ERK Pathway Inhibitors: How Low Should We Go?

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Summary: Resistance to RAF inhibitors is generally accompanied by reactivation of extracellular signal-regulated kinase (ERK) signaling. SCH772984, a selective, ATP-competitive inhibitor of ERK1 and ERK2, is effective in BRAF-mutant models in which resistance is the result of ERK reactivation. SCH772984 may also have a role in the treatment of tumors in which ERK is dysregulated by mutant RAS, NF1, or activated receptor tyrosine kinases, settings in which current RAF inhibitors are ineffective. Cancer Discov; 3(7); 719–21. © 2013 AACR.

See related article by Morris et al., p. 742 (11).

The mitogen-activated protein kinase (MAPK) pathway is a key regulator of cellular proliferation and survival. The pathway is a three-tiered kinase cascade consisting of the RAF, MEK (MAP-ERK kinase), and ERK (extracellular signal-regulated kinase) kinases (Fig. 1). In normal cells, RAS activates RAF kinases, in part by promoting the formation of RAF dimers. Active RAF in turn phosphorylates and activates MEK1 and MEK2, which upon activation phosphorylate ERK1 and ERK2. ERK exerts its cellular effects by regulating the activity and expression of multiple nuclear transcription factors and cytosolic proteins. Somatic alterations in MAPK pathway components that deregulate the pathway are highly prevalent in human cancer. ERK pathway activation in tumors can result from mutations in all three RAS genes (KRAS, NRAS, HRAS), mutations in BRAF and MAP2K1 (MEKI), loss of NF1 function due to mutation, deletion, and/or promoter methylation, and activation of RAS by cell surface receptors.

Intensive efforts have been directed toward the identification of preclinical and clinical development of selective inhibitors of MAPK signaling for use as anticancer therapies. Clinically useful, direct inhibitors of oncogenic RAS have yet to be identified. One alternative approach is to target the downstream effector kinases responsible for RAS-mediated transformation. Great success has been achieved with the use of selective inhibitors of RAF (vemurafenib and dabrafenib). Vemurafenib is U.S. Food and Drug Administration–approved for patients with BRAF-mutant melanoma and has shown unprecedented clinical activity in this setting (1). Vemurafenib, however, inhibits ERK pathway activity only in tumors that harbor mutations in BRAF and is ineffective in cancers in which ERK activity is driven by RAS mutations or receptor tyrosine kinase (RTK) activation (2). In fact, ATP-competitive RAF inhibitors enhance ERK signaling in BRAF–wild-type cells. The mechanistic basis for this “paradoxical” activation of ERK signaling, namely, drug-mediated transactivation of RAF dimers (3), has implications for the development of novel therapeutic strategies seeking to address both intrinsic and acquired resistance to RAF inhibitors.

Vemurafenib and dabrafenib induce tumor regression in most patients with BRAFV600E melanoma, but complete remissions are rare and responses are often temporary (1). Several mechanisms of resistance to vemurafenib have been identified in clinical samples. The majority result in reactivation of ERK signaling despite continued presence of the drug by increasing cellular RAS-GTP levels (RAS mutation, NF1 loss, expression of upstream RTKs) or by causing mutant BRAF to dimerize in a RAS-independent manner (BRAF splice variants) (4, 5). Others bypass tumor dependence on mutant RAF by activating ERK in a RAF-independent manner (MEK1 mutation) or through activation of parallel signaling pathways such as the phosphoinositide 3-kinase/AKT pathway (6, 7). The effects of vemurafenib on ERK activity in BRAF-mutant cells can also be attenuated by the relief of ERK-dependent negative feedback that in untreated cells suppresses RTK signaling upstream of the mutant oncogene. This adaptive response to RAF inhibition occurs rapidly (within hours), limits the effectiveness of the drug, and may facilitate the selection of drug-resistant clones (8, 9).

The observation that vemurafenib resistance is often mediated by the reactivation of ERK signaling is the basis for ongoing clinical trials combining RAF and MEK inhibitors. By inhibiting RAF dimer-dependent ERK activation, cotreatment with a MEK inhibitor results in more potent and durable suppression of ERK signaling and greater antitumor effects in preclinical models (8). Combination therapy may also delay or prevent the emergence of preexisting drug-resistant clones, thus extending the duration of response. In support of this approach, a recent randomized trial comparing the combination of dabrafenib and trametinib to dabrafenib monotherapy noted a significant prolongation of progression-free survival with the combination (9.4 months as compared with 5.8 months in the monotherapy group) in patients with BRAF-mutant melanoma (10). As discussed above, RAF inhibitors
paradoxically enhance ERK signaling in BRAF–wild-type cells, and many of the toxicities associated with the use of these agents can be attributed to increased ERK activation in normal tissues. MEK inhibitors suppress ERK activity in normal cells and, therefore, if titrated appropriately, attenuate the ERK-associated toxicities of the RAF inhibitor. Consistent with this model, the incidence of squamous carcinomas, keratoacanthomas, and other skin toxicities is lower in patients treated with the RAF and MEK inhibitor combination than with either agent alone (10). In sum, the utility of RAF inhibitors is confined to tumors with mutant BRAF and limited by the emergence of drug-resistant ERK activation. Thus, there is an urgent need for new inhibitors of the MAPK pathway for patients with vemurafenib-resistant BRAF-mutant melanomas and for tumors in which ERK activity is driven by activation of RAS.

