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Application of genome-wide CRISPR/Cas9 screen to identify synthetic lethality with MCL-1 inhibition in lung cancer

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Background/Aims Lung cancer is among the most diagnosed cancers and the leading cause of cancer-related deaths. Histologically, it is divided into small cell lung cancer and more prevalent non-small cell lung cancer (NSCLC). Recent reports demonstrated frequent amplifications of anti-apoptotic gene myeloid cell leukemia 1 (MCL-1) in NSCLC, contributing to tumor cell survival and treatment resistance. Pharmacologic inhibition of MCL-1 protein showed promising effects in pre-clinical models, but the malignant cells frequently exhibit resistance to this mono-therapy. The aim of this study is to uncover synthetic lethal interactions between MCL-1 inhibition and specific genes and thereby identify potential new targets for combination treatment approaches. Methods/Results To reveal synthetic lethal relationships with MCL-1 inhibitors in NSCLC, we employed a genome-wide pooled CRISPR/Cas9 screen. MCL-1 inhibitor-resistant A549 cells were lentivirally transduced with Cas9 and a whole-genome CRISPR knock-out guide RNA library, and treated for 12 days with MCL-1 inhibitor. At the end of the treatment period, genomic DNA was extracted and next generation sequencing applied to identify differences in guide RNA expression in control and MCL-1 inhibitor-treated cells. SgRNAs against co-essential genes should be lost in the treated cells during in the screening process. Bioinformatic analysis revealed that guide RNAs against 26 genes were significantly downregulated upon MCL-1 inhibition. One of the obtained hits was the BCL2L1 gene that encodes for another pro-survival protein named BCL-XL, a well-known resistance factor to a variety of therapies. Indeed, when we combined the MCL-1 inhibitor with specific inhibitors against BCL-XL, A549 cells were strongly sensitized and cell death induction was observed at very low concentrations of MCL-1 inhibitor. Conclusion Our data indicate the existence of a synthetic lethal relationship between MCL-1 inhibitor and multiple genes in NSCLC.