ANTICANCER DRUGS

Keeping one step ahead

Inhibiting the oncogenic kinase BCR–ABL1, which causes chronic myeloid leukaemia (CML), is a paradigm for clinically successful targeted therapy. However, drug-resistant mutations frequently emerge during clinical treatment. A new study shows that attempting to inhibit drug-resistant BCR–ABL1 mutants can result in a counterproductive activation of oncogenic signalling, and suggests a synergistic strategy to overcome this resistance.

Richard Marais and colleagues studied the effects of various protein kinase inhibitors on human melanoma cells that express oncogenic $NRAS^{Q61L}$. They noticed that imatinib, nilotinib and dasatininb, which are all inhibitors of BCR–ABL1, paradoxically hyperactivated oncogenic signalling through the RAF–MEK–ERK kinase pathway. This also occurred in cells with activating KRAS mutations.

One possible mechanism of hyperactivating RAF–MEK–ERK signalling in RAS-mutant cells is through the partial inhibition of BRAF and CRAF: these kinases become active as both homodimers and heterodimers; when one RAF monomer is inhibited it can bind and activate a non-drug-bound RAF monomer. The authors confirmed that all three BCR–ABL1 inhibitors induced homodimerization and heterodimerization of BRAF and CRAF, and that the activation of signalling was dependent on a physical interaction between these RAF proteins and an activated RAS protein.

Are these potential off-target effects of BCR–ABL1 inhibitors on RAF proteins also seen in more relevant cell types expressing BCR–ABL1? In Ba/F3 mouse pro-B cells and human CML cells that both expressed BCR–ABL1, treatment with imatinib, nilotinib or dasatinib blocked RAF–MEK–ERK oncogenic signalling. However, in equivalent cells that expressed $BCR–ABL1^{T315I}$ (a clinically observed BCR–ABL1 mutant that is resistant to all of these inhibitors), treatment caused BRAF–CRAF heterodimerization and the hyperactivation of RAF–MEK–ERK signalling. Overall, these results suggest a model in which activation of RAS proteins (through mutation or through BCR–ABL1 activity) primes cells for RAF–MEK–ERK pathway hyperactivation through the off-target effects of BCR–ABL1 inhibitors on RAF proteins.

To test whether the RAF–MEK–ERK pathway hyperactivation could be therapeutically counteracted, the authors tested nilotinib in combination with a MEK inhibitor in Ba/F3 cells and in human CML cell lines that both expressed $BCR–ABL1^{T315I}$: these agents inhibited cell growth and induced apoptosis only in combination. Moreover, nilotinib synergized with a MEK inhibitor in primary, patient-derived $BCR–ABL1^{T315I}$ CML cells *ex vivo*, and also in Ba/F3 $BCR–ABL1^{T315I}$ mouse allografts *in vivo* when treatment started concurrently with the injection of cells. This synergy was also seen in a human CML cell line in which the resistance to BCR–ABL1 inhibitors was mediated by the overexpression of the tyrosine kinase LYN rather than by secondary BCR–ABL1 mutations.

It will be interesting to determine the effectiveness of this combination, relative to other therapeutic strategies, for treating established, drug-resistant CML in mice, and hopefully in patients with CML.

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ORIGINAL RESEARCH PAPER Packer, L. M. *et al.* Nilotinib and MEK inhibitors induce synthetic lethality through paradoxical activation of RAF in drug-resistant chronic myeloid leukemia. *Cancer Cell* **20**, 715–727 (2011)

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