential effects of estrogens and androgens on HCC development. Indeed, in mice in which both *Foxa1* and *Foxa2* had been specifically deleted in liver cells, the sexual dimorphism was completely reversed, with females developing multiple, large tumors and males exhibiting reduced tumor growth. Furthermore, *Foxa1/2* loss led to a dramatic reduction in genome-wide ER and AR binding and reversed expression of FOXA target genes. The vast majority of genes differentially expressed in males and females were co-occupied by either AR or ER and FOXA1/2, and both estrogen response elements (ERE) and androgen response elements (ARE) clustered near FOXA binding sites. Collectively, these findings suggest that gender-specific co-regulation of a common set of target genes by FOXA1/2 and steroid hormone receptors underlies the sexual dimorphism observed in HCC. Multiple FOXA2 binding site mutations that impaired FOXA2 and ER binding and altered target gene expression were specifically identified in the livers of women with HCC, providing further evidence that disease-causing single-nucleotide polymorphisms may lie in *cis*-regulatory elements and that deregulated FOXA binding may play a role in human hepatocarcinogenesis. ■

Li Z, Tuteja G, Schug J, Kaestner KH. Foxa1 and Foxa2 are essential for sexual dimorphism in liver cancer. Cell 2012;148:72–83.

AACR American Association for Cancer Research

CANCER DISCOVERY

FOXA1 AND FOXA2 are Required for HCC Sexual Dimorphism

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