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 anchor-age-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.


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 FOXA1/2 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.

FOXA1 AND FOXA2 are Required for HCC Sexual Dimorphism

Cancer Discovery 2012;2:201. Published OnlineFirst February 2, 2012.

Access the most recent version of this article at: doi:10.1158/2159-8290.CD-RW2012-014

Sign up to receive free email-alerts related to this article or journal.

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.