With the goal of addressing this unmet medical need, Morris and colleagues (11) report in this issue of Cancer Discovery the identification and functional characterization of a novel, selective ERK inhibitor. The investigators initially conducted an affinity-based screen to identify compounds that bind selectively to the unphosphorylated form of ERK2. Additional synthetic chemistry efforts then led to the identification of SCH772984, a highly selective, ATP-competitive inhibitor of ERK1 and ERK2 (IC₅₀ values of 4 and 1 nmol/L, respectively). In addition to its direct effect on ERK kinase activity, SCH772984 also inhibits MEK-mediated phosphorylation of ERK, presumably through an allosteric mechanism. In contrast to RAF inhibitors, both MEK (trametinib) and ERK inhibitors downregulate ERK activity in both tumor cells and normal cells. Dotted arrows represent presumed activation.

**Figure 1.** MAPK pathway inhibitors. RAS activation promotes the formation of RAF dimers. RAF phosphorylates MEK, which upon activation phosphorylates ERK. ERK regulates both cytosolic targets and nuclear transcription factors, thus promoting proliferation, survival, and other hallmarks of transformation. ERK pathway activity is regulated by negative feedback at multiple levels, including the transcriptional activation of SPROUTY (SPRY) and DUSP proteins that negatively regulate the pathway at the level of RTKs, RAS, RAF, and ERK. ERK also phosphorylates and thus regulates CRAF activity directly. The RAF inhibitors vemurafenib and dabrafenib inhibit ERK activation only in BRAF-mutant tumors. These agents induce a paradoxical activation of ERK in BRAF–wild-type cells via transactivation of RAF dimers. SCH772984 is an ATP-competitive inhibitor of ERK. SCH772984 also inhibits MEK-mediated phosphorylation of ERK, presumably through an allosteric mechanism. In contrast to RAF inhibitors, both MEK (trametinib) and ERK inhibitors downregulate ERK activity in both tumor cells and normal cells. Dotted hammers represent pathway-induced feedback inhibition. Dotted arrows represent presumed activation.
as monotherapy in patients with BRAF-mutant tumors that initially responded to but then developed resistance to RAF inhibitors. As with MEK inhibitors, testing of ERK inhibitors in combination with RAF inhibitors is also warranted. RAF inhibitors and ERK inhibitors have opposing activity in normal cells and, thus, the RAF/ERK combination may be less toxic than the use of either drug alone, as has been noted with the RAF/MEK combination. While the mechanisms of resistance to SCH772984 will likely differ from those of MEK inhibitors, the kinetics with which drug-resistant clones emerge may prove similar. The ability of SCH772984 to block phosphorylation of ERK may, however, make this compound less susceptible than MEK inhibitors to relief of upstream negative feedback. Furthermore, as ERK is the primary downstream effector of MAPK pathway activation, ERK inhibitors may prove to be less susceptible to oncogenic bypass than inhibitors of RAF and MEK.

In summary, the data reported by Morris and colleagues (11) in this issue of Cancer Discovery support the study of ATP-competitive ERK inhibitors in patients whose tumors exhibit mutational activation of the MAPK pathway. As with MEK inhibitors, the combination of RAF and ERK inhibitors may have greater antitumor effects and less toxicity than either agent alone in patients with BRAF-mutant tumors. ERK inhibitors may also have a role in the treatment of tumors in which ERK is dysregulated by mutant RAS, NF1, or activated RTKs, settings in which vemurafenib is ineffective. The primary unanswered question is whether ERK inhibitors will in fact prove superior to MEK inhibitors in clinical practice. As ERK inhibitors downregulate ERK signaling in both tumor and normal cells, skin rash and other toxicities attributable to ERK pathway inhibition in normal cells will likely be dose limiting. Clinical trials are thus needed to determine whether the narrow therapeutic index associated with unopposed ERK pathway inhibition in normal cells will limit the use of ERK inhibitors in RAS mutant/activated tumors, as has been the case with MEK inhibitors. Given the expected narrow therapeutic index of ERK inhibitors, early clinical trials should explore intermittent treatment schedules and consider the sequential alteration of MEK and ERK inhibition as strategies to minimize drug toxicity and to delay the emergence of drug-resistant clones (12).

Disclosure of Potential Conflicts of Interest

N. Rosen has received commercial research support from Chugai and Merck and is a consultant/advisory board member of Astra-Zeneca, Chugai, and Novartis. D.B. Solit is a consultant/advisory board member of Pfizer, Onyx, Chugai, Novartis, Endo Pharmaceuticals, and Merck. No potential conflicts of interest were disclosed by the other author.

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