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LEUKAEMIA

Targeted therapy re-enABLed?

Targeted therapies that are toxic only to cells with specific oncogenic lesions can be highly effective until resistance mechanisms emerge. A new study identifies BCL-6 overexpression as a resistance mechanism that arises during the targeted treatment of breakpoint cluster region (*BCR*)–*ABL1*-positive leukaemias and suggests a potential therapeutic opportunity to overcome this resistance.

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The *BCR–ABL1* fusion gene is found in nearly all chronic myeloid leukaemias (CMLs) and in ~25% of acute lymphoblastic leukaemias (ALLs); the resultant oncogenic protein can be targeted by tyrosine kinase inhibitors such as imatinib. On the basis that the acute cellular response to treatment could reveal protective feedback signalling and hence potential resistance mechanisms, Markus Müschen and colleagues analysed gene expression changes following imatinib treatment of human *BCR–ABL1* ALL and CML cell lines. They discovered that BCL-6 — a transcriptional repressor previously found to be subjected to oncogenic translocations in lymphomas — was highly upregulated. This upregulation appears to be due to reduced signalling through known downstream mediators of BCR–ABL1 signalling: BCL-6 induction by imatinib in ALL cells was abrogated by a constitutively active STAT5A mutant or by deletion of *Pten* (which reactivates the PI3K–AKT pathway).

To investigate whether BCL-6 was cytoprotective through transcriptional repression of known tumour suppressor genes, the authors used chromatin immunoprecipitation and showed that imatinib treatment causes a modest recruitment of BCL-6 to the promoters of the genes encoding p53, p21 and p27. As evidence that BCL-6 is functionally involved in the repression of tumour suppressor pathways, the authors found that ALL cells deficient for BCL-6 displayed upregulation of p53 and ARF, slower cell cycle progression, impaired colony forming ability and enhanced senescence induction. In addition, loss of BCL-6 reduced the *in vivo* transplantation efficiency of ALL cells, indicating a defective stem cell function. However, whether these effects of complete BCL-6 loss can be extrapolated to normal versus upregulated BCL-6 expression remains to be determined.

As proof that the BCL-6 expression level directly influences the response to imatinib (rather than merely being a readout of BCR–ABL1 inhibition) the authors found that loss or overexpression of BCL-6 had the expected effects on the *in vitro* sensitivity of ALL cells to imatinib.

Can this BCL-6-mediated resistance be overcome for therapeutic benefit? In an *in vivo* treatment study of xenografted ALL, treatment with retro-inverso BCL-6 peptide inhibitor (RI-BPI) sensitized the leukaemias to an alternative BCR–ABL1 inhibitor, nilotinib, and increased the survival of the mice. This suggests that BCL-6 inhibition may hold promise for overcoming clinical resistance to BCR–ABL1 inhibition.

This report reinforces the view that the status of signalling pathways downstream of BCR–ABL1 can be an important determinant of the therapeutic response to inhibition (in addition to the primary *BCR–ABL1* translocation and secondary mutations within the fusion gene). Also, in light of the defects seen in BCL-6-deficient cells, it will be interesting to further investigate the safety of systemic BCL-6 inhibition. Finally, whether BCL-6 inhibition can additionally sensitize CML to imatinib, or other cancers to other targeted agents, remains to be seen.

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ORIGINAL RESEARCH PAPER Duy, C. *et al. BCL6* enables Ph$^+$ acute lymphoblastic leukaemia cells to survive *BCR–ABL1* kinase inhibition. *Nature* **473**, 384–388 (2011)

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