FRONTLINE CML DRUGS DRIVE PARADOXICAL RAF ACTIVATION

Although RAF inhibitors are effective in cells with mutant *BRAF*, in settings of constitutively active RAS signaling, they paradoxically activate downstream mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK) and extracellular signal-regulated kinase (ERK) signaling by inducing BRAF and CRAF hetero- or homodimerization. To determine if other kinase inhibitors act in a similar manner, Packer and colleagues evaluated the ability of a panel of compounds to induce MEK and ERK phosphorylation in *RAS*-mutant melanoma cells. Surprisingly, imatinib, nilotinib, and dasatinib, 3 small-molecule ABL inhibitors used to treat chronic myelogenous leukemia (CML), stimulated robust MEK and ERK phosphorylation at low, physiologically relevant concentrations in *RAS*-mutant but not *BRAF*-mutant cells. Imatinib, nilotinib, and dasatinib all bound and weakly inhibited BRAF and CRAF kinase activity but induced robust, RAS-dependent RAF dimerization and MEK/ERK activation in cells expressing the drug-resistant BCR-ABL^{T315I} mutation. RAS is known to be activated downstream of BCR-ABL; therefore, the authors posited that, because BCR-ABL^{T315I} is resistant to imatinib, nilotinib, and dasatinib, RAS activity persists and can stimulate BRAF and CRAF to promote proliferation. The authors demonstrated that paradoxical MEK/ERK pathway activation is indeed an important drug resistance mechanism in CML, as nilotinib synergized with the MEK inhibitor PD184352 to inhibit the growth of drug-resistant BCR-ABL^{T315I} CML cells. The synthetic lethal interaction between nilotinib and PD184352 was likewise observed in cells expressing compound *BCR-ABL* mutants that also underlie clinical resistance, as well as in drug-resistant CML cells without acquired *BCR-ABL* mutations. Together, these results reveal an unexpected dependence of drug-resistant CML cells on MEK/ERK signaling and suggest that exploitation of the synthetic lethal interaction between nilotinib and MEK inhibitors may be an effective approach in patients with CML who have developed resistance through acquired *BCR-ABL* mutations.

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