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Substituents Based on Pharmacogenomics with Highly Variable Prognoses

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DESCRIPTION

Pharmacogenomics is critical for personalised drug therapy and is becoming increasingly important in precision medicine decision-making. However, pharmacogenomics-based molecular subtypes and their potential clinical significance in Lung Adenocarcinoma remain largely unexplored (LUAD). Three reproducible molecular subtypes were discovered, each of which was an independent prognostic factor and was strongly associated with stage, survival status, and accepted molecular subtypes. Non-Small Cell Lung Cancer (NSCLC) is a malignant tumour with a high incidence and cancer-related mortality, the most common pathological subclass being Lung Adenocarcinoma (LUAD). Many FDA-approved drugs are available for LUAD patients, including chemotherapy agents, targeted agents, and Immune Checkpoint Blockers (ICBs). For NSCLC patients who do not have driver mutations, platinum-based chemotherapy is the primary first-line treatment. The standard treatment for lung cancer patients with driver mutations is targeted therapy, such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors. ICB has emerged as a novel therapeutic strategy for patients with unrespectable NSCLC in recent years. Despite multiple therapeutic options, LUAD patients have a dismal survival prognosis, with a 5-year relative survival rate of only 21%. Individual therapeutic responses could account for the low survival rate. Tumor heterogeneity, such as varying tumour microenvironment (TME) patterns or cancer cell types, is a major contributor to low response rates and drug resistance. As a result, LUAD patients are encouraged to devise a precise classification strategy. Currently, LUAD molecular subtypes are determined by genomic, transcriptomic, and epigenetic changes, as well as their combination. The most widely accepted molecular subtypes, Terminal Respiratory Unit (TRU), Proximal Inflammatory (PI), and Proximal Proliferative (PP), were described in 2014 using 230 LUAD samples from The Cancer Genome Atlas (TCGA) cohort (PP). Despite the fact that different molecular subtypes have different biological behaviours and prognoses, they have limitations in guiding clinical management decisions. To achieve precision medication for different populations, we must develop a novel pharmacogenomics-based classifier. The most commonly used models for determining drug efficacy are cancer cell lines. The large-scale high-throughput sequencing technique allows for genome-wide drug response analysis in cell lines. As a result, we have access to a large amount of pharmacogenomics data.

Profiling of Relative Inhibition Simultaneously in Mixtures (PRISM), the Cancer Therapeutics Response Portal, and other pharmacogenomics resources are available (CTRP), and the Genomics of Cancer Drug Sensitivity (GDSC). The PRISM and CTRP cell models are from the Cancer Cell Line Encyclopaedia (CCLE). Some drugs overlap and are approved by the FDA for LUAD patients. As a result, we can use multiple pharmacogenomics databases to obtain data on multiple drug responses. PRISM and GDSC were used to obtain drug response data for LUAD cell lines. This study included nine FDA-approved and widely used drugs for the treatment of LUAD: gefitinib, erlotinib, afatinib, crizotinib, cisplatin, docetaxel, etoposide, paclitaxel, and vinorelbine. Cell lines were classified as sensitive, partial response, or resistance for each drug based on the mean 0.5 Standard Deviations (SD) of the IC_{50}, log10 (IC_{50}), EC_{50}, or log10 (EC_{50}) values. Cell lines that had an IC_{50}, log10 (IC_{50}), EC_{50}, or log10 (EC_{50}) value greater than the mean +0.5 SD were considered drug resistant. Cell lines with an IC_{50}, log10 (IC_{50}), EC_{50}, or log10 (EC_{50}) value less than the mean 0.5 SD were considered sensitive to the drug, while those with an IC_{50}, log10 (IC_{50}), EC_{50}, or log10 (EC_{50}) value between the mean +0.5 SD and the mean 0.5 SD were considered partially responsive to the drug. In evaluating chemotherapeutic response in solid tumours, this classification corresponds to the RECIST 1.1 system (i.e., complete response, partial response, and stable disease/disease progression). The CCLE was used to obtain the corresponding expression data of LUAD cell lines from PRISM, and the GDSC1000 resource was used to obtain the expression data of LUAD cell lines from GDSC. CCLE expression data were collected using RNA-seq and transformed into log2 (TPM+1). The expression array data for GDSC1000 was obtained from the Affymetrix Human Genome U219 array platform and normalized using the Robust Multi-Array average (RMA) algorithm. Taking into account the various methods of generating expression data, each gene expression was transformed into a Z-score across samples in CCLE and GDSCA1000 cell lines. Our pharmacogenomics-based integrative classification revealed potential subtype-related and patient-specific therapeutic strategies.