Overcoming Resistance to MAPK Pathway Inhibitors

Michael A. Davies, Scott Kopetz

Correspondence to: Scott Kopetz, MD, PhD, Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 426, Houston, TX 77030 (e-mail: skopetz@mdanderson.org).

The MAPK pathway is one of the most heavily studied pathways in cancer. The MAPK pathway is an important regulator of many processes that are critical to the malignant phenotype, and a variety of genetic alterations that activate the pathway have been detected in many different kinds of cancer. As a result, the development of inhibitors against the pathway has been an active area of investigation for many years.

After many years of negative results, the clinical value of this pathway has now been validated by the results of several clinical trials in patients with metastatic melanoma. Activating mutations in BRAF are present in approximately 45% of cutaneous melanoma patients, whereas another 20% harbor activating mutations in NRAS (1). These mutations, particularly the most common BRAF mutation (V600E), result in constitutive activation of the MAPK pathway. Two different small molecule inhibitors of V600-mutant BRAF proteins, vemurafenib and dabrafenib, have demonstrated statistically significant improvement in clinical response rate, progression-free survival, and overall survival compared with chemotherapy in randomized phase III trials in metastatic melanoma patients with BRAF V600 mutations (2,3). Treatment with trametinib, a small-molecule inhibitor of MEK1/2, has recently also been shown to improve these outcomes in a randomized phase III trial in BRAF V600-mutant metastatic melanoma patients (4). Although these responses have provided tremendous clinical benefit in this highly aggressive disease, unfortunately the duration of the responses to the BRAF and the MEK inhibitors has been relatively short (median = 5 months).

An improved understanding of the mechanisms of resistance to these agents may identify rational, more effective combinatorial approaches. In this issue of the Journal, Smith et al. (5) studied human melanoma cells with both induced and de novo resistance to MEK inhibitors in vitro. In this study, resistance to cell killing by MEK inhibitors in human melanoma cells corresponded with overexpression of MITF, a transcription factor that regulates many genes involved in melanogenesis and is amplified in approximately 20% of melanomas (6). The investigators demonstrated that MITF expression in these cells was regulated epigenetically by signaling related to transforming growth factor beta (TGF-β) (5). Specifically, resistance correlated with increased expression of SMURF2, a ubiquitin ligase that downregulates the expression of inhibitory SMADs, including those that regulate the PAX3 transcription factor. Inhibition of MITF expression, either by treatment with TGF-β or by small interfering RNA–mediated knockdown of SMURF2, PAX3, or MITF, sensitized the melanoma cells to apoptosis induction by MEK inhibitors. Examination of commercial cDNA arrays demonstrated that clinical samples of stage III and stage IV melanoma metastases exhibited higher levels of SMURF2 mRNA than normal skin and that SMURF2 levels correlated with PAX3 expression. Of note, there was no comparison to nontransformed melanocytes, primary melanomas, or clinical features/outcomes.

These findings add to the growing list of factors associated with resistance to MAPK pathway inhibitors. Previously, a random mutagenesis screen demonstrated that several mutations in MEKI could cause resistance to MEK inhibitors in BRAF-mutant melanomas (7). This finding was validated clinically by the identification of MEKI mutations in progressing tumors in patients after initial clinical responses to MEK inhibitors. Some MEKI mutations have also been implicated in resistance to selective BRAF inhibitors, but other mutations have been identified in the tumors of patients that responded to these agents (8,9). Both amplification and alternative splicing of the BRAF gene have also been identified in BRAF-mutant clinical specimens and cell lines with induced resistance to apoptosis induction by BRAF inhibitors (10,11). However, cells with these aberrations retain their sensitivity to MEK inhibition. In contrast, concurrent activation of the PI3K–AKT pathway has been shown to inhibit apoptosis induction by BRAF and MEK inhibitors. Activation of the PI3K–AKT pathway in BRAF-mutant melanomas has been shown to be mediated in a tumor-intrinsic manner by loss of PTEN and by overexpression of receptor tyrosine kinases and also extrinsically by production of hepatocyte growth factor by the tumor microenvironment (12–15). Although almost all of these melanoma-based studies have been conducted in BRAF-mutant models, a recent study in a genetically engineered mouse model of NRAS-mutant melanomas demonstrated markedly synergistic antitumor effects in vivo for combined inhibition of MEK and CDK4 (16). Interestingly, the major molecular difference between this combination and single-agent MEK inhibition was not superior apoptosis induction but, instead, markedly increased reduction of cellular proliferation.

The implied role for TGF-β signaling and MITF in MEK inhibitor resistance in melanoma may have clinical implications. However, as Smith et al. (5) noted, additional studies are needed to determine if the changes that have been observed in their cell lines also correlate with either de novo or secondary resistance to MEK inhibitors in patient samples. Of note, the functional and predictive significance of TGF-β, SMURF2, PAX3, and MITF in sensitivity to selective BRAF inhibitors was not reported in the study. Smith et al. (5) did report that inhibition of SMURF2 did not sensitize a BRAF-mutant colon cancer cell line to MEK inhibitor–induced apoptosis; they also noted that this cell line did not express MITF. Although previous studies have identified MITF amplification as a melanoma lineage-specific phenomenon (6), it is possible that upregulation of MITF mRNA and protein expression could be more pervasive in colon cancer and/or other tumor types in which MAPK pathway inhibitors are being tested (17). The marked heterogeneity of MITF expression in the examined melanoma cell lines supports the rationale for broader testing of this hypothesis.

If studies of clinical specimens further support a role for increased SMURF2 and/or MITF expression in resistance to MAPK pathway inhibitors, the clinical challenge will be how to exploit this information to improve outcomes in patients. At this
time, there is no specific therapeutic strategy to directly inhibit either of these targets; however, the identification of the downstream effectors that mediate the resistance could illuminate potential therapeutic strategies. The experiments reported by Smith et al. (5) did not exclude the possibility of overlap of SMURF2/PAX3/MITF-mediated resistance with other MEK-independent resistance mechanisms, such as cell cycle regulation, receptor tyrosine kinase expression, or PI3K–AKT pathway activation. A broad cataloging of these and other emerging resistance mechanisms in clinically annotated specimens may shed further insights into the heterogeneity of MAPK pathway inhibitor resistance and ultimately enhance the clinical benefit of targeting the MAPK pathway in patients.

References


Notes

Dr. Kopetz has provided compensated consulting to GSK, Roche, AstraZeneca, and receives research support from AstraZeneca. Dr. Davies has provided compensated consulting to GSK, Genentech, and Novartis, and has received research support from AstraZeneca, GSK, Genentech, Merck, Myriad, and Oncothyreon.

Affiliation of authors: Departments of Melanoma Medical Oncology and Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX (MAD, SK).