Déjà Vu: EGF Receptors Drive Resistance to BRAF Inhibitors

In 2002 (1), the first cancer genome resequencing study was published. It reported that the BRAF gene is mutated in approximately 7% of human cancers, and it took less than a decade for this seminal discovery to impact the clinical management of human cancer. There are 3 RAF genes in humans (ARAF, BRAF, and CRAF), and they encode protein kinases that are components of a signaling pathway activated downstream of receptor tyrosine kinases (RTK) and the small G-protein RAS (Fig. 1A). RAF proteins activate MAP-ERK kinase (MEK), which then activates extracellular-regulated kinase (ERK) to regulate cell growth and survival (Fig. 1A).

BRAF mutations are common in melanoma (~50%), colorectal cancer (~15%), and papillary thyroid cancer (~40%; http://cancer.sanger.ac.uk/cosmic/), and this discovery led to rapid increases in our understanding of the molecular mechanisms underlying tumorigenesis in those cancers and ignited a hunt for a BRAF-targeting drug. This investment paid off 2 years ago when vemurafenib (PLX4032/RG7204) was approved for treatment of BRAF-mutant melanoma by the U.S. Food and Drug Administration, receiving Canadian and European licenses a few months later.

Vemurafenib is a potent and selective BRAF inhibitor that increases progression-free and overall survival in approximately 80% of patients with melanoma whose tumors carry BRAF mutations (2, 3). In its wake are several equally promising BRAF drugs, such as dabrafenib (4), and several MEK inhibitors, such as trametinib (5) and selumetinib (6), which are also active in these patients. Thus, following advances in chronic myeloid leukemia, gastrointestinal stromal tumors, and lung cancer, BRAF and MEK inhibitors have made personalized medicine a reality for patients with melanoma and changed the perception that this disease is essentially untreatable.

Curiously, despite the remarkable responses to BRAF/MEK inhibitors in melanoma, the response of other BRAF-driven cancers to these drugs is very disappointing. Only approximately 5% of BRAF-mutant colorectal patients respond to vemurafenib (7), and thyroid cancers do not respond to selumetinib (8). In this issue of Cancer Discovery, Montero-Conde and colleagues (9) investigate the reasons underlying the intrinsic resistance of BRAF-mutant thyroid cancer cells to BRAF inhibitors. They show that while BRAF and MEK inhibitors induce sustained ERK inhibition in BRAF-mutant melanoma cells, they induce only transient ERK inhibition in BRAF-mutant thyroid cancer cells and that the rapid rebound in signaling is due to increased signaling by HER3, a member of the EGF receptor family.

HER3 activation appears to be part of a generalized hyperactivation of RTKs, but it is HER3 together with the closely related HER2 that reactivates RAS-ERK signaling and allows the cells to bypass the growth-inhibitory effects of BRAF inhibition (Fig. 1B). Notably, vemurafenib increases neuregulin-1 (NRG1) (the HER3 ligand) production. Intriguingly, the authors also found that oncogenic BRAF normally blocks HER3 expression through the transcriptional repressors C-terminal binding protein 1 and 2 (CTBP1/2), so BRAF inhibition increases HER3 expression (Fig. 1B). Thus, they have revealed the release of a feedback loop from oncogenic BRAF to HER3 and a general call to arms by this pathway that releases the cells’ addiction to oncogenic BRAF when BRAF is inhibited.

This all sounds curiously familiar. Last year, it was shown that colorectal cells are also insensitive to vemurafenib because of elevated HER1 (EGF receptor) signaling (10, 11). Here, again, vemurafenib only induced transient ERK inhibition with the rebound being driven by HER1, which signaled through RAS to AKT (10, 11). In elegant experiments, it was also shown that in colorectal cells, oncogenic BRAF drives expression of CDC25C, a phosphatase that negatively regulates HER1 (11). Thus, when BRAF was inhibited, CDC25C expression was lost, leading to HER1 activation. Thus, although the molecular details differ in both thyroid and colorectal cancers, BRAF inhibitors release a feedback loop that activates intrinsic resistance against themselves (Fig. 1B).

Increased RTK signaling also mediates acquired resistance to BRAF inhibitors in melanoma cells. A disappointment with BRAF and MEK drugs is that despite remarkable
Figure 1. Mechanisms of resistance to BRAF inhibitors. A, gray rectangle: mutant BRAF (BRAF\textsuperscript{V600E}) hyperactivates ERK signaling and promotes tumor cell proliferation and survival, but BRAF and MEK drugs inhibit the pathway and block tumor progression. Main figure: resistance to BRAF inhibitors is mediated by several mechanisms, including expression of a truncated form of mutant BRAF, increased expression of mutant BRAF or wild-type CRAF, acquisition of mutations in RAS or MEK, expression of MAP3K8/COT, loss of PTEN expression, activation of the receptor tyrosine kinases PDGFR\textbeta, IGF-IR, HER1, and HER2/HER3, or increased activation of MET through the increased secretion of hepatocyte growth factor (HGF) by the stromal compartment.

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B, EGF family receptors mediate resistance to BRAF inhibitors. In colorectal cells, BRAF inhibits HER1 by inducing CDC25C, so BRAF inhibition by vemurafenib (Vem) releases the block to HER1 activation by reducing CDC25C expression. In thyroid cancer cells, HER3 expression is inhibited by BRAF through the CTBP1/2 transcriptional repressors, so BRAF inhibition by vemurafenib results in increased HER3 expression, and it also increases NRG1 expression through unknown mechanisms. In melanoma, BRAF inhibition by vemurafenib drives HER1 signaling by increasing EGF secretion, increasing HER1 expression and suppressing MIG6 activity through unknown mechanisms.

Disclosure of Potential Conflicts of Interest
R. Marais has received honoraria from the Roche Speakers Bureau; is a consultant/advisory board member of Servier and GSK; and has given expert testimony for The Institute of Cancer Research. As a former employee of The Institute of Cancer Research, R. Marais also participates in a “Rewards to Inventors Scheme,” which could provide financial benefits for contributions to programs that are commercialized. No potential conflicts of interest were disclosed by the other author.

Grant Support
R. Marais is supported by 2 grants from Cancer Research UK (C107/A10433 and C5759/A12328).

Published online May 8, 2013.

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