HAEMATOLOGICAL CANCER PROMISING RESULTS OF BCL2 INHIBITION

Although often associated with a favorable prognosis, acute lymphoblastic leukaemia (ALL) is sometimes refractory to treatment. Studies have shown that the *TCF3-HLF* fusion transcript defines a group of patients with ALL who have a particularly poor prognosis. Using an integrated drug-response profiling approach in patient-derived xenografts, an international collaborative group lead by Martin Stanulla and Jean-Pierre Bourquin identified alternative treatment options for this deadly disease.

Combining genomic and functional studies to further profile *TCF3-HLF*-positive ALL, they found that the *TCF3-HLF* translocation occurs only in B-lymphoid progenitor cells and is accompanied by genetic alterations in *PAX5*, *BTG1* or *VPREB1* that impair pro-B cell differentiation into pre-B cells. Comparison with samples containing the *TCF3-PBX1* fusion, which is associated with a better prognosis, indicated that although both fusions occur in B-lymphoid cells, *TCF3-HLF* promotes transcriptional reprogramming towards a drug-resistant very immature state.

The researchers generated leukaemia xenografts for all the samples included in this study. The molecular features in these xenografts closely resembled the original patient samples. Drug-activity profiling in the xenografts revealed that *TCF3-HLF* ALL has a unique sensitivity to the BCL2-targeting agent venetoclax. Combination of this drug with conventional antileukaemic therapy induced prolonged remissions in patient-derived xenografts.

This study describes a valuable preclinical model to evaluate different treatment strategies for patients with ALL, which could provide a solid rationale for clinical trials. On the basis of these results, translational scientists at different centres across the world have proposed a joint effort to test venetoclax as part of a combination therapy for several ALL subtypes. As Bourquin notes, “this effort would help identify the right group of patients for treatment with the drug combinations that are right for them.” Importantly, he also states that, “it would be up to the pharmaceutical industry to take the challenge and collaborate with us in initiatives that will have a great impact for patients.”

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Original article Fischer, U. *et al.* Genomics and drug profiling of fatal *TCF3-HLF*-positive acute lymphoblastic leukemia identifies recurrent mutation patterns and therapeutic options. *Nat. Genet.* doi:10.1038/ng.3362