Immunotherapy resistance

Immunotherapy has transformed cancer treatments; however, a large fraction of patients encounter resistance. Such resistance is mediated by complex factors, often involving interactions between multiple genes. Thus, it is crucially important to identify genetic interactions between genes that are significantly mutated in cancer patients and those involved in immune responses, ideally the ones that currently have chemical compounds for direct targeting. To systematically interrogate such genetic interactions that mediate cancer cells' response to T cell killing, Park et al. designed an asymmetric dual perturbation library targeting the matched combinations between significantly mutated tumor suppressors and immune resistance genes. They performed a combinatorial double knockout screen on 1159 gene pairs and identified those where joint loss-of-function renders altered cellular response to T cell cytotoxicity. They also performed comparative transcriptomics-based analyses on tumor and normal samples from TCGA and GTEx cohorts, mutational profiling analyses, and survival analysis to further characterize the significance of identified hits in clinical patients. Interactions between significantly mutated tumor suppressors and potentially druggable immune resistance genes may offer insights on potential new concepts of how to target clinically relevant cancer mutations with currently available agents [1)]

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1)
Park JJ, Codina A, Ye L, Lam S, Guo J, Clark P, Zhou X, Peng L, Chen S. Double knockout CRISPR screen for cancer resistance to T cell cytotoxicity. J Hematol Oncol. 2022 Dec 1;15(1):172. doi: 10.1186/s13045-022-01389-y. PMID: 36456981.