Charting Cancer Pharmacological Dependency

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One primary cancer drug discovery approach is to identify agents that modulate single proteins (e.g., EGFR for lung cancer). This approach led to the discovery of many successful drugs (e.g., EGFR inhibitor Gefitinib); however, some oncogenes (e.g., MYC and RAS) are still challenging to target, partially due to the lack of favorable binding pockets. One alternative is to target the protein on which the function of the undruggable oncogenes depends (for example, targeting MYC via CDK4 inhibition); however, such dependencies are largely unelucidated. The cancer dependency map projects led by the Broad Institute and Sanger Institute produced large amounts of data for defining genetic dependencies, which covered cancer cell fitness with 18,333 gene knockout experiments in 1210 cancer cell lines along with molecular profiles of these cell lines. These genetic-based data provide opportunities for identifying targets as a surrogate for traditional undruggable proteins such as suppressors; however, more pharmacological evidence is expected to support the dependency. By leveraging open drug-induced gene expression change (GEC) signatures from the Library of Integrative Network-based Cellular Signatures (LINCS) L1000 dataset (Level 5)\(^1\) and drug-target binding affinities from the ChEMBL (v25)\(^2\) dataset, we built ParmacoDepMap, a dependency map between gene expression and druggable protein activity, to provide a strategy for pharmacologically modulating expression of oncogenes under different cellular contexts. ParmacoDepMap consists of 115,252 pharmacological dependencies between 978 landmark genes and 1723 druggable proteins in individual cell lines or across 15 cancer cell lines. Universally, 938 genes were connected to at least one drug target. For an individual cell line, this number ranges from 20 to 907, with a median of 125. On average, the expression of one gene could be regulated by nine druggable targets, while one druggable target could regulate the expression of 21 genes. In addition, we identified biomarkers to predict pharmacological dependencies via gene expression analysis using the Cancer Cell Line Encyclopedia database. ParmacoDepMap can be further validated and augmented, providing more accurate solutions for oncogene intervention and therapeutic development. In the future, we will also collaborate with bench scientists to identify new biomarkers for MYC related cancer treatment and screen compounds or drug combinations.

References