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Systematic investigation of disease- and genotype-specific vulnerabilities in primary blood cancer using high-throughput *ex vivo* drug screening

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Chronic lymphocytic leukaemia (CLL) is an indolent B-cell non-Hodgkin lymphoma presenting with an asymptomatic accumulation of monoclonal lymphocytes in peripheral blood, bone marrow, and lymphatic tissue. Although CLL patients have a high five-year survival in general, certain genotypes can worsen prognosis and require intensive therapy. Hence, determination of genomic markers becomes important to predict prognosis and to support treatment decision. In the past years, therapy with B-cell receptor (BCR) signalling inhibitors has been established in first-line therapy beside chemo- and immunotherapy.
In this study, ex vivo drug screening with 63 compounds in five concentrations was used to investigate drug response in 17 blood cancers with focus on CLL. In total, the study comprised 722 primary samples derived from 493 patients. 456 samples were analysed for disease-specific vulnerabilities, and genomic data of CLL patients were integrated to identify known and novel genotype-phenotype associations. In addition, longitudinal stability of drug response was evaluated using 285 samples from 113 patients (111 CLL) obtained at different time points over the clinical course.
Results were highly reproducible on the platform and drug response pattern was entity-specific. In CLL, main predictors of drug response were immunoglobulin heavy chain variable region (IGHV) status and tumour protein 53 (TP53) mutation status. Unmutated IGHV was associated with high response to BCR signalling inhibitors and predicted for both poor overall survival (OS) and short time to next treatment (TTT). TP53 mutated samples were more resistant to chemotherapeutics and to mouse double minute homologue 2 (MDM2) inhibition, and TP53 mutation was associated with poor OS and TTT. CLL harbouring trisomy(12) was exclusively sensitive to mitogen-activated protein kinase kinase (MEK) and extracellular signal-regulated kinase (ERK) inhibitors, and DEAD-box helicase 3 X-linked (DDX3X) mutated CLL responded well to Bruton's tyrosine kinase (BTK) and spleen tyrosine kinase (SYK) inhibitors.
B-cell and T-cell acute lymphoblastic leukaemia (B-ALL/T-ALL) were highly vulnerable to inhibition of DNA damage response signalling. Furthermore, B-ALL was the most sensitive disease to phosphoinositide 3-kinase (PI3K)/mechanistic target of rapamycin (mTOR) signalling inhibition.
The longitudinal part of the study revealed that cells of most patients possessed stable drug response over time. However, cells of patients undergoing targeted therapy with BCR signalling inhibitors acquired sensitivities in bromodomain and extraterminal domain (BET) inhibitors and TW-37, a dual B-cell lymphoma 2 (BCL-2)/myeloid cell leukaemia 1 (MCL-1) inhibitor. Results need to be confirmed in validation experiments.
In conclusion, ex vivo drug screening is an important source of preclinical discovery in primary blood cancer, provides a biological basis for clinical studies, and represents a tool to support individual treatment decision.