GENETICS

TKI resistance: finding the crack in the BIM

Treatment with tyrosine kinase inhibitors (TKIs) can be effective in the majority of patients with cancers such as non-small-cell lung cancer (NSCLC) with mutations in *EGFR*, and chronic myeloid leukemia (CML) driven by the gene fusion *BCR-ABL*. However, 20% of patients have primary resistance to treatment with TKIs, and finding the origin of this intrinsic resistance is crucial when searching for an effective way to treat these patients.

Yijun Ruan and collaborators wondered whether sensitivity to TKIs might be affected by polymorphisms in genes involved in the apoptotic response to these drugs. To address this question, the researchers used parallel genomic sequencing to assess samples from five patients with CML who were resistant (three patients) or sensitive (two patients) to TKIs. The analysis revealed

a polymorphism in the gene encoding BCL2-like 11 (*BIM*) in those patients with primary resistance. This polymorphism resulted in expression of BIM isoforms that lacked the pro-apoptotic BH3 domain; a type of mutation that seems to be fairly common in East Asian populations (15%).

The influence of this polymorphism on resistance to TKIs was confirmed by a retrospective study that included 203 patients with CML from East Asian origin. This study compared the clinical response to the TKI imatinib in patients with and without mutations in *BIM*, and established an association between the polymorphism in *BIM* and clinical resistance to imatinib. In another study in patients with NSCLC, the presence of the polymorphism was predictive of a significantly shorter progression-free survival (6.6 months in patients with the polymorphism compared with 11.9 months in those without it).

Thankfully, it seems that overcoming this type of resistance to TKIs might be as

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straightforward as restoring BIM function with BH3-mimetic drugs, which are already being studied in clinical trials in combination with chemotherapy.

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Original article Ng, K. P. *et al.* A common BIM deletion polymorphism mediates intrinsic resistance and inferior responses to tyrosine kinase inhibitors in cancer. *Nat. Med.* doi:10.1038/nm.2